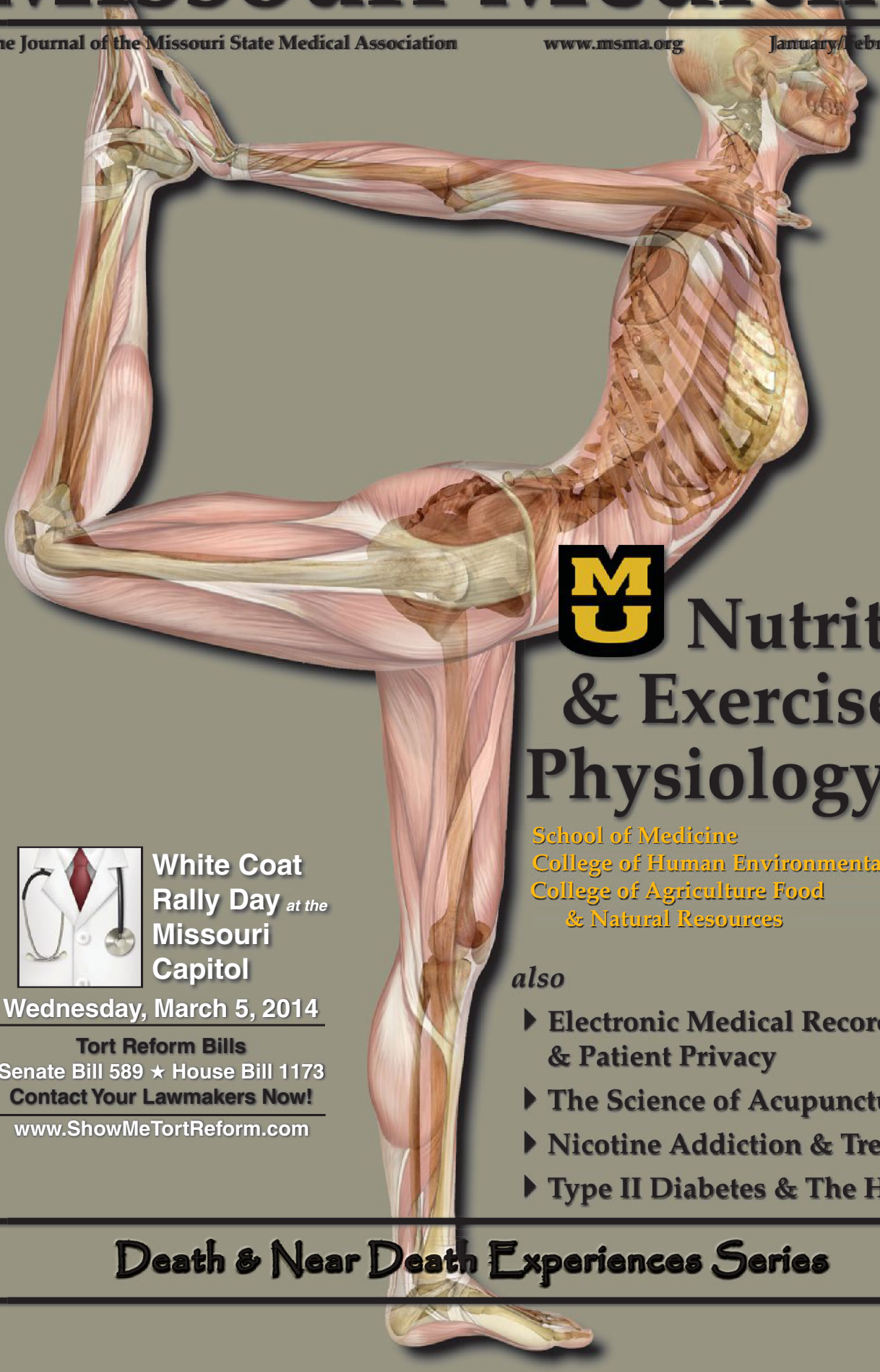
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Missouri State Medical Association

113 Madison Street ◆ P.O. Box 1028 ◆ Jefferson City, MO 65102
800-869-6762 ◆ Fax: 573-636-8552 ◆ www.msma.org/MissouriMedicine
Editor: John C. Hagan, III, MD ◆ jhagan@bizkc.rr.com
Managing Editor: Lizabeth R. S. Fleenor ◆ lfleenor@msma.org

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About *Missouri Medicine*

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Missouri Medicine Editorial Board

Owner & Publisher

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Missouri Medicine Editor*

John C. Hagan, III, MD
9401 North Oak Trafficway, Ste. 200
Kansas City, MO 64155
Tel: 816-478-1230 / Fax: 816-454-8478
jhagan@bizkc.rr.com

Managing Editor

Lizabeth R. S. Fleenor
Missouri State Medical Association
113 Madison Street / P.O. Box 1028
Jefferson City, MO 65102
800-869-6762 / Fax: 573-636-8552
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MSMA Office & Staff Contact Information

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Executive Vice President: Tom Holloway	Tel Ext - 123	tholloway@msma.org
Communications: Lizabeth Fleenor	Tel Ext - 134	lfleenor@msma.org
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Membership Database: Lois Chronister	Tel Ext - 127	lois@msma.org
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Today, I'm serving up a "Blue Plate Special"

Blue Plate Special = 'Surf and Turf' Surgery



John C. Hagan, III, MD, FACS, is a Kansas City ophthalmologist and Missouri Medicine Editor since 2000. Contact: jhagan@bizkc.rr.com

As a surgeon, I acknowledge that I never had much fondness for blue plate specials. Maybe you know them by a different moniker: 'two-fer', 'double-hitter', or 'schedule-killer'.

The recipe for putting a wooden stake through the heart of your surgical day begins with a note from your scheduler: "Doctor Hagan, Mrs. Jones called and wants to have you do her cataract surgery and Dr. Bloodless do her hemorrhoid surgery at the same time." Almost always we were able to convince patients that trying to do two things at once would do justice to neither.

So I'm serving up my own Blue Plate Special; this month I'm featuring two topics:

1. Following up on the "2014 'Must Do' Tick List" (Nov/Dec 2013)
2. Directing your attention to the outstanding series of articles in this issue by Missouri University Department of Nutrition & Exercise Physiology, beginning on page 39.

First Course-Physician Advocacy

I'm always somewhat uncomfortable if I'm not the most compulsive physician in the room. Thus, our ophthalmology group has 100% membership in the Missouri State Medical Association and 2014 dues are paid; I have mailed my $1,000 check for Super Diamond membership to the Missouri Medical Political Action Committee (MMPAC). My staff has scheduled me out of the office March 5, 2014, to attend the Tort Reform White Coat Rally Day. Through MSMA we're working with various hospitals and the medical schools statewide to allow their employed physicians and trainees to attend in numbers that will impress the legislators and draw crucial media coverage. Missourians must understand the hatchet job that trial lawyers and their state Supreme Court minions have done on "Show-Me" health care.

I've recruited a new member to MSMA. (Frederick W. Fraunfelder, MD, MBA, the new MU Department of Ophthalmology Chair). But advocacy is a team sport. Time to put yourself into play! At the state level, each and every physician can make a difference. Tort Reform enactment in 2005 proved that. Pay your MSMA dues now. If not a member of MSMA join us as we are the leading state advocate for our patients and our profession. While your checkbook is out make a generous contribution to MMPAC ($150 for members, $500 for MSMA officers and leadership, and for the MMPAC Committee members, please join me in the Super Diamond level with your check for $1,000).

Contact your state Senator and Representatives and start hammering home this session's mantra, "Re-enact tort reform! Take health care back from the tort kings and queens." Read the weekly MSMA *Legislative Report*.

Did I say, "Cancel your schedule on March 5 and join your fellow physicians in Jefferson City for the White Coat Day Rally for Tort Reform?" Yes, I think I did.

Did I say, "Bring your staff wearing white coats?" No, I didn't. Just shows, it pays to be compulsive.

Tort Reform Bills: Senate Bill 589 House Bill 1173

Second Course-Exercise & Nutrition

Properly dosed, exercise and nutrition are as close to magic elixirs for most of mankind's illnesses and ailments as physicians are ever likely to have in their armamentarium.

Missouri Medicine has been at the forefront of national and international medical research in documenting that too much exercise can be as toxic and noxious as too little.[1-4] For endurance over-exercisers, especially after age 40, do not do maximum 'red-line' exercise for longer than 55 minutes. Your marathon-running editor wishes he had got that memo before his excessive exercise induced atrial fibrillation and astoundingly egregious coronary artery calcium score developed. For under-exercisers, who represent the greatest number of patients we interact with on a daily basis, a half hour of walking-type exercise can accrue most of the many benefits for health and fitness.

Physicians, their staff and patients, indeed everyone should view this video: www.youtube.com/watch?v=Y6U728AZnV0 by MSMA member James O'Keefe, MD, and Magic Message Chalk-Talk at www.youtube.com/watch?v=aUaInS6HIGoby by Michael Evans, MD.

This *Missouri Medicine* theme issue coordinated by Christopher Hardin, PhD, and the Missouri University Department of Nutrition & Exercise Physiology adds further knowledge and documentation about the most important and under-utilized "wonder drugs": diet and exercise.

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MM

ObamaCare 2016: Happy Yet?

by Bradley S. Allen, MD



The website problems can be solved. But the doctor shortage is a nightmare.

Three years after the disastrous launch of the Affordable Care Act, most of the website troubles finally have been ironed out. People are now able to log on to the government's ACA website and most of the state health-insurance exchanges. The public has grudgingly come to accept higher insurance premiums, new taxes and increases in part-time workers who were formerly full-time. But Americans are irate anyway—because now they're seeing the health-care law's destructive effect on the fundamental nature of the way their care is delivered.

Even before the ACA's launch in 2013, many physicians—seeing the changes in their profession that lay ahead—had begun talking their children out of going to medical school. After the launch, compensation fell, while nothing in the ACA stopped lawsuits and malpractice premiums from rising. Doctors must now see many more patients each day to meet expenses, all while dealing with the mountains of paperwork mandated by the health-care law.

The forecast shortage of doctors has become a real problem. It started in 2014 when the ACA cut $716 billion from Medicare to accommodate 30 million newly "insured" people through an expansion of Medicaid. More important, the predicted shortage of 42,000 primary-care physicians and that of specialists (such as heart surgeons) was vastly underestimated. It didn't take into account the ACA's effect on doctors retiring early, refusing new patients or going into concierge medicine. These estimates also ignored the millions of immigrants who would be seeking a physician after having been granted legal status.

It is surprising that the doctor shortage was not better anticipated: After all, when Massachusetts mandated health insurance in 2006, the

wait to see a physician in some specialties increased considerably, the shortage of primary-care physicians escalated and more doctors stopped accepting new patients. In 2013, the Massachusetts Medical Society noted waiting times from 50 days to 128 days in some areas for new patients to see an internist, for instance.

But doctor shortages are only the beginning.

Even before the ACA cut $716 billion from its budget, Medicare only reimbursed hospitals and doctors for 70%-85% of their costs. Once this cut further reduced reimbursements, and the ACA added stacks of paperwork, more doctors refused to accept Medicare: It just didn't cover expenses.

Then there is the ACA's Medicare (government) board that dictates and rations care, and the board has begun to cut reimbursements. Some physicians now refuse even to take patients over 50-years old, not wanting to be burdened with them when they reach Medicare age. Seniors aren't happy.

Medicaid in 2016 has similar problems. A third of physicians refused to accept new Medicaid patients in 2013, and with Medicaid's expansion and government cuts, the numbers of doctors who don't take Medicaid skyrocketed. The uninsured poor now have insurance, but they can't find a doctor, so essentially the ACA was of no help.

The loss of private practice is another big problem. Because of regulations and other government disincentives to self employment, doctors began working for hospitals in the early 2000s, leaving less than half in private practice by 2013. The ACA rapidly accelerated this trend, so that now very few private practices remain.

When doctors are employed like factory workers by hospitals, data from the Medical Group Management Association and others indicate, their productivity falls—sometimes by more than 25%. They see fewer patients and perform fewer timely procedures, exacerbating the troubles caused by physician shortages. Continuity of care also declines, since now a physician's responsibilities end when his shift is over.

Of those doctors still in private practice, many have taken refuge from the health-care law by going into concierge medicine, where the patient pays an annual fee (typically $500-$3,000 a year per individual) to a primary-care physician. This doctor provides enhanced care, grants quicker appointments and spends more time with each patient, working with a base of 300-600 patients instead of the 3,000-5,000 typical in the ACA era. Doctors and patients who can afford it love concierge medicine: It allows treatment to be administered as the doctor sees fit, instead of as if the patient is on an assembly line with care directed on orders from Washington.

Patients who can't afford concierge medicine but have seen their doctor take that route are out of luck: They have been added to the swelling rolls of patients taken care of by the shrinking pool of physicians. So even people with "private" insurance have found that the quality of their health care declined. Nowadays, many are forced instead to see a nurse or other health-care provider. The traditional doctor-patient relationship is now reserved primarily for those who can pay extra.

Concierge-type care was easily expanded to specialists. The top surgeons now simply opt out of Medicare or become "out of network" providers, allowing them to bill patients directly. Many have joined the plastic surgeons and ophthalmologists who work on a straight fee-for-service basis.

Equally important: With the best and most successful doctors disappearing into concierge medicine or refusing new Medicare and Medicaid patients, replacing these experienced physicians with bright young doctors to work with the "general public" has become difficult. Why? Because such doctors are hard to find—going into medicine doesn't have the professional allure it once did.

With an average of $300,000 in student loans, eight years of college and medical school, and three to seven years as underpaid, overworked residents, a prospective physician in the ACA era would be starting a career at age 30 in a job that requires working 70-80 hours a week in an assembly-line fashion to earn perhaps $100,000 a year. No wonder so many qualified individuals these days are choosing careers on Wall Street or in Silicon Valley instead of medicine.

It is also no wonder that three years ago members of Congress got themselves exempted from the Affordable Care Act. They may have passed the law, but they're not stupid.

Bradley Allen, MD, is a pediatric heart surgeon, and former professor and surgical director of the Children's Heart Institute in Houston.

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MM

With EMRs, doctors have the choice of either working longer hours or seeing fewer patients.

The Electronic Medical Records Fiasco

by Arthur Gale, MD

Not surprisingly it turns out that the main beneficiary of electronic medical records is the electronic health care industry.



Arthur H. Gale, MD, MSMA member since 1976, is a Missouri Medicine Contributing Editor. He practices Internal Medicine in St. Louis.
Contact: agalemd@aol.com
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Electronic medical records were supposed to save $81 billion per year according to a 2005 report by the RAND Corporation an independent think tank and research organization. The report anticipated that over a 15-year period $150 billion could be saved in outpatient care and $350 billion could be saved in inpatient care.

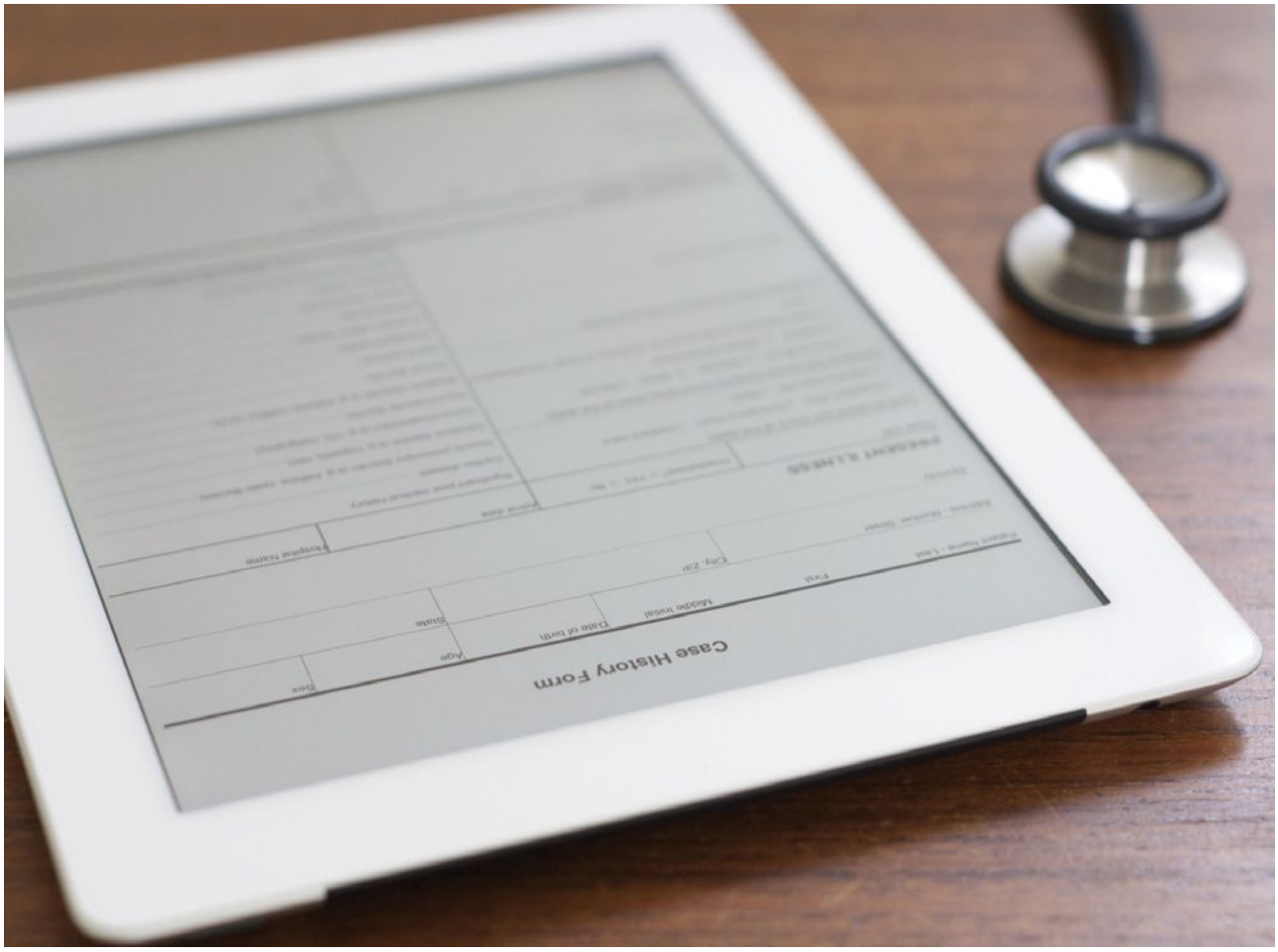
The report was widely praised within the technology industry and persuaded Congress and the Obama administration to authorize billions of dollars in federal stimulus money in 2009 to help hospitals and doctors pay for the installation of electronic medical records.

Now a recent 2013 report from the Rand Corporation showed that the conversion to electronic medical records has failed to produce any savings at all. In fact there is increasing concern that electronic medical records have actually increased costs by making it easier for hospitals and other providers to bill for services. RAND acknowledged its earlier report was "overly optimistic."

Not surprisingly it turns out that the main beneficiary of electronic medical records is the electronic health care industry. The RAND study was paid for by General Electric, the Cerner Corporation, and other companies that extracted enormous profits from EMR sales. Cerner's revenue nearly tripled to a projected $3 billion in 2013 from $1 billion in 2005.[1]

This conflict of interest is similar to the conflicts of interest that occurred when the stock and bond ratings companies Standard and Poor and Moody's gave triple A ratings to worthless subprime loans that led to the stock market crash in 2008. The analyses by the ratings companies were paid for by the very companies they were supposed to evaluate. A number of lawsuits and investigations have been initiated against the ratings companies. It is unlikely that anything will happen to the RAND corporation or the companies that funded its recommendations.

Many doctors have lost money after purchasing EMRs. More than 210,000 physicians have received payments through the government stimulus program. Despite these subsidies a Health Affairs study found that only 27% of physicians made money using them. Smaller offices, those with five doctors or less, struggled the most to make EMRs profitable. With EMRs, doctors have the choice of either working longer hours or seeing fewer patients.[2]



What about quality of care? Quality of care was supposed to improve with EMRs. There have been a number of studies that show EMRs may actually reduce quality. Most mistakes using EMRs are not technical such as in writing prescriptions but are from misdiagnosis.

A study of orthopedic surgeons compared hand held electronic medical records with paper records. There were 48 wrong or redundant in the computerized record and eight in the paper-based cohort. A 2008 study on the quality of care in more than 15,000 patients with congestive heart failure resulted in little discernible improvement in quality of care. A group of Canadian researchers recently reviewed more than 3,700 published papers on EMR use in primary care. They found no evidence of benefits accruing to patients.[3] A 2013 report from *American Medical News* showed that hospital staffs often cut and paste incorrect data. The error then gets propagated virally on a daily basis.[4] Finally, in a 2012 survey of over 13,000 physicians only one in three physicians felt that EMRs improved quality.[5]

In health care, our government makes top down decisions giving glowing reports on potential cost savings and improvement in quality in the various programs it proposes. There is little or no input from practicing physicians who on a daily basis must live with the results of these decisions. Perhaps, before wasting billions of dollars on projects whose major beneficiaries are often large private corporations our government would do better if it would first seek the input of those who understand the practice of medicine best - physicians.

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How to Protect Medical Information In the Electronic Era

Patient Medical Information At Risk From Stolen Computers

by Kimela West, JD

There have been an increasing number of health care data breaches related to the use of laptops or other portable devices that store, contain or are used to access patient medical information.



Kimela West, JD, is an associate in the St. Louis, Missouri office of Husch Blackwell LLP. The Firm acts as outside general counsel to the MSMA. The information contained in this article should not be construed as legal advice or legal opinion on any specific facts or circumstances. The contents are intended for general informational purposes only, and readers are encouraged to consult their own attorney regarding specific legal questions.
Contact: kimela.west@huschblackwell.com

Stolen laptop computers that contain patients' medical information seem to be weekly news in the media. Keeping medical information secure is a challenge for many health care organizations, and as three recent incidents show, inadequate data security can affect huge numbers of people as well as the liability of the breaching company.

In Chicago, the theft of four computers from Illinois-based Advocate Health Care has potentially placed the personal information of more than four million patients in jeopardy. The computers, which were taken on July 15, 2013, contained names, addresses, social security numbers, and dates of birth. The incident marks one of the biggest health care breaches yet. The health system was subsequently slapped with a class action lawsuit filed by affected patients.

In Los Angeles, medical information of about 729,000 patients was compromised by the theft of two laptops belonging to a California hospital group. The laptops, owned by AHMC based in the San Gabriel Valley, contained health and personal information about patients treated at six hospitals in the region. The AHMC Healthcare breach is the 11th biggest health care data breach to date, according to data from the Department of Health and Human Services.

A laptop computer that stored unencrypted demographic information of about 5,500 patients was taken in early October 2013 from Seton Healthcare Family's McCarthy Community Health Center in Austin, Texas. The files on the laptop included names, addresses, phone numbers, birthdates, Seton medical record, and patient account numbers, social security numbers, diagnoses, immunizations, and insurance information. Though Seton Healthcare Family requires that computers use encryption, the stolen laptop did not have the encryption software installed.

There have been an increasing number of health care data breaches related to the use of laptops or other portable devices that store, contain or are used to access patient medical information. The potential consequences for these latest breaches under the HIPAA Omnibus Rule[1] (the "Rule") are likely to be severe. The Rule formally adopts the following penalty scheme for violations occurring after February 18, 2009:

- For violations where a covered entity did not know and, by exercising reasonable diligence, would not have known that the covered entity violated a provision, a penalty of not less than $100 or more than $50,000 for each violation.

- For a violation due to reasonable cause and not to willful neglect, a penalty of not less than $1,000 or more than $50,000 for each violation.
- For a violation due to willful neglect that was timely corrected, a penalty of not less than $10,000 or more than $50,000 for each violation.
- For a violation due to willful neglect that was not timely corrected, a penalty of not less than $50,000 for each violation; the penalty for violations of the same requirement or prohibition under any of these categories may not exceed $1.5 million in a calendar year.

With all violation categories, penalty amounts will be determined on a case-by-case basis depending on five factors: (i) nature and extent of the violation; (ii) nature and extent of the harm resulting from the violation; (iii) history of prior compliance and noncompliance; (iv) financial condition of the entity; and (v) such other matters as justice may require.

The Rule establishes new standards for evaluating and addressing potential breaches of protected health information ("PHI"). The Rule lowers the standard for breach notification. Under the previous rule, breaches were not required to be reported to the Department of Health and Human Services ("HHS") unless they posed a "significant risk of reputational, financial or other harm" to individuals. The new standard presumes that a reportable breach has occurred unless the covered entity or business associate, through the use of a multi-factor risk assessment, determines that there is a low probability that PHI has been compromised by the unauthorized use or disclosure.

To demonstrate that there is a low probability that a breach compromised PHI, a health care organization must perform a risk assessment that addresses the following minimum standards:

- The nature and extent of the PHI involved, including the types of identifiers and the likelihood of re-identification;
- The unauthorized person who used the PHI or to whom the disclosure was made, and whether the PHI was actually acquired or viewed;
- Whether the PHI was actually acquired or viewed; and
- The extent to which the risk to the PHI has been mitigated.

A health care organization must be able to quickly perform a risk assessment that will:

(1) review a potential breach;

(2) identify whether it is reportable and if it is reportable provide notice of the breach to all individuals whose PHI was subject to the breach;

(3) provide notice to the Secretary of the HHS and, in some instances, to one or more prominent media outlets and

(4) remediate the problem (i.e. offering credit monitoring to individuals whose PHI was subject to the breach).

Despite steep penalties under the Rule which holds covered entities and business associates more accountable for failing to adequately protect patients' medical information, including PHI some health care organizations continue to make the same old avoidable mistakes. For example, this is Advocate Health Care's second health care data breach in recent years. There was the theft of a laptop back in November 2009, which was also unencrypted. The stolen laptop had the medical records of 812 individuals. Leon Rodriguez, director of the Office for Civil Rights ("OCR"), the agency responsible for investigating HIPAA data breaches and violations has promised an increase in investigations and monetary penalties for health care organizations that have failed to take patient privacy seriously. OCR has already collected millions from health care organizations who grossly violated HIPAA.[2]

Safeguarding Patient Medical Information on Mobile Devices such as Laptops, Tablets and Smartphones

Recently, the OCR and the Department of Health and Human Services Office of the National Coordinator for Health Information Technology ("ONC") launched an educational initiative offering practical tips on ways to maintain the privacy and security of patient medical information when using mobile devices such as laptops, tablets and smartphones.[3] The proposals contained in the on-line materials published by OCR/ONC include, among others:

- Using device passwords and other user authentication;
- Activating screen locks after periods of non-use;
- Installing or enabling encryption;
- Installing or activating remote wiping and/or disabling;

- Disabling or avoiding use of file-shared applications;
- Installing or enabling firewalls;
- Installing, enabling or updating security software;
- Researching apps before downloading;
- Maintaining physical control of mobile devices;
- Ensuring adequate controls when using Wi-Fi; and
- Deleting all stored protected health information before reusing or discarding a device.

Although these recommendations are not required by HIPAA, they lay the foundation for best practices and should likely be analyzed and documented as part of any risk assessment undertaken in accordance with the HIPAA security rule.

Developing Mobile Device Policies: A Five-Step Approach

The key to adequately addressing the aforementioned privacy and security recommendations is implementing and updating policies that specifically discuss the use of mobile devices by workforce members. To assist with the development of such policies, the OCR/ONC suggest the following five-step approach:

1. Decide whether mobile devices will be used to access, retrieve, store or create protected health information. Risks associated with such decisions include:
   - Loss of a device;
   - Theft of a device;
   - Inadvertent download of viruses and malware;
   - Use of an unsecured Wi-Fi network; and
   - Unintentional and unauthorized disclosure of protected health information when sharing devices with friends, family and/or coworkers.

2. Compare the risk of mobile device use to relative benefits. Conduct ongoing risk assessments which address in the documented analysis:
   - Personally-owned versus organizationally-owned devices;
   - Devices which communicate with the organization's internal networks;
   - Information accessed, received, stored, and transmitted by or with devices; and
   - Requirements of the HIPAA security rule.

3. Identify the organization's mobile device risk management strategy, including evaluation and implementation of privacy and security safeguards.

4. Document the following when implementing the organization's mobile device program:
   - How devices will be managed and tracked;
   - Whether health care professionals will be allowed to use their own devices or connect to internal systems through their own devices;
   - Which security/configuration settings will be required;
   - Whether health information may be stored on devices;
   - Whether apps may be downloaded to devices;
   - Whether health information may be used or disclosed in text messages;
   - How devices will be wiped or disabled when lost or when employees leave the organization;
   - When training of workforce members will occur; and
   - How members of the workforce will be held accountable for failure to comply with the organization's policies.

5. Conduct ongoing training addressing, among others, the following topics:
   - Threats and vulnerabilities associated with mobile device use;
   - Methods for securing devices and protecting health information; and
   - Best practices for avoiding privacy and security mistakes when using devices.

With OCR enforcement on the rise related to mobile devices such as laptops, and individuals suffering an unauthorized release of their PHI health care organizations should conduct or have conducted by qualified consultants or attorneys a risk assessment of their current compliance. Even if such an effort does not detect all vulnerabilities within the organization, the mere fact that such an effort has been expended with complete documentation of the review and implementation of remedial measures can work to diminish the penalties assessed by the OCR.

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3. See www.HealthIT.gov/mobiledevices.

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5 HIPAA Violations You Need to Know

Doctors do not plan ahead to violate HIPAA, but in this digital age they may be unknowingly violating these regulations and putting Patient Health Information (PHI) at risk. Here, we outline five common ways you may be breaking HIPAA privacy and security rules accidently:

1) Texting PHI to members of your care team

It's a simple scenario: you've just left the office, and your nurse texts you that Mrs. Smith is having a reaction to the medication you prescribed. She has given you her information to return the call. You may know this is illegal, but feel justified because it is a serious case. In reality, this information has just passed from your nurse's phone, through her phone carrier, to your phone carrier, and then to you – four potential areas where this unsecure message could be intercepted or breached.

2) Taking a photo of a patient on your mobile phone

To some this will sound silly, to others, it is as common as verifying a rash with a colleague. Simple enough, but if these photos are viewed by eyes they are not intended for, you may be in violation.

3) Receiving text messages from your answering service

Many physicians believe that if they receive a message from a third party, then they are not responsible for any violation of HIPAA. They may verify it is encrypted on their end, but if it pops onto your screen, it is certainly not secure on your end – and this is where your responsibility lies.

4) Allowing your child to borrow your phone that contains PHI

Many folks allow their kids to play with their phones. If your phone has an app that can access PHI, then you may be guilty of a HIPAA breach if anyone views this information that is not you.

5) Not reporting a lost or stolen device that contains PHI

Losing your smartphone or tablet is a total pain, but many do not realize that if you have patient information in that device, you could be held responsible for a HIPAA breach. DocbookMD uniquely provides you extra security to avoid each of these potential pitfalls.

DocbookMD: MSMA Member-Only Benefit

DocbookMD is constantly developing new features for the app based on the three philosophies on which the company was founded: Physician-Centric, Patient-Oriented, and Community-Minded. Whether you are in a rural setting, urban setting, or hospital setting, DocbookMD wants each feature to be applicable everywhere. When we join together as physicians, we have the power to transform medical communication and improve patient care. Download the latest version of DocbookMD today to take advantage of the newest features. ONLY MSMA MEMBERS can take advantage of this app. Visit www.docbookmd.com or use your smart phone's app store to download the free app.

Is This the Last Straw?

Every major change in health care regulation leaves me wondering "Is this the last straw?" I'm not likely to quit medicine, but cutting way back on my practice or stopping participation in Medicare and insurance plans to solely practice cosmetic surgery sounds increasingly appealing. Barbe and co-authors[1] nicely summarized the challenges posed by the October 1, 2014, requirement to transition to ICD-10 diagnosis coding. Vice-president Joe Biden might summarize this transition as a "big !%*@!+# deal!"

The practicalities of such a change in claim submission leaves me "challenged." The existing ICD-9 diagnosis coding system is often poorly descriptive, but at least I know my codes by memory for 95% of encounters, and have a handle on how insurance carriers will deal with these claims. This transition takes place under the guise of compliance with international standards, creating a more "granular" coding system to show exactly what we are doing, and allowing for the Center for Medicare Services (CMS) to abandon the presumption of innocence "pay and chase" approach to fraud and abuse, and transition to an immediate "flag" to a claim that triggers review, denial, or whatever the auditors are in the mood for. It was previously estimated that every hour of medical care necessitates 30 minutes of paperwork within a medical practice, although the combination of EHR, other requirements, and the complex and unfamiliar ICD-10 coding promises to push us toward collapse with a closer to 1:1 ratio.[2]

Take heart in the "granularity" of ICD-10. There are more than 68,000 codes cover situations that I never envisioned,[3] with three codes for burns from flaming water-skis (presumably a big help to the emergency providers at the state's large lakes), and nine codes relating to injuries caused by parrots, with specific codes for macaws, other psittacines, turkeys, ducks, geese, and "other birds" (I had no idea parrots and psittacines were so special to the health care system). Providers are cautioned to provide the exact diagnosis code in these and all other situations to avoid the large statutory penalties spelled out years ago in the Kennedy-Kassebaum (HIPAA 1996) Act and other federal abominations that govern our practices.

In all seriousness, compliance with ICD-10 will be a very significant, costly, and time-consuming process. Compliance by itself delivers no "health care" to any patient. The large and complex billing and collection systems of American medicine have been tuned and debugged for years to deal with the current ICD-9 diagnosis coding system. It is highly probable that there will be significant (I estimate one to three months) delays in many claim payments after October 1, 2014 while the physicians and their billers learn to submit clean claims and insurance companies and other payers learn to process and pay on them. IT consultants will be raking in the $$$ with this. Sadly, overt fraud may be even easier for perpetrators to commit at the outset of this transition, as payers have no data on ICD-10 codes for comparison.[4] Perhaps it is a good idea for every entity in health care to have 60 days or more in operational expenses on hand at the start of this journey in October.[5]

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John Holds, MD
MSMA member since 1991
Ophthalmology
Des Peres, Missouri

Does Study Paint True Image?

Last month's *Missouri Medicine*[1] painted a spectacular image of the American health care system in "Interesting Statistics about the U.S. Health Care System," presented by the Physicians Foundation. I wish the facts were as encouraging as their article.

Their basic premise seemed to be that our nation's health care shortcomings are little more than variations in statistical methodology, lack of personal responsibility, and the non-transparent nature of health care. Additional facts and context suggest more profound problems, and an obvious solution.

It is true that the United States excels at technology: we have the world's best five-year survival rates for almost every type of cancer,[2] the most imaging equipment and the most images,[3] and rank among the fastest at access to specialists and elective surgery.[4] The American health care business model drives towards more specialization, intervention, and capital investment. Benefit as we may from some of this, there is little in our model that aligns with public health, prevention and lifestyle education.

As the article pointed out, 25% of Canadians wait at least four months for elective surgery. But remember, per person health care costs in Canada are roughly half those in the United States. Were they to spend as much on health care as we do, surely they could reduce those waiting times. Most important, countless interviews with Canadians reveal that though they are unhappy about their waiting time for elective surgery, they recognize this as an appropriate trade-off to knowing that a major non-elective problem will be quickly addressed with no risk of personal financial hardships or bankruptcies. They accept waiting for an elective procedure, knowing that cancer will not make them sell their house.[5]

In addition to our abysmal performance on life expectancy, infant mortality, maternal mortality, and a long list of other critical metrics, a 2011 report in Health Policy that showed we have the highest rate of death from reasons that were amenable to health care (ischemic heart disease, stroke, diabetes, bacterial infections, etc.).[6]

As one example, diabetics in the USA are more than three times as likely as those in almost any other modern nation to receive a lower extremity amputation.[7] Those diabetics with financial barriers are less likely to have had an eye or foot exam within 12 months, or even an A1C checked. As a result, this group has increased risk of retinopathies, strokes, and non-healing foot sores.[8] Our financial barriers impede care and reflect poorly on our nation's success at medical management of chronic diseases.

Finally, there is the suggestion that increasing patient responsibilities for the cost of health care would unfetter the power of the free market to drive down costs. While this logic applies to commodity markets such as air travel and automobile purchases, there will always be a discrepancy in knowledge and power between physicians and patients, rendering meaningless the notion of a free market in health care. The vast majority of health care costs are incurred by the sickest patients, and sick people are not particularly interested in shopping for the best deal. They're sick, often desperate, and want the care that their personal physician identifies as the best. Would more "skin in the game" resolve our health care crisis, this would have already occurred. In 2011, Americans spent $968 out-of-pocket on health care, compared to $640 in Canada and $315 in the United Kingdom, both countries where their national health care program has kept overall costs to roughly half that here.[9]

This cost-shifting places a tremendous burden on our nation's health outcomes. The Commonwealth Fund reports steady increases from 2003-2012 in Americans with medical problems but no physician visit (22% - 29%), not filling prescriptions at all (23%-27%), skipping needed diagnostic tests (19%-27%), and not getting specialty visits (13% to 20%).[10] Breast cancer patients with higher copayments are less likely to take aromatase inhibitors.[11] Children with high prescription co-pays use their asthma inhalers less and are hospitalized more.[12] When Medicare HMOs increase their copays, there are fewer outpatient visits but longer and more frequent hospitalizations.[13]

We continue on track for patients bearing an ever-increasing percentage of their health care costs. In 2006, 10% of American workers had health care deductibles above $1,000. In 2013, that number nearly quadrupled to 38%.[14]

Over 40% of Americans identify cost as the key driver of their health care access problems, far more than any other modern nation.[15]

Moving beyond the insurance reforms and vital patient protections built into the Affordable Care Act, there is a much more robust solution hiding in plain sight. We can improve Medicare – include in it the features that many seniors purchase as a "supplement" or "wrap" – and provide that to all Americans. By eliminating the private insurance industry's bureaucracy, administration, and astonishing profits, our nation would save $400 billion,[17] more than enough to provide all Americans access to comprehensive health care.[18]

We Americans cherish our ability to choose our own physician and hospital, but these critical decisions are increasingly taken away from us under the current system. Many health plans today try to exclude tertiary care medical centers from their "network"[19] as a dodge to keep their costs down… and avoid having the more seriously ill select them as their insurer. A truly free market in health care would mean that Americans, like Canadians and those in every other modern nation, could pick the physician and hospital they believe most meets their needs, instead of

having to defer to the decisions of an insurance company more interested in their quarterly profits than the long term health of the population.

We can afford a single payer system that preserves the private delivery of medicine, and Americans are literally dying for it. Everybody in, nobody out.

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Ed Weisbart, MD
MSMA member since 2003
Family Practice
Creve Coeur, Missouri

Potential to be the Best

In the Nov/Dec issue of *Missouri Medicine* (110:6, 450-451, 2013), a litany of items attempts to explain away the many shortfalls of the United States health care system. Rather than explaining our deficiencies away, wouldn't it be better to ask what the medical profession could do to improve health, life expectancy and quality of life? Wouldn't it be more productive to see that the many areas where American medicine excels are available to all Americans?

The author asks whether "a better assessment of a health care system's effectiveness is how it addresses actual illnesses." That is one valid assessment but it overlooks our dreadful performance in the prevention of "actual illnesses." Shouldn't we be focusing more on the delivery of primary care, preventive measures and the broad concept of "public health?" With our great wealth and medical capability we can find the means to provide universal access to comprehensive health care.

We spend more than any other country on earth for health care and we do not produce the best results. Some 31% of health care spending supports a wasteful, complicated insurance system while the public Medicare system operates with an overhead of less than 5%. Wouldn't it be fiscally prudent to stop this waste?

We could correct the shortcomings of the Medicare system and offer it to all Americans and thereby decrease the restrictions and lack of choice imposed by insurance companies, reduce health care disparities and the malpractice burden and save money.

We have the potential to be the best. We should be working toward that goal for the benefit of all.

William M. Fogarty, Jr., MD
MSMA member since 1977
Clinical Professor of Internal Medicine
Saint Louis University School of Medicine
St. Louis, Missouri

The Physicians Foundation Responds

Dr. Weisbart does make some cogent arguments. I estimate probably about 15 percent of physicians agree with him and prefer a single-payer system. I am not an apologist for insurers, but after the debacle of the rollout of the Affordable Care Act and its other complications and unintended side-effects, does anyone really have confidence in the federal government to administer all health care (one sixth of the economy)? Does anyone feel that physicians will be treated fairly in such a system? And if physicians are not treated fair, patients will also not fare any better. It comes down to one's trust of government. Drs. Weisbart and Fogarty have more trust than I do but they are entitled to their opinions. Physicians are not exactly treated fairly now, as we all know, but I do believe that physicians and their patients will have tougher sledding under single-payer. But if the public and physicians think that the new regulations under the ACA are onerous now, just wait until the government runs it all.

I understand what Dr. Fogarty is saying, my intention was not to pat ourselves on the back but simply respond to all the critics out there using questionable or misleading statistics. No one is suggesting that we have a perfect system - far from it - but we all tire of misleading information from so many critics that suggests that U.S. health care ranks with third world countries. Dr. Weisbart's comments on infant mortality and life expectancy have no foundation in fact.

Timothy B. Norbeck, MD
CEO, The Physicians Foundation

There's No Such Thing as "Healthy Obesity"

Overweight and obesity are the fastest-growing causes of morbidity and death in the U.S. Obesity is a chronic metabolic disorder associated with increased cardiovascular morbidity and mortality. However, despite the fact that obesity is

associated with increased health hazards, in recent years there have been some confusing and contradicting reports of "healthy obesity," "benign obesity" and "obesity paradox." These reports unfortunately have tried to undermine the severity of this alarming problem.

Dr. Caroline Kramer and colleagues highlighted the worsening obesity issue in their meta-analysis published December 2013 in Annals of Internal Medicine.[1] They reported increased incidences of cardiovascular disease and all-cause mortality among obese adults for both metabolically unhealthy and metabolically 'healthy' people of various weights and emphasized "there is no such thing as healthy obesity." The authors compared the cardiovascular and all-cause mortality for healthy and unhealthy obese groups. In their meta-analysis with a follow-up of 10 years, metabolically healthy obese adults had an increased risk for all-cause mortality and cardiovascular disease. The data for their study came from eight prospective studies published during the past decade. Metabolic health was defined by the presence or absence of metabolic syndrome as per Adult Treatment Panel III (ATP III) criteria or by the International Diabetes Federation (IDF). Excess weight is associated initially with subclinical metabolic and vascular dysfunction that ultimately leads to increased cardiovascular events and mortality.

The concept of "benign obesity" was originated from reports that evaluated metabolically healthy obese individuals over a short period of time. The authors claim their results do not support this concept of "benign obesity." I applaud Dr. Kramer and her colleagues on their excellent work to clarify that there is no '"healthy"' pattern of obesity. In fact the metabolically unhealthy adults, including those of mild obesity, exhibited the highest relative risk for cardiovascular events and all-cause mortality. My colleague and I also highlighted the increased cardiovascular risks in obesity as well as among "normal weight obese" (NWO) individuals in our review article recently published in *Missouri Medicine*.[2] NWO adults have increased atherosclerotic plaques in their arteries and worse clinical outcomes than those who have normal or smaller waist-to-hip ratios. NWO individuals have an increased risk for diabetes and cardiovascular disease compared with individuals who are metabolically healthy and of normal weight.

I strongly suggest that clinicians should pay more attention to this group of NWO individuals as they are likely to perceive themselves as healthy. Irrespective of metabolic status, if someone is obese or has normal weight obesity, he/she should be considered at risk. The data from the Kramer et al. meta-analysis further strengthen the fact that obesity, at any level or severity, is not a benign condition and is never "healthy."

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M. Javed Ashraf, MD, MPH
Member since 2014
University of Missouri-Kansas City
School of Medicine
Department of Cardiology
Kansas City, Missouri

I'm Really Hacked: A Cautionary Tale

I turned on my computer; it seemed to have taken the day off. Nothing came up when I tried to open my e-mail program. I had lost all my e-mail contacts, my past messages, important files - everything. I broke out in cold sweat. I panicked. It got worse. From a friend, I then received a forward of a fraudulent, virus generated e-mail alleging I was stranded in the Philippines. My wallet, money and passport were stolen. Calling on our friendship, would they wire money for me to return home? This fraudulent email went to the 1400+ addresses in my contacts file. I never delete anything - a self-confessed pack rat-hoarder of e-mail messages and addresses. I never backed up any programs or files. Hacking and malicious computer viruses were something that happens to other people.

I called ATT, my internet provider, and asked what to do. They referred me to my e-mail provider Yahoo. Yahoo sympathetically stated they could not help me recover my files, addresses, or inform my friends and contacts that the plea for money was deceitful. This scam is so ubiquitous that identifying or convicting the e-thief(s) was out of the question. Yahoo did refer me to a hacked computer firm in India. Even though they were half way around the world "they could feel my pain." For a mere $200 they would make my pain go away. Was this also a scam? Somewhat nauseous, I went ahead and gave them my credit card number. My faith in humanity and technology was somewhat restored when all of the purloined information and files were successfully retrieved. To "un-hack" my computer, the procedure took 10 hours from an early Sunday morning through that evening. A St. Louis information technician told me later he would have charged about the same amount.

My wife received many telephone calls asking why I was in the Philippines or if my passport ever

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Good News From MSMA Members

Missouri Medicine announces new additions to its Contributing Editor and Editorial Boards. Members are selected on the basis of exceptional professional accomplishments and expertise in their specialty.



Justin M. Albani, MD, FACS, MSMA member since 2006, Parkville, Urologist, has accepted the position of Contributing Editor. He replaces **Milamari Cunningham, MD**, MSMA member since 1978, who retired from this position.



James S. Magera, MD, FACS, MSMA member since 2010, has accepted the position of Editorial Board for Urology. Both Drs. Albani and Magera practice at Urology Specialists, PC, in Liberty and North Kansas City.



Nathanial S. Nolan, MSMA member since 2012, is the first recipient of The Arthur Gale Freedom of Expression Award, to be presented annually to the author of the best commentary article published in Missouri Medicine, in honor of Arthur Gale, MD, one of the Journal's Contributing Editors and MSMA member since 1976. This prestigious and monetary award is offered to encourage MSMA physicians to submit personal perspective essays on issues that are topical and provocative. His article, "We Can Do Better Than Work Restrictions," was published in the November/December 2013 issue. He will be recognized with his award at MSMA's Annual Convention in April.

Carol Blum, MD, MSMA member since 1991, Excelsior Springs, helped sponsor the 21st Annual Dinner and Auction raising funds for the Excelsior Springs Hospital and Health Care Foundation.

Richard Aron Burke, MD, member since 2006, Rock Port, was presented the 2013 Family Physician of the Year Award at the Missouri Academy of Family Physicians 65th Annual Scientific Assembly.

F. Michael Caldwell, MD, MSMA member since 2002, Poplar Bluff, has been appointed to the Saint Francis Medical Partners Board of Directors.

David Chalk, MD, MSMA member since 1993, Washington, held an opening ceremony and ribbon cutting for the new critical care unit at Mercy Hospital Washington.

Todd M. Craig, MD, FAAFP, MSMA member since 2002, Washington, is among the first 400-plus physicians nationwide to earn Board Certification status in Clinical Informatics by the American Board of Preventive Medicine.

Benjamin Cullen, DO, MSMA member since 2013, and **Michele Neblock, MD,** MSMA member since 2010, both of Troy, contributed donations to the Terry L. Robertson Center, a resource for women and children who are victims of domestic violence at the Lincoln County Medical Center.

Roger Francis, MD, MSMA member since 1983, and **R. John Torontow, MD,** MSMA member since 1970, both of El Dorado Springs, sponsored the Fifth Annual Endowment Fundraiser and Dessert Auction for providing future funding support of Cedar County Memorial Hospital's equipment and service expansions.

Janet Hankins, MD, MSMA member since 1994, Clinton, has successfully completed the American Board of Family Medicine Certification Examination.

Azam Khaja, MD, MSMA member since 2013, Columbia, spoke to Rotary members regarding technologies available through Moberly Regional Medical Center, and the new guidelines for prescribing statins to deal with cholesterol and heart health.

Doug Kiburz, MD, MSMA member since 1987, Sedalia, helped sponsor an event with the Friends of Sedalia Katy Depot celebrating the history of aprons, the ladies who wore them and the love they put into the food they prepared.

Bob Koch, MD, MSMA member since 2012, Boonville, was recognized by the Cooper County Memorial Hospital Board of Trustees for his two years of service as Medical Staff President.

Wm. Marshall, MD, MSMA member since 1977, Glasgow, was chosen as the Glasgow Citizen of the Year for 2012 by the Glasgow Board of Alderman.

Robert Martin, MD, MSMA member since 1991, West Plains, has been recognized as a long-time coach for the Docs and Jocks Team raising money for Boys & Girls Club.

Erik J. Meidl, MD, MSMA member since 1996, Hannibal, recently served as a guest speaker at St. Anthony Hospital in Alton, Illinois, on "Ethical Issues in Hospice Care."

August Ritter, MD, MSMA member since 2002, Cape Girardeau, performed the first ankle replacement in Southeast Missouri, since the mid-1970s, on Bill Hollida of Silva.

Robert Shaw, MD, MSMA member since 1980, Willow Springs, was thankful to be able to assist with annual Willow Springs Community Thanksgiving Dinner after sustaining serious injuries in a bicycling accident earlier in the year.

Jim Thornton, MD, MSMA member since 1990, Hannibal, is among the volunteers who provided help for new parents at a free five-session class offered by First Presbyterian Church in January.

Hope Tinker, MD, MSMA member since 2013, Glasgow, will serve as medical director of the Glasgow Clinic set to open July 15, 2014, and will see patients several days per month.

Philip D. Tweedy, MD, MSMA member since 2001, Hannibal, has met the requirements for board recertification from the American Board of Internal Medicine.

Peter Weiss, MD, MSMA member since 1996, St. Louis, is among 2,000 volunteers and more than 100 St. Louis businesses assisting the Cancer Support Community provide networking groups, workshops, nutritional programs, exercise classes, art and music therapy to those affected by cancer.

Anne Winkler, MD, PhD, MSMA member since 2003, Springfield, was selected as one of 50 to participate in a nationwide rheumatoid arthritis assessment group called the Rheumatoid Arthritis Performance Project.

Jenny Yu, MSMA student member since 2012 from Washington University, won second place in the oral competition category of Immunology/Infectious Disease/ Inflammation of the AMA-MSS Research Symposium part of the AMA Interim Meeting.

CORRESPONDENCE, continued

turned up. Others asked how she enjoyed our recent tropical vacation. My fellow ophthalmologists said if the email had asked for a loan because of poor Medicare reimbursement and rising overhead that they would have concluded it was real and sent money. I'm a real tightwad so I am now using old surgical gloves, masks and caps for anti-virus protection.

I am hoping that this information will be of use to some tech-challenged readers: keep your firewall always on, turn your computer off when not in use, install and update anti-virus and anti-spyware software, be careful what you download, don't open attachments that look suspicious or from unknown persons. Consider a remote, automatic commercial back up service. For complete recommendations on how to protect your computer see the FBI link www.fbi.gov/scams-safety/computer_protect.

Hopes this letter helps - in the meantime I am awaiting my share of many millions of dollars from the widowed Nigerian woman…

George Bohigian MD
MSMA member since 1977
Professor of Clinical Ophthalmology
Department of Ophthalmology and Visual Sciences
Washington University School of Medicine
St. Louis, Missouri

[Editor's Note: On page 10, see article on stolen lap tops and devices to think how scary this situation could have been for Dr. Bohigian.]

Errata

A source for information on the November/ December 2013 article, "German Medical Association Finally Apologizes for Atrocities Committed by German Physicians Under the Nazis" was inadvertently not printed. The source for the captions for the photos was Wikipedia.

Missouri State Medical Association

156th Annual Convention

April 4-6, 2014 - St. Louis Airport Renaissance Hotel

Make hotel reservations prior to March 12, 2014 to take advantage of MSMA's Convention room rate.
Call the St. Louis Renaissance Airport Hotel directly at 1-800-468-3571 or
Online at http://www.marriott.com

Pre-Convention Meetings

Thursday, April 3

2:15 pm	MSMA Insurance Agency Board Meeting
3:30 pm	MSMA Executive Committee
3:30-6:30 pm	Convention Registration
3:30-6:30 pm	Exhibitor Setup & Registration
5:00 pm	**MSMA Council Meeting**
6:30 pm	Alliance Dutch Treat Dinner [Offsite]
6:30 pm	University of Missouri Awards Reception & Dinner [Offsite @ Norwood Hills Country Club]
7:00 pm	**MSMA Council Reception & Dinner**

Convention Meetings

Friday, April 4

6:30 am-4:00 pm	Convention Registration
6:30 am	University of Missouri Breakfast
6:45 am	Moneta Breakfast
7:00 am	**Exhibit Hall Opens/Continental Breakfast for all Conferees**
8:00 am	**Opening Session MSMA House of Delegates**
8:30 am	Alliance Board Meeting
10:00 am	Alliance General Assembly - Session I
10:00-11:30 am	**Reference Committee A**
10:30 am-Noon	**Reference Committee B**
11:00 am	Physicians Health Committee Meeting & Luncheon
Noon	SLMMS Caucus & Luncheon
Noon	MMSGKC Caucus & Luncheon
Noon	"Spirit of the Alliance" Awards Luncheon
1:30 pm	**MSMA General Session**
2:30 pm	Medical Student Section Meeting
3:30 pm	**MSMA General Session**
2:30 pm	Alliance Past President's Reception
5:00 pm	OMSS Business Meeting
5:30 pm	Medical School Alumni Receptions
7:00 pm	Alliance Foundation Fundraiser & Mystery Dinner

Saturday, April 5

6:30 am-4:00 pm	Convention Registration
7:00 am	**Exhibit Hall Opens/Continental Breakfast for all Conferees**
All Day	CME Programs, Lectures & Meal Functions
7:30 am	Missouri State Medical Foundation Meeting
8:00 am	**MSMA General Session**
8:30 am	Alliance General Assembly - Session II
9:00 am	International Medical Graduate Section Meeting
10:00 am	**MSMA General Session**
10:00 am	MMPAC Meeting
10:30 am	Exhibit Hall Closes
Noon	Alliance Installation Luncheon
12:15 pm	**MSMA General Session**
1:00 pm	AMA Issues
1:00 pm	Resident Fellow Section Meeting
1:30 pm	**MSMA General Session**
2:30 pm	Alliance Board Meeting
3:00 pm	OMSS Educational Session
3:00 pm	Component/Specialty Society Leaders Meeting
5:15 pm	Reception: 50-Year Pin Recipients & MSMA Past Presidents
6:30 pm	**MSMA Presidential Inauguration**
7:30 pm	**MSMA Presidential Reception** *Entertainment, Hearty Hors d'oeuvres & Cash Bar*

Sunday, April 6

7:00 am	District Breakfasts & Caucuses
8:15 am	**Second MSMA House of Delegates**
Immediately Following Closure of the HOD	MSMA Council Meeting

Complete Program at www.msma.org/annualconvention

Subject to Change. Refer to Convention Official Program for times and meeting locations. All meetings held at the St. Louis Renaissance Airport Hotel unless noted. Updates on CME Program, Lectures & Meal Functions at www.msma.org/annualconvention. For more information, contact MSMA's Benita Stennis, at 800-869-6762 or bstennis@msma.org.

GENERAL SESSION TOPICS & SPECIAL EVENTS



American Medical Association Presentation
Ardis Dee Hoven, MD
AMA President
Friday, April 4 ◆ 8:00 am



Physicians Collaboration + Evidence = Quality
Kansas City Metropolitan Physicians Association Accountable Care Organization
Nathan Granger, MD
& Jill Watson, MBA, CAE
Friday, April 4 ◆ 1:30 pm





Update on MoHealth Net - Missouri's Medicaid System
Joe Parks, MD
Friday, April 4 ◆ 3:30 pm



FDA's Risk Evaluation & Mitigation Strategies
Jerry Harrison, MD
Saturday, April 5 ◆ 8:00 am



Update of Women's Health Issues
Amy Loden, MD
Saturday, April 5 ◆ 10:00 am



ICD-10 Are You Ready?
Mary Bourland, MD
Saturday, April 5 ◆ 12:15 pm



Chronic Pain Management for Primary Care
Thomas G. Johans, MD
Saturday, April 5 ◆ 1:30 pm





Proactive Strategies for Physicians to Reduce Risk Solutions to Communication Challenges & Preventing Error
Michael Handler, MD
& Becky Miller, MHA
Saturday, April 5 ◆ 3:00 pm

PLUS

Foundation Fundraiser Mystery Dinner Theater / Multiple Medical Specialties Programming
Two-Day Exhibit Showcase / House of Delegates / Presidential Inauguration & Reception

www.msma.org/annualconvention



What Do Physicians & Pilots Have in Common?

by James B. Wolfe, MD



James B. Wolfe, MSMA member since 1978, is the 2013-2014 MSMA President and an ENT surgeon from Springfield, Missouri.
Contact: jbwolfemd@hotmail.com

For many years I have maintained that the long term mission of the liberal Washington legislators has been the transformation of medicine into a system similar to the aviation industry. In my optimism I assumed that the transformation would occur after I had passed from the scene.

With the passage of the Affordable Care Act which contains Section 1311(h)(1)(B) I have revised my time estimation. Until recently, I, as most physicians, was unaware of the Section and its implications. For those of you who are still in the dark let me provide you with the essentials of the Section: it gives the Secretary of Health and Human Services (HHS) blanket authority to dictate how doctors treat patients, and starting in 2015 it bars Federal exchange insurance companies from doing business with any non-compliant physicians. The December 2, 2013, Federal Register revealed that the actual rules under which hospitals will operate currently are being written.

Presently "HHS is in the process of researching... standards" for exchange insurers contracting with health care providers. Therefore, we have no way of knowing what they will contain when HHS issues the rules. However, based on previous comments by Dr. Ezekiel Emanuel (President Obama's key health adviser when ACA was written) and those of Dr. Donald Berwick (President Obama's nominee to run the Centers for Medicare and Medicaid), one can conclude that "quality of care" is going to be used to significantly reduce medical expenditures. Dr. Emanuel has advocated "top-down federal rules to allocate resources based on social justice," and Dr. Berwick has said that resources should be allocated based on important sub-groups, rather than the individual patient in the doctor's office.

These comments, taken together, strongly suggest that the Federal government is getting ready to implement the "Golden Rule": He who has the Gold makes the Rules; and promulgate rules that will severely restrict physicians' ability to treat patients freely.

This brings us to how pilots and physicians are similarly viewed by the Federal government. For many years the Federal Aviation Administration (FAA) has controlled the actions of pilots through a collection of rules known as the Aeronautical Information Manual. These rules can be fairly general or very specific depending on the area covered by the rules. The pilots' greatest defense when these rules are violated can also be the greatest liability: the final responsibility for the operation of the aircraft resides with the pilot. He/she is the "captain of the ship," and therefore has the final responsibility for the safe operation of the aircraft. The way the FAA has written rules pilots can find themselves in a "Catch-22." If they obey the rules and something bad happens that, in retrospect using 20/20 hindsight vision, the pilot should have known would have produced an adverse situation, the pilot is at fault. Additionally, if the pilot deviates from the rules to avoid a problem the pilot will still come under FAA review with the same 20/20 hindsight vision. Do you see the similarities with physicians and our practice of medicine?

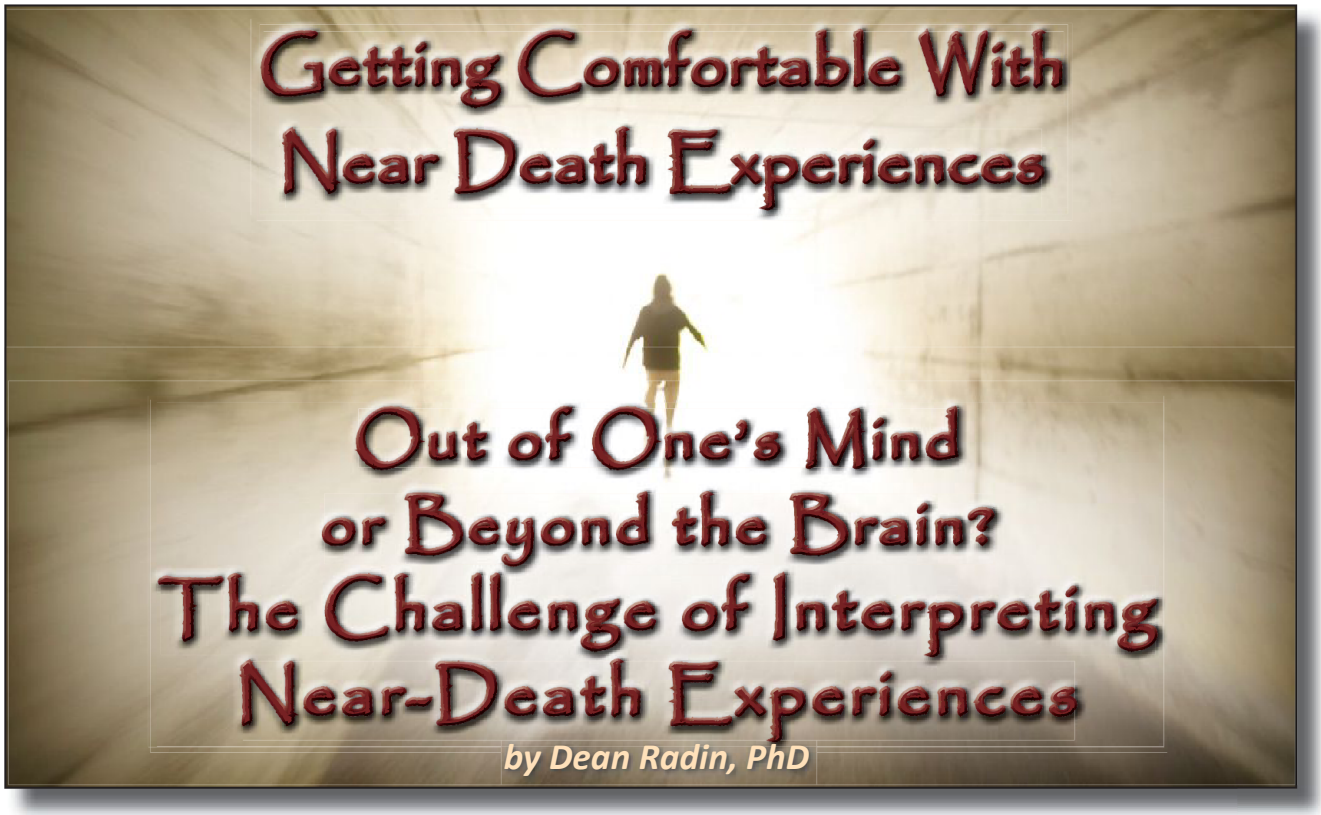
Over the last decade we have seen a continuous expansion of "cookbook medicine" with the evolution of treatment protocols. Several specialty societies and states have published these templates. Deviation from these standards is viewed as sub-standard care. Plaintiff attorneys are already using these guidelines as a basis for law suits. In addition to section 1311 we also must now contend with registries formulated under the auspices of the Physician Consortium for Performance Improvement, a creation of the AMA. Taken together, all of these protocols/registries are creating a very narrow path along which physicians can safely traverse while treating patients.

Unfortunately, even staying within these perimeters does not assure physicians that they will not experience adverse effects based on patient outcomes. It has been asserted that all of the hoops through which a physician must jump in order to be paid for "performance" will in time be included in the electronic medical record system so the requirements will not be onerous. While we can expect the EMR venders to produce this type of product, there is no assurance that this will occur any time in the near future. In the meantime physicians will be saddled with the task of making sure all of the items on the "checklist" are completed.

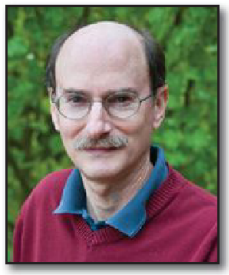
If and when protocols/registries are incorporated in the EMR we will then have an "autopilot" which will allow common chronic diseases evaluated and treated by computer generated pathways. The physician will have the responsibility of monitoring the progress of the patient and making adjustments to the treatment pathway as indicated. This is essentially what commercial pilots now do on airlines; taking the controls in case of an adverse event, take-offs, and some landings.

As an organization dedicated to serving its members, MSMA will continue to monitor, advocate for, and educate its members on changes in the health care scene. With regards to Section 1311 (h)(1)(B) your Council recently authorized letters be sent to our Missouri Congressional Delegation asking they support a bill offered by Rep. Phil Gingrey (R-Ga) that would repeal that onerous section. I would encourage every Missouri physician to do the same since that small short section could have a profound effect on the future practice of medicine.

As always, I welcome comments and questions from our membership. My e-mail address is jbwolfemd@hotmail.com and my home telephone number is 417-882-6680. MM



Philosophers have vigorously debated the mind-brain relationship without resolution for thousands of years, so further discussion or reliance on anecdotes is not likely to resolve this question.



Dean Radin, PhD, is Chief Scientist at the Institute of Noetic Sciences (IONS) and Adjunct Faculty in the Department of Psychology at Sonoma State University.
Contact: dradin@noetic.org

Abstract

With one exception, near-death experiences (NDEs) may be interpreted as unusual forms of hallucinations associated with the injured or dying brain. The exception involves perceptions described from vantage points outside the body that are later confirmed to be correct and could not have been inferred. Over a century of laboratory studies have investigated whether it is possible in principle for the mind to transcend the physical boundaries of the brain. The cumulative experimental database strongly indicates that it can. It is not clear that this implies the mind is separate from the brain, but it does suggest that a comprehensive explanation for NDEs will require revisions to present scientific assumptions about the brain-mind relationship.

Introduction

Neuroscientist Francis Crick famously quipped that the mind – the self-aware, subjective aspect of the brain – is "nothing but a pack of neurons." Crick asserted that all mental activity, all of "your joys and your sorrows, your memories and your ambitions, your sense of identity and free will, are in fact no more than the behaviour of a vast assembly of nerve cells and their associated molecules."[1] This proposal, which is now a central tenet in the neurosciences,[2] suggests that near-death experiences (NDEs) are best understood as hallucinations caused by distortions in neural activity as the brain shuts down. No other explanation is possible, because from the "pack of neurons" perspective mind and brain are identical, in which case visions of distant environments or discussions with disembodied entities are both examples of bizarre dreams.

Among counterarguments to such brain-based explanations is the observation that NDEs are reported even when the brain's electrical activity, as reflected in an electroencephalogram (EEG), has flat-lined.[3, 4] This would seem to rule out hallucinations and dreams because if the brain is completely inactive then the mind must also be inactive. So NDEs could not be reported, but *ipso facto* they are reported, and so mind and brain cannot be identical.

At face value this line of reasoning seems persuasive, but it has been challenged by the recent discovery that brains continue to show activity below what was once considered to be flat-lined conditions in deep coma and in the dying brain. In 2013, Kroeger, et al. reported that a "novel brain phenomenon is observable in both humans and animals during coma that is deeper than the one reflected by the isoelectric EEG",[5] and Borjigin, et al. found evidence contrary to the assumption that the brain is hypoactive during cardiac arrest, and in particular that, "High-frequency neurophysiological activity in the near-death state exceeded levels found during the conscious waking state [, … demonstrating] that the mammalian brain can, albeit paradoxically, generate neural correlates of heightened conscious processing at near-death."[6]

Based on these discoveries, if NDEs exclusively consisted of dream-like images, however vivid, convincing or unusual they may seem, then brain-oriented explanations would be plausible. But hallucinations do not cover the full phenomenology. Some NDEs also include perceptions reportedly from outside the body that could not have been inferred from information received through the ordinary senses, and that are verifiably correct.[7] This does not happen very often, but that it happens at all challenges the assumption that NDEs must be figments of the imagination, or that those reporting these experiences were discombobulated and, in a sense, going out of their minds.

From a conventional view "distant perception" experiences are often explained as coincidence, selective memory, confabulation, or they are simply ignored as impossible. But are such explanations correct? Is it possible to go out of one's brain without going out of one's mind? Philosophers have vigorously debated the mind-brain relationship without resolution for thousands of years, so further discussion or reliance on anecdotes is not likely to resolve this question. Fortunately, about a century ago a new approach was initiated in hopes of breaking the deadlock. Experiments were conducted under rigorously controlled conditions to see if distant perception was possible.

Origins

In 1876, physicist Sir William Barrett from the Royal College of Science in Dublin, Ireland, presented experimental evidence in favor of what he called "thought transference" to the British Association for the Advancement of Science. Six years later, Barrett helped found the London-based Society for Psychical Research (SPR), the first scientific organization established for the study of exceptional mental capacities known today as psychic or "psi" phenomena.

Many prominent figures in science, scholarship, and politics became members of the SPR. The early roster included Sir Oliver Lodge, known for his contributions to the development of wireless telegraphy; Baron (John Strutt) Rayleigh, who was later awarded the Nobel Prize for his discovery of the inert gas argon; Rayleigh's spouse Evelyn Balfour, sister of Arthur James Balfour, Prime Minister of Britain; and Henry Sidgwick, Professor of Moral Philosophy at Cambridge University. American members included Samuel P. Langley, Director of the Smithsonian Institution, William James of Harvard University, Simon Newcomb, President of the American Association for the Advancement of Science, and Edward C. Pickering, Director of the Harvard Observatory.

Over the years, members of the SPR and other scientific organizations developed increasingly stringent methods to study reports of mind-to-mind communication, distance perception, apparitions, and related phenomena. Scientists and scholars of the day were intrigued, as we are today, by the frequency and the credibility of such reports, so they sought to establish whether reports of psi experiences were real or hallucinations.

Challenges associated with studying these mental phenomena led to a series of methodological advancements, some of which have become gold-standard tools in psychology, the neurosciences and medical research. They include the use of double-blind protocols to control for expectation effects, statistical techniques for evaluating human performance, the human electroencephalograph (EEG), and methods for objectively consolidating and assessing replication rates across experiments, known today as meta-analysis.[8, 9]

Surveys of the general population collected by the SPR and others were used to classify and create taxonomies of reported psi experiences. Four categories proved to be most amenable to laboratory study. They were mind-to-mind communication (now called *telepathy*), perception of information beyond the reach of the ordinary senses (*clairvoyance*), perception through time (*precognition*), and direct mind-matter interactions (*psychokinesis*). Publications of experiments exploring these experiences attracted a great deal of critical attention, which led to new methods and designs to address potential artifacts. Improved studies were conducted, and this cycle was repeated over many decades.

A century of scientific studies indicate that perception is not bound by the limitations of the brain, at least not by any means that are presently understood.

Experiments

The literature of psi research reports thousands of experiments and a growing number of meta-analyses.[9] It is not possible within the scope of a single article to do justice to this massive database, so one class of experiments will suffice: investigations of the claim of mind-to-mind communication, or telepathy.

Some may imagine that research on telepathy still involves the use of ESP (extrasensory perception) cards, which were popularized by Duke University psychologist Joseph B. Rhine starting in the 1930s.[10] Dozens of experiments conducted by Rhine and others were published, comprising a cumulative database of over four million card guessing trials collected from the 1880s to the 1940s.[11] Analysis of that database persuaded many scientists that ESP was an established faculty of the mind. One example of a scientist who was impressed by the state of the evidence was Alan Turing, a seminal figure in the foundations of modern computer science and the mastermind who helped break the German Enigma cryptograph machine during the Second World War.[12] In discussing the problem of how to differentiate between machine and human intelligence, Turing wrote:

"I assume that the reader is familiar with the idea of extrasensory perception, and the meaning of the four items of it, viz., telepathy, clairvoyance, precognition and psychokinesis. These disturbing phenomena seem to deny all our usual scientific ideas. How we should like to discredit them! Unfortunately the statistical evidence, at least for telepathy, is overwhelming.... Many scientific theories seem to remain workable in practice, in spite of clashing with ESP; that in fact one can get along very nicely if one forgets about it. This is rather cold comfort, and one fears that *thinking* is just the kind of phenomenon where ESP may be especially relevant.[13]

Turing's opinion was prescient in that this line of research was indeed forgotten by most scientists and scholars. But it was also a victim of unfavorable timing. Rhine's work reached its pinnacle during a period in which it became fashionable for academic psychologists to deny the existence of any form of mental activity, including consciousness itself, largely due to the rising influence of psychologist B. F. Skinner's brand of behaviorism.[14] But psi research did not disappear entirely for a very simple reason: Many people, including academics, continued to report psychic experiences.

By the 1970s, a new method for studying telepathy was designed to overcome two problems encountered in studies involving ESP cards. Those experiments were easy to conduct but the test design often involved guessing dozens to hundreds of cards in a row, so boredom and biases introduced by knowledge of previous guesses (the gambler's fallacy) were inevitable. These problems contributed to what came to be known as the "decline effect," a systematic decrease in performance over repeated testing.

The new design was called the *ganzfeld* telepathy experiment, where ganzfeld is a German word meaning "whole field." The technique involved mild, unpatterned visual and auditory stimulation. In preparation for a ganzfeld session, an experimenter E collected a large set of photographs (in some experiments video clips were used instead of photos). The photos were arranged into separate pools, each pool containing four photos as different from one other in content and appearance as possible. Later, when a test session began, E escorted the "receiver" R into an electromagnetically shielded room and asked R to relax in a comfortable, reclining chair. E placed halved ping-pong balls over R's eyes and headphones playing white noise over R's ears. Then E directed a red light to shine on R's face, and R was asked to keep his or her eyes open and to speak aloud any impressions that came to mind. E left the room and within a few minutes the ganzfeld stimulation reliably produced a hypnagogic, dream-like state in R. E continued to monitor R's shielded room to ensure that no ordinary form of communication could reach R.

Meanwhile, an assistant A escorted a "sender" S to a distant location where A randomly selected one pool of four images from the larger set of prepared pools, and then randomly selected one of the four images out of the pool.

That image, called the *target*, was to be mentally sent by S to R. In some versions of this experiment, R's voice was audio recorded and transmitted by one-way audio link to S. This provided S with performance feedback to help optimize the sending process.

After the sending period ended, E – who, like R, was blind to the target – took R out of the ganzfeld condition and together they reviewed R's mental impressions while examining four images, the target along with three decoys (the three unselected images from the randomly chosen pool). The images they examined were duplicates of the photos handled by S (in more recent times they could be images on a computer screen), preventing clues about the target from accidentally being conveyed from S to R or E. After examining the four images, R ranked them according to how well each matched his or her impressions of the target during the sending period. If R ranked the target image as 1, the best possible match, then the test session was considered a hit otherwise it was a miss.

This method unambiguously established chance expectation, because if telepathy did not exist then the best that R could do, on average, would be to rank the correct target first one in four times, for a 25% chance expected hit rate. A ganzfeld test session consisted of a single "guess" in which R was free to describe virtually anything that came to mind. This obviated problems of boredom and guessing strategies that plagued tests using ESP cards, but it also required far more effort to gain a single datapoint. On average, the advantages outweighed the disadvantages, and today this simple design has been repeatedly tested in many variations for over 40 years. Researchers familiar with these studies, including confirmed skeptics, agree that when properly conducted this method contains no known flaws that might produce spurious results.[15]

From 1974 through 2004, 88 ganzfeld experiments were reported. Together they resulted in 1,008 hits in 3,145 sessions, for a combined average hit rate of 32% as compared to the chance-expected 25%.[16] This hit rate is associated with odds against chance of 29 million trillion to 1. Arguments that this result might have been due to successful studies being reported more often than unsuccessful studies, known as the "file-drawer effect," have been analyzed and reanalyzed, and critics familiar with this literature have agreed that selective reporting practices are insufficient to nullify the positive results.[8]

When the ganzfeld telepathy database is updated with new publications reported through 2010, 1,323 hits are reported in 4,196 trials, for average hit rate of 31.5%.[17] The additional data increases the overall odds against chance to 13 billion trillion to 1. These analyses have been published and critiqued in peer-reviewed journals, and similar successful results have been reported by researchers who explicitly stated that they did not believe in the existence of psychic abilities.[18, 16, 17, 19]

If scientific evidence were analogous to forensic evidence presented in a courtroom, then one could justifiably say that this one class of experiments demonstrates the existence of telepathy beyond a reasonable doubt. When conceptually similar experiments are added to the evidential database, including controlled laboratory tests of the "feeling of being stared at,"[20] and correlation of EEG[21-25] and functional MRIs between isolated couples,[26-28] the weight of the cumulative evidence is even stronger.

The bottom line is that there is now strong evidence, confirmed using Bayesian statistical methods that take into account analysts' prior expectations,[19] indicating that the mind can indeed transcend the physical constraints of the brain. This conclusion is bolstered by other classes of experiments that also provide strong statistical evidence for clairvoyance,[22, 29] precognition,[30,31] and mind-matter interactions.[32, 33]

Discussion

A century of scientific studies indicate that perception is not bound by the limitations of the brain, at least not by any means that are presently understood. Theoretical explanations continue to lag behind the empirical data, but this is common in the history of science. For example, herbal preparations containing salicylates were used for thousands of years before Aspirin's mechanism of action was identified.[34] And even with robust effects that are easy to demonstrate, like magnetism, it took hundreds of years before useful explanatory theories were formed.[35] Thus, given that no one knows how consciousness can arise out of (presumably) unconscious matter, it is not surprising that science has to yet provide a satisfactory explanation for telepathy and other subtle psychic capacities.[36, 37]

Theoretical explanations aside, how does the existence of psi influence our understanding of NDEs? The main implication is that it reduces the likelihood that reports of distant perceptions can only be due to confabulation or coincidence. In any given anecdotal report it is not possible to know with certainty that the information was obtained psychically. But experimental data suggests that it *could* have been obtained that way.

Does distant perception imply that a disembodied consciousness literally leaves the body, or that NDEs provide evidence for the persistence of consciousness after bodily death? The evidence to date is insufficient to answer such questions because everything we know about psi comes

from tests conducted with living persons. Studies involving mediumship, which investigate individuals who claim to be able to communicate with the deceased, have attempted to probe the boundaries between life and death, but of course all such experiments ultimately involve reports from living persons; purported participation by the deceased is inferred.[38, 39] To further complicate matters, there is both anecdotal and experimental evidence that non-ordinary states of consciousness (e.g., dreaming, meditating, under the influence of psychedelic compounds) are more conducive to psi phenomena.[17] Given that near-death is a prime exemplar of a non-ordinary state it may be that some of the strikingly vivid aspects of NDEs arise because of clearer forms of psi perception that are filtered out by a normally functioning brain.

The bottom line is that NDEs in light of psi research suggest that one or more of today's assumptions about the mind-brain relationship are probably wrong. An improved understanding of NDEs may well be found to involve a host of mundane brain-oriented effects, but it may also include glimpses of realities that are presently beyond our imagination. Given the revolutionary changes in our understanding of the physical world over the last century through the development of relativity and quantum mechanics, it is virtually certain that the scientific worldview of the next century will include entirely new ways of thinking about space, time, and – given the challenge of NDEs – consciousness.

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- Nocturnist
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- Maternal Fetal Medicine
- Neonatology
- Neurology
- Neurosurgery
- OB/GYN – Traditional
- OB/GYN Hospitalist
- Occupational Medicine
- Ophthalmology
- Optometry
- Oral & Maxillofacial Surgery
- Orthopedic Surgery
- Otolaryngology
- Pain Management
- Pathology
- Plastic Surgery
- Podiatry
- Psychiatry
- Pediatrics
- Pediatric Emergency Medicine
- Pediatric Endocrinology
- Pediatric GI
- Pediatric Hem/Onc
- Pediatric Internal Medicine
- Pediatric Neurology
- Pediatric Surgery
- Pediatric Urgent Care
- Physical Medicine and Rehabilitation
- Pulmonology/Critical Care/Sleep Medicine
- Radiation Oncology
- Radiology-Interventional
- Rheumatology
- Robotics
- Trauma Surgery
- Urology
- Vascular Surgery

For more information, please contact: Angie Abraham, MBA
Executive Director of Physician Recruitment • Mercy Clinic
Phone: 877-880-6650 | Fax: 888-290-8300
Email: angie.abraham@mercy.net

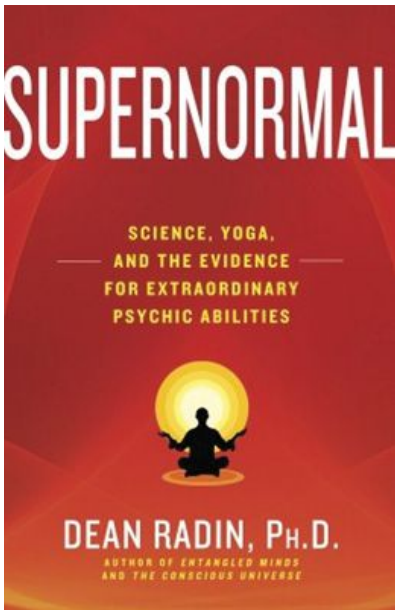
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SUPERNORMAL

Science, Yoga, and the Evidence for Extraordinary Psychic Abilities

by Dean Radin, PhD

BOOK REVIEW

Supernormal (Random House, 2013) examines legends about supernormal abilities associated with the disciplined practice of yoga. The book discusses the origins of yoga, how it differs from what is typically practiced today in health clubs around the world, and whether the traditional yogic superpowers are best understood as superstitions, embellished tales, or something more. Based on a thorough examination of several classes of relevant scientific studies, it is revealed that some of the legendary abilities are genuine. These findings challenge commonly held assumptions about the nature of human consciousness, and it raises doubts about the modern tendency to uncritically dismiss ancient wisdom as hopelessly naïve or primitive. Some of those ancients were probably wiser than we know.

Dean Radin, PhD, has been studying the frontiers of human consciousness for over 30 years. He is presently Chief Scientist at the Institute of Noetic Sciences. He was previously at Princeton University, University of Edinburgh, and AT&T Bell Laboratories. He is author or coauthor of over 200 technical and popular articles, two dozen book chapters, and three books including the bestselling, award-winning The Conscious Universe (HarperOne, 1997), Entangled Minds (Simon & Schuster, 2006), and Supernormal (Random House, 2013).

Pills are *NOT* a Party!

Pills are *NOT* a Party! is a fifteen-minute animated DVD which educates middle school youth on the dangers of indiscriminate drug use. The DVD will encourage discussion and provide teaching opportunities about:

- **The dangers of abusing prescription and over-the-counter (OTC) drugs**
- **The consequences of giving in to peer pressure**
- **The dangers of pill parties**
- **The legal implications of taking drugs prescribed for another person**
- **How to dispose of medications properly**

Proper Prescription Pete, a talking pill bottle, teaches the viewer:

- **How drugs work in the body**
- **The possible side effects and life threatening consequences from taking random medications**
- **To take only prescription drugs that are prescribed for them**
- **Some drugs severely impair your ability to make healthy choices and safe decisions**

Prescription and over-the-counter drug abuse affects your life!

PLAYABLE ON DVD PLAYERS ON TELEVISIONS AND MAC AND PC COMPUTERS



For more information about Greene County Medical Society Alliance Educational DVDs, e-mail director@gcms.us or call 417/887-1017.

Major contributors for **Pills are *NOT* a Party!** include CoxHealth, Ferrell Duncan Clinic, and Mercy Hospital Springfield.

UNIVERSITY *of* MISSOURI

Associate Dean for Rural Health

The University of Missouri (MU) School of Medicine is seeking nominations and applications for the position of Associate Dean for Rural Health. We seek an energetic and dynamic leader who has a track record of successful innovation and improvement in medical education in rural settings. The successful candidate will lead the Rural Track Program across the professional development continuum, ensuring that these efforts are in alignment with the MU School of Medicine (SOM) goal to educate physicians to provide effective patient-centered care for the people of Missouri and beyond. This individual will ensure rural cultural awareness across the SOM. They will nourish relationships between the SOM and rural track program stakeholders, including state legislators, interested foundations, AHEC leaders, rural clinical faculty, health system administrators, community leaders, and national-level rural health partners. This position reports to the Senior Associate Dean for Education.

MU is the state's major public research university and one of the few institutions in the country with colleges of medicine, veterinary medicine, agriculture, engineering, nursing and health professions on one campus. The Rural Track Program is nationally recognized for its comprehensive multifaceted approach. For medical students this includes a preadmissions program, summer community program, third-year rural clerkships with innovative community integration activities and fourth-year rural electives. Recent articles in peer-reviewed journals such as Academic Medicine highlight this work. (See **http://medicine.missouri.edu/ahec/home.html**). MU SOM contributes leadership to the state-wide Missouri Area Health Education Center (MAHEC), the National AHEC organization and the National Rural Health Association.

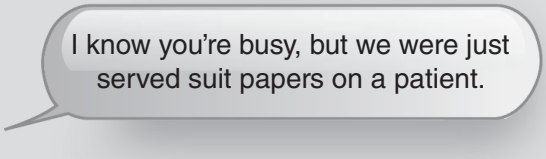
Applicants must have a demonstrated progression of leadership responsibilities in an academic setting. Also required are a strong record of successful partnerships with rural communities, involvement in rural physician workforce issues, improvement in medical education, interprofessional collaboration, scholarly contributions and commitment to diversity. Applicants must possess an MD, PhD or equivalent degree and qualify for a faculty appointment (rank and track based on experience).

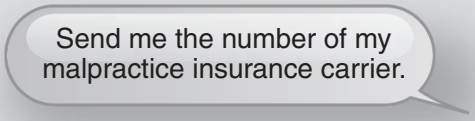
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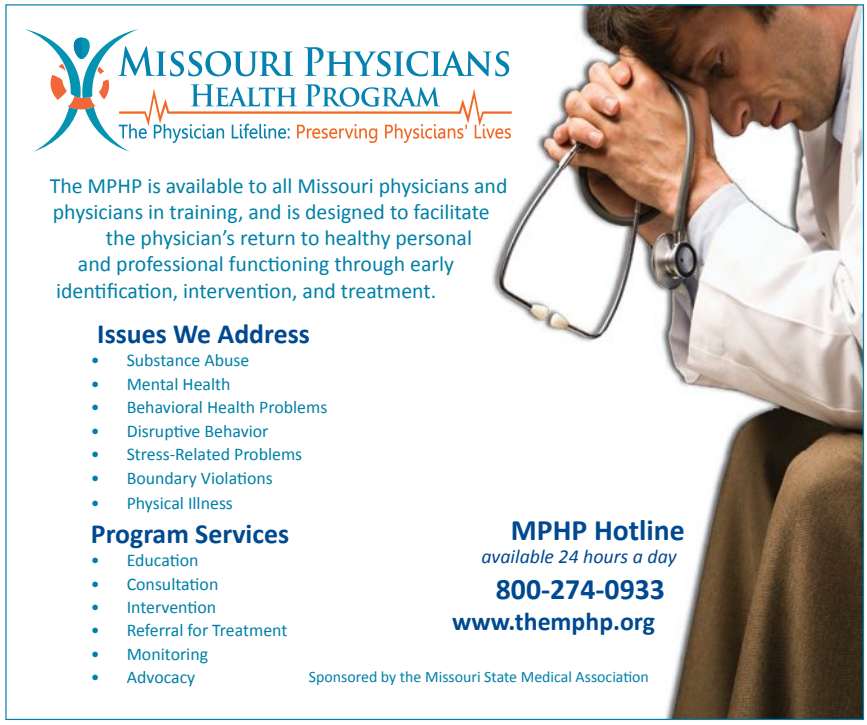
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Anne Peterson, MD
Anonymous Foundation
Audrain Medical Center
Barnes Jewish Hospital
Barnes Jewish Hospital Med. Staff Assn.
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Acupuncture: A Western Physician's Experience

by Thomas G. Johans, MD

The Western physician is skeptical of how a small thin needle placed in an area that is not represented by any dermatome pattern or nerve pathway could have an effect on the human physiology.



Thomas G. Johans, MD, is board certified in anesthesiology, pain management, and acupuncture and practices at the DesPeres office of the WAAI Pain Management Services.
Contact: tjohans@aol.com

Introduction

To an American physician, the entire concept of acupuncture is shrouded in a veil of intrigue and mystery. This is partly due to its origins that are deeply seated in a land far away and described in a tongue that is difficult to understand and interpret. The Western physician is skeptical of how a small thin needle placed in an area that is not represented by any dermatome pattern or nerve pathway could have an effect on the human physiology. The theories used in the application of acupuncture are millennia old are more poetic than scientific. Indeed, with the inception of evidence-based medicine that insists on randomized controlled studies as the gold standard, acupuncture with its clinical observations and broad speculations struggles to find a home in American medicine. It is of little wonder, then, that acupuncture in the United States is considered clinical quackery and any witnessed success, chicanery.

Nonetheless, there is something intriguing about acupuncture that appeals to the inquisitive American physician. This curiosity continues to fill acupuncture training schools with board certified, actively practicing, physicians, and clinicians. What is it about acupuncture that tickles our fancy and for some physicians, has a career-changing effect on how they care for their patients?

West Meets East

On July 26, 1971, the *New York Times* ran an article that would shake the bedrock of Western medicine. Even though it headlined Dr. Christian Barnard's first heart-lung transplant, there was an inconspicuous article tucked away in the middle of the paper that involved a *Times* reporter

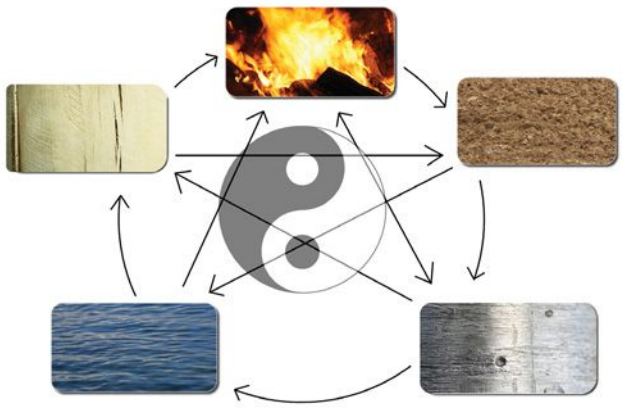
named James Reston who had to undergo an emergency appendectomy while covering a news story in Peking. He tolerated the appendectomy very well but after his spinal anesthetic wore off, experienced considerable postoperative pain and nausea. Instead of narcotics and anti-emetics, he was treated with the insertion of "three long thin needles in the outer part of his right elbow and below his knees" that relieved his abdominal discomfort and pain. This little article created a tidal wave of interest among patients and physicians alike throughout the country. Was it possible that getting stuck with a few needles could cure disease and relieve pain?

The public outcry prompted President Nixon in 1972, with delegates from the National Academy of Sciences and the National Institute of Health, to travel to China to learn more of what acupuncture could offer. Between 1977 and 1984, the analgesic effect of acupuncture was strongly linked to the release of endogenous opioids which prompted the relaxation of physician skepticism and an interest among physicians to matriculate for special acupuncture training. The UCLA School of Medicine, under the tutelage of Joseph Helms, MD would go on to train hundreds of board certified physicians every year in acupuncture. All of this led to the National Institutes of Health forming a 12-member panel with 25 experts from a variety of medical and biomedical fields to pen an official NIH Consensus Statement on the "state of the art information regarding the appropriate use of acupuncture." This statement was published in 1999 which concluded that promising results have emerged showing efficacy of acupuncture in nausea and vomiting, postoperative dental pain, addiction and stroke rehabilitation, fibromyalgia and myofascial pain syndromes, headache, and menstrual cramps, tennis elbow, carpal tunnel syndrome, and asthma.

Origins

Since the inception of acupuncture predates written history, we are left to speculate on its origins. It is the author's prediction that scientists 5,000 years ago were no less clever and intuitive than scientists today. These Chinese scientists probably noticed that if they rubbed their temporalis muscles, they could relieve a headache; or rubbing the great toe could make a toothache go away; by eating a certain herb could ease abdominal cramping. They keenly observed that there were certain specific areas on the body that when stimulated or suppressed, would have distinct and reproducible effects on bodily functions. Much like modern neurosurgeons mapping the homunculi of the human cerebral cortex with electrodes, these scientists probed the surface of the body and cataloged the location of each of these points, their usefulness and their ability to relieve pain and cure illnesses. Mappings of these points became the textbook for future acupuncturists to study and memorize.

Figure 1
Instead of atoms and molecules as the basic elements of life, Chinese scientists formed their theories using the five basic elements that they were able to see and touch: fire, earth, metal, water and wood.



Even though these ancient Chinese descriptions of disease appear bizarre to a modern day physician, they nonetheless represent thousands of years of experimentation, modification, and application that might be considered genius. Keep in mind, all of this was done without the luxury of having at their fingertips the valuable contributions of Newtonian mathematics, the physics of Einstein or even Gray's anatomy. Instead of atoms and molecules as the basic elements of life, they formed their theories using the five basic elements that they were able to see and touch; to be specific: fire, earth, metal, water and wood (see Figure 1).

They also observed that each of these five elements represented a phase in nature. Just as the seasons would slowly evolve into the next so does the human body, as a part of this cosmic evolution, undergo similar phase forces. The Chinese felt that the human body is but a microcosm of the macrocosmic universe. They witnessed the spring trees slowly be consumed by the hot solar temperatures of summer. The resultant ash would produce a deep rich soil that would fertilize and nourish the earth for the agricultural growing season. Over time, this earth forms the rocks, mountains and ultimately metals. These mountainous rocks then give up the springs of water that cultivate the soil to grow new trees (a.k.a. the Sheng cycle). They likewise observed that each phase has control of the other phases: the

water of winter can quench the fires of summer; the wood of spring can be controlled by the metal of the ax; the earth of harvest time can control the water of winter by the building of dams (a.k.a. the Ke cycle).

One of the first written texts involving Chinese medicine was the Yellow Emperor's Inner Canon or Neijing. The doctrine of the Neijing proposed a life of moderation, equanimity and morality; or simply, "the way" (Tao). Illness and pain are not only a consequence of external forces such as viruses, cancers and diseases but also from internal forces caused by not fully following the Tao. This would not only include a poor diet, smoking and not exercising but also personality traits such as uncontrolled anger, resentment, lust, and envy. Acupuncture allows for the body to come into harmony with these forces and the person to regain "the way" to health. Acupuncture is the embodiment of the holistic approach to medicine as it serves not only to remedy the external derangement of the body but also affect the psychological and spiritual aspect of the individual as well.

Personality

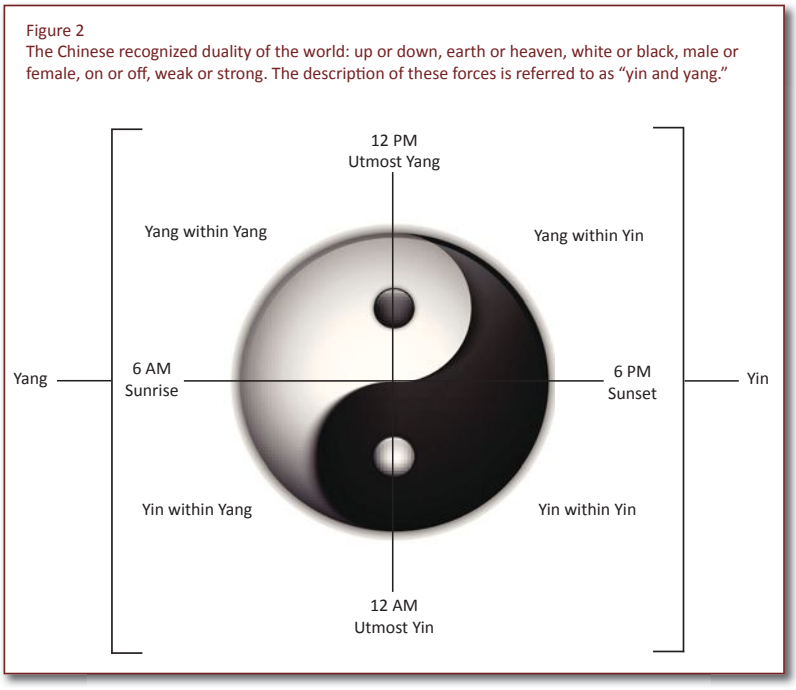
How a patient's disease is evaluated and treated is strongly dependent on the patient's personality rather than where the disease or pain is located. Our ancient counterparts observed that all human personalities fall into five distinct categories and assigned each trait to one of the five phases. Again, over years of observation and examination, they could identify typical illnesses and diseases that occurred with each of the five phases; the detection of the personality of that phase allowed them to identify which phase was influencing the disease.

A person who seeks challenges and pushes themselves to the limit, does well under pressure, loves action and movement, and always wants to be the best would be a personality representing the Wood phase (Spring). A Wood person is a multi-tasker who juggles 10 projects at once but can't complete anyone of them because of their incessant desire to seek new adventures. Whereas these may be laudable traits, this personality can be plagued with being impatient, have volatile emotions including explosive anger, will more often abuse stimulants and suffer from muscle spasms and myofascial pain syndromes. A Fire (Summer) personality relishes in excitement. The Fire person is passionate and sensual, very dramatic, and charismatic. This person is on fire with life and appears tireless in the quest for the zest of life. But if this is allowed to proceed unchecked, they can suffer from agitation and frenzy, nervous exhaustion, insomnia, palpitations, and sweating. The peacemaker is the epitome of all that is maternal; this is the Earth (Harvest) personality. This person wants to be needed, is loyal to a fault, represents security, and safety, and seeks togetherness, serenity, and stability. This person can also be overwhelmed with worry, obsession, overprotectiveness, meddling, lethargy, indigestion and water retention.

The rough, tough Marlborough man, who feels that it is either "his way or the highway" exudes the attributes of the Metal (Autumn) personality. This person lives a life of definition and structure, respects virtue, and authority, lives according to principle and reveres ceremony. The marine who follows their Code or the clergy who would die for their faith are perfect examples of this commendable personality. If not tempered, these forces can make the person indifferent and formal, autocratic, strict and self-righteous. The philosopher best represents the Water (Winter) personality. This person is often very articulate and clever, can be rather critical and scrutinizing, always is in pursuit of knowledge but comes across as timid and shy. Again, if untethered, these people can become very isolated and lonely, appear tactless and unforgiving, suffer from a suspicious nature and become emotionally inaccessible.

Then it is not surprising to find in western medical literature references citing the strong correlations of acupuncture's five-phase personality paradigm with the Myers-Briggs personality indicators used by psychiatrists today.

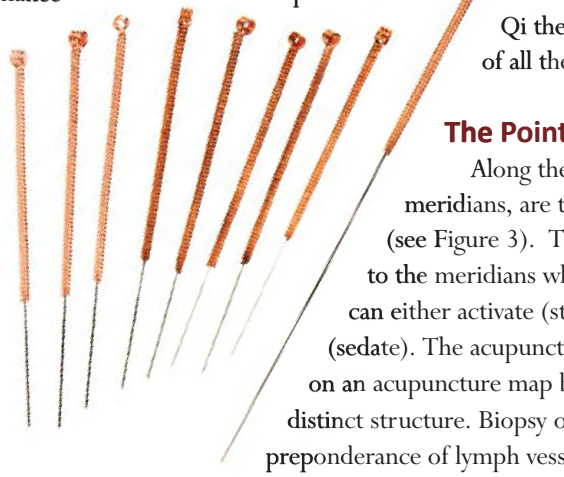
Figure 2
The Chinese recognized duality of the world: up or down, earth or heaven, white or black, male or female, on or off, weak or strong. The description of these forces is referred to as "yin and yang."



Notice that these personality phases have distinct manifestations: suppressed and diminutive or explosive and overwhelming. The Chinese recognized this duality of the world: up or down, earth or heaven, white or black, male or female, on or off, weak or strong. The description of these forces is referred to as "yin and yang." These forces are not at war with each other but are manifestations of the same force as if on a sliding scale. A yang manifestation of a Fire personality might be fever, passion and agitation whereas a yin presentation would be cold, clammy and apathetic. The goal here is to balance these forces so as not to have a propensity of yin over yang or yang over yin. This is well demonstrated with the Pacqua symbol where yin and yang are mutually entwined in such a way that no matter how you slice this symbol, there will never be a pure yin or pure yang state; the two are always balanced (See Figure 2).

Meridians

The goal of acupuncture is the maintenance of the smooth and unaltered flow of the vivifying force, referred to as Qi, through specific channels (meridians) to nourish and give sustenance to the body. The food we eat and the air we breathe are transformed into this very rarefied energy source that gives us life. Depending on the religious and cultural milieu acupuncture is being practiced, this term has had different names; such as "spiritus" by the Jesuit missionaries, the Greeks, "pneuma," the Indians yogi "prana." Parcelsus use the term "quintessence" and Galvani "animal electricity." When in this rarefied form, Qi flows smoothly through the meridians and all is well. If there is an obstruction to this flow caused by disease, the Qi backs up and becomes stagnate causing this rarefied gas to coalesce into a liquid and then to a thick sticky phloegm that prevents its flow through the meridians. Masses and tumors build up behind this obstruction causing pain and the hampering of bodily functions. The intent of acupuncture is to effect a change in these meridians so as to restore the flow of the rarefied Qi through the meridians.



Each of the five phases is represented by a hollow yang organ meridian (found on the dorsal or yang side of the body with the Qi flowing caudally from heaven to earth), and a yin solid organ meridian (found the ventral part of the body with the Qi flowing from earth to the heavens). Each meridian has its own specific acupuncture points that in of themselves, have distinct and separate qualities and functions.

The Liver-Gallbladder meridian represents the Wood personality phase and assures smooth movement of Qi to the muscles, tendons, and ligaments. Interestingly, it is also responsible for proper planning and decision making. Any cerebral event from epilepsy to migraine headaches would involve this meridian. The Heart-Small Intestine meridian represents the Fire personality phase which stores Shen (joy and spirit) and is considered the seat of consciousness. The Spleen-Stomach meridian represents the Earth personality phase and is the principal organ of digestion that transforms the food we consume and the air we breathe into Qi. It also governs the blood by keeping it in the vessels and influences thought and concentration. The Lung-Large Intestine meridian represents the Metal personality which is responsible for the formation and movement of Qi. The Kidney-Bladder meridian represented by the Water personality phase is responsible for the storage and nourishment of Qi thereby influencing the energy of all the organs.

The Point and the Needle

Along these sagitally arranged meridians, are the acupuncture points (see Figure 3). These points act as portals to the meridians where the acupuncturist can either activate (stimulate) or inactivate (sedate). The acupuncture point is not just a point on an acupuncture map but is in fact a physically distinct structure. Biopsy of these points reveals a preponderance of lymph vessels and sympathetic nerve fibers. The high salt content of lymph and interstitial fluid might explain the reason why there is a marked drop in the otherwise very high electrical resistance of the skin over these points. Indeed, acupuncture points are often identified using a cutaneous galvanometer.

Originally, the ancient acupuncturist would stimulate these points with heat. They would fashion a cigar from the dried leaves of the ubiquitous Asian mudwort plant (called moxa), light it and place it close to the skin creating a comforting warmth (referred to as moxibustion). But when this heat is applied to an acupuncture point, there is a definite deep sensation of an almost primal experience. If the point was in a yin state characterized as cold, clammy and sore, adding heat to the point would stimulate it and effect a positive change. When a point along the meridian was hot to the touch, throbbing and swollen, then leaving that point alone or cooling the area with water would sedate or inactivate this point.

Figure 3
The goal of acupuncture is the maintenance of the smooth and unaltered flow of the vivifying force, referred to as Qi, through specific channels (meridians) to nourish and give sustenance to the body. Along these sagitally arranged meridians, are the acupuncture points. These points act as portals to the meridians where the acupuncturist can either activate (stimulate) or inactivate (sedate).



With the refinement of metals and ability to make small sharp objects, moxibustion was replaced with the use of thin needles. The design and construction of the needle is important to its function. The needle is a solid pencil tipped pin with a 30 gauge shaft originally made of steel or iron with a handle made of copper, silver or bronze wrappings. Once placed in an acupuncture point, it can either be stimulate or sedate the point depending on how the needle is manipulated. Modern acupuncturists will stimulate a needle with an electric current. There is now over a century's evidence of the beneficial effect of electrical stimulation of different tissues. Slow frequency high intensity electrical stimulation of strategically placed acupuncture needles can release periaqueductal midbrain endorphins creating an analgesic morphine-like effect whereas high frequency low intensity can cause the release of intracerebral norepinephrine creating a descending analgesic effect seen with the amitryptiline and cymbalta. Since acupuncture predates these electric contributions to medicine, how did the ancients create these effects? According to the Thomson-Kelvin effect, electrons will flow along a thermal gradient.

One would anticipate, then that if an electric conductor (steel needle) placed across a thermal gradient (room temperature 70 degrees F and body temperature of 98 degrees F) will cause the flow of electrons and polarize the needle with the tip becoming positive to the negative handle (Seebec effect). If the tip becomes positive in relation to this negative handle, the point is sedated or inactivated. If on the other hand, there is a reversal of temperature of handle to tip with the application of heat to the handle, then the tip will become negative relative to its handle. This will tonify or activate the point. The ancient acupuncturists found that they could activate a point by twirling the needle or applying smoldering moxa to the handle. In fact, these manipulations of the needle can create measurable amperage of current across two acupuncture needles.

Case Report

There is no better way of illustrating the application and value of acupuncture than a case report. Lupe Morales (not her real name) is a 20-year old Mexican-American employee of a fast food restaurant who presents with severe and unrelenting migraine headaches located over the side of her head and temporo-mandibular joint. This headache is associated with intense pain and muscle spasms in her neck and shoulders. Lupe has noticed that extra strength coffee will suppress her headache and she finds that she can't do without the caffeine stimulant to "get her going" in the morning.

She is studying to be a graphic artist but the long hours in front of a computer screen seems to intensify her neck and shoulder pain which aggravates her headaches. She is thinking of dropping her coursework anyway because she is afraid to face the challenge of hard work and study. She is timid and lacks self-confidence. Her headaches seemed to be associated with her menstrual periods which are normal but she has been known to miss them due to anxiety. She loves dark chocolate and her digestion considered "finicky." She was acutely myopic at puberty when her headaches began. She has mild spring allergies. Her facial features are flat

due to chronic jaw clenching and headaches.

Lupe's anxious and inhibited affect, the stiffness in her neck and shoulders, and her chief complaint of headaches, point to a Wood personality involving the liver-gallbladder meridian (Jue Yin presentation). That her headaches sometime respond to caffeinated coffee underlines the deficient nature of her problem as caffeine is a strong adrenergic stimulant to the liver and sympathetic nervous system. She is Yin in appearance and emits a desire to be invisible rather than to receive attention.

Treatment is directed to reinforcing her deficient Yin energy in the meridian by placing needles in acupuncture points along the liver and gallbladder meridians and tonifying (stimulating) these points most notably LR 3, LR 14 and GB 34. Liver 3 point is one of the four most important points of the body and is an excellent point for tonification along the meridian. Liver 14 is referred to as a mu point of the liver which is a point that has a direct energy input into the liver which will be very therapeutic to those who suffer from a deficiency in Yin energy. To balance the energy between the Yin solid liver organ and the hollow gallbladder Yang organ of the meridian, GB 34 is also piquered. This point is the strongest of all gall bladder points which influences tendons and muscles. The liver points are connected to an electric stimulator (LR3 (-) and LR 14(+)) and she is given a treatment for 12 minutes.

Examination of her neck and shoulders reveal trigger points that when palpated, cause sudden and intense muscle contraction and pain. Her obvious myofascial pain is treated by piquering these trigger points with small needles and then left without stimulation (to allow the backed up Qi to disperse) for 10 minutes. Palpation after this treatment shows the trigger points to be less active but the large areas of muscle contraction is still very painful to her. For this reason, small glass jars or "cups" are heated and placed on these areas. As they cool, a vacuum in the cup is created thus pulling the skin and muscle into the cup. Thick, dark venous oozing is seen coming from the previous needle punctures during the 10 minutes the cups are applied. The vacuum is then released causing the patient to feel a sensation of release of the spasm and muscular contraction. These muscles are then massaged with herbal creams and heated with a near infra-red lamp for 15 minutes (see Figure 4).

Figure 4
Small glass jars or "cups" are heated and placed on areas previously punctured by needled. As they cool, a vacuum in the cup is created thus pulling the skin and muscle into the cup. Thick, dark venous oozing is seen coming from the previous needle punctures during the 10 minutes the cups are applied. The vacuum is then released causing the patient to feel a sensation of release of the spasm and muscular contraction.



After the treatment, the patient is noticeably improved with painless range of motion of her neck and shoulders. She remarks that her usual afternoon migraine headache was uncharacteristically absent. She was encouraged to pursue her dreams as a graphic artist and not be frightened to take on some risk in her life. She was given information on Tai Chi classes to help in stretching and strengthening her muscles particularly of her neck and shoulders. QiGong breathing exercises and yoga courses were also encouraged to help reduce her anxiety and strengthen her self-esteem.

Conclusion

As a Western educated anesthesiologist/chronic pain physician who also practices acupuncture, I feel I am in a unique position to evaluate the advantages and disadvantages of acupuncture. I would like to conclude this article with these personal insights.

1. Acupuncture will never replace surgical anesthesia. It can provide significant help in reducing the need of postoperative narcotics and anti-emetics.

2. Acupuncture is not a single treatment. It is meant to be a part of a life-changing holistic treatment modality. Whereas acupuncture applied in focal areas of pain from an acute injury will offer significant relief of pain and a more

American Academy of Medical Acupuncture

by Claudia Harsh, MD

The American Academy of Medical Acupuncture (AAMA) recently celebrated its 25th anniversary. Founded in 1987, the organization currently represents more than 1,300 physician acupuncturists in North America and many others from around the globe. This premier organization supports its members by encouraging new research and dialogue through conferences, symposia, and special events. Members are held to high standards of training and proficiency.

Physician acupuncturists may apply for membership in the AAMA if they have completed medical school and residency training (seven to ten years post graduate training) and a minimum of 220 hours of acupuncture training (120 hours didactic and 100 hours of clinical training) along with two years of acupuncture practice. A pathway to Board Certification is possible through the American Board of Medical Acupuncture if a case list is created and reviewed, and a certification exam is passed.

Most physician acupuncturists practice their individual specialty of medicine in addition to their acupuncture practice, (e.g. Neurology, Family Medicine, Gynecology, Pain Management, Psychiatry, etc.) This provides the "best of both worlds" blending traditional Chinese medicine principles with Western medical training.

Insurance reimbursement for medical acupuncture varies across the country. A recent roundtable discussion in the journal *Medical Acupuncture*[1] reviewed the current state of reimbursement. Some communities see no reimbursement for acupuncture while some areas of the country have 20 – 30% coverage of the procedure by insurance companies. Many medical practices figure out what reimbursement strategy can work in their individual communities and apply it to their type of medical practice.



Claudia E. Harsh, MD is the chair of the Education Committee for the AAMA. She is a board certified ob-gyn who practices medicine in Dallas, Texas. In addition to providing gynecology surveillance and survivorship care for Texas Oncology PA she also does acupuncture and integrative medicine at the Virginia Cvetko Integrative Medicine Center at Baylor University Medical Center in Dallas. Dr. Harsh has practiced medical acupuncture for 10 years and is the author of the book "Finding Grace and Balance in the Cycle of Life: Exploring Integrative Gynecology," published in 2010.

1. Niemtzow R. et al. Insurance Reimbursement: An Expert Discussion on Best Practices and Avoiding Pitfalls; Med Acupunct. 2013; 25(6): 376-85.

rapid recovery, for chronic illnesses, acupuncture with other significant dietary and lifestyle changes may take months of visits to fully appreciate its effect.

3. Acupuncture in the St. Louis area is poorly if not compensated by insurance companies; it can become very expensive for the patient.

4. Acupuncture is not voodoo. Its effect is not a placebo response. It is not devil worship.

5. Acupuncture improperly applied by poorly trained practitioners will result in a unsatisfactory results like any other medical modality.

6. In my hands, acupuncture is not an alternative medical discipline but an adjunct or complementary support to western medicine that deserves to be included in the curriculum of every western educated physician.

Resources

1. Helms, JM. Acupuncture Energetics: a clinical approach for physicians. Medical Acupuncture Publishers. Berkley. 1995. *Dr Helms is the author's mentor and teacher. Every aspect of this present article is referenced in this text. For the physician interested in acupuncture, this text is a mandatory read.*

2. Helms, JM. Getting to know you. A physician explains how acupuncture helps you be the best you. Medical Acupuncture Publishers. Berkley. 2007. *This is an outstanding book for the prospective patient or an interested practitioner.*

3. Website: WWW.HMIACUPUNCTURE.COM. *This website is an encyclopedic compendium of evidence that should satisfy even the most discretionary of advocates of evidence based medicine.*

MM

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A 'Fitting' Message: Exercise More, Eat Less

by Christopher Hardin, PhD

A key provision of maintaining or improving general health is increased physical activity and effective, regular exercise.



Christopher Hardin, PhD, is the Professor and Chair in the Department of Nutrition and Exercise Physiology and Professor in the Department of Medical Pharmacology and Physiology at Missouri University.
Contact: hardinc@missouri.edu

As the population in Missouri ages and as health care costs continue to present a challenge to governments, employers and individuals, there is a greater awareness that lifestyle choices and changes will be critical in improving health and decreasing costs in the coming years. A key provision of maintaining or improving general health is increased physical activity and effective, regular exercise. This is even more important in light of the growing epidemic of obesity and inactivity in American society. The difficulty faced by health care providers and patients is that there exists some public confusion and uncertainty about what lifestyle changes are healthy and substantiated by good science and which ones are based on myth and the influence of lobbying dollars. Although no single compendium of articles can address all of the issues in this huge spectrum of nutrition and physical activity research, in this issue of *Missouri Medicine* there are six articles that shed substantial light on strategies that can be beneficially implemented for prevention and treatment of lifestyle related diseases associated with obesity and inactivity.

Is linoleic acid pro-inflammatory and should vegetable oils rich in linoleic acid be avoided? Kevin Fritsche summarizes the proposals that omega-polyunsaturated fatty acids (PUFA) such as linoleic acid may cause increases in inflammation. His recent meta-analysis of the literature clearly demonstrates that the science does not currently support the proposal that linoleic acid is pro-inflammatory and therefore the current recommendations for dietary intake of omega-6 PUFA are based on the best available evidence.

Health care providers often lack the time with patients to adequately assess lifestyle behaviors and recommend appropriate and customized changes. Sara Gable and Aneesh Tosh provide motivational interview techniques and some straightforward advice to quick assessment of lifestyle behaviors for children within the context of their specific family environment. These evidence-based strategies will help physicians assess lifestyle risks and suggest lifestyle changes specific to the patient and their family.

Although the obesity epidemic has gained wide attention, it appears to correlate with another major nutritionally centered epidemic of vitamin D deficiency. Catherine Peterson and Anthony Belenchia make a convincing case that there may be a partial causal link between these two epidemics. Vitamin D deficiency is not only found disproportionately in obese patients but correcting the deficiency improves glycemic control in the patients. This simple and

Fit To Recommend: Editor's Choice

Fitbit™ Wireless Activity Trackers



- Tracks steps, distance, calories burned and stairs climbed.
- Monitors your sleep and wakes you with a silent alarm.
- Wirelessly syncs to computers and select smartphones.
- Sweat, rain, and splash proof.
- Includes clip, wireless sync dongle, charging cable and sleep band.

Source: www.fitbit.com

Editor's Note

I have the 'Zip' Fitbit and my wife has the 'One' Fitbit. These are much better than the multitude of pedometers we've tried in the past. Weekly summaries available on free personalized account at fitbit.com website. I target 10,000 steps/day.

Standing Desks - Purported Benefits

A 2013 study by the University of Chester showed that using a standing desk caused the heart to beat an average of 10 beats faster per minute than when sitting. This equates to an additional 50 calories an hour burnt. Extrapolated over an average of 3 hours standing a day, 5 days a week, it equates to 750 calories a week; 30,000 extra calories burnt a year.



Prolonged stationary periods are linked with problems of blood glucose control and reduced production of the enzyme lipoprotein lipase, both of which contribute to an increased risk of heart attack. The study found the blood glucose of those using standing desks "fell back to normal levels after a meal far more quickly" than those who sat. One volunteer with arthritis also reported improved symptoms after using a standing desk.



Manufacturers of standing desks point to several studies showing reduced back injuries or less back pain for the users of standing desks. In February 2010, Olivia Judson wrote a post in the Opinionator (an online commentary section of the *New York Times*) about the benefits of using a standing desk. A study published in Diabetes Care established a relationship between ill health and a sedentary lifestyle and a study by the American Cancer Society published in July 2010, found that "time spent sitting was independently associated with total mortality, regardless of physical activity level."

Source: wikipedia.com

Editor's Note

Alternating use of both the standing and sitting position at work is desirable to minimize potential long time orthopedic and venous stasis problems. "Walk as much as possible" is as "sitting is the new smoking."

safe intervention appears to be one effective treatment in obese patients and may confer a variety of other health benefits.

It would certainly be easier to restrict caloric intake if we weren't so hungry all of the time. In this issue Heather Leidy considers studies of ad libitum feeding of free living people with different protein intakes which indicate that weight control is enhanced and fat mass loss is enhanced with a higher protein diet. Further studies suggest a direct effect of protein on increasing satiety throughout the day. Approximately 30 grams of protein (approximately 1½ servings of high quality protein) per eating session seems to confer the increased satiety. Increasing high quality dietary protein may be an effective way to reduce appetite, maintain better weight control and improve body composition.

As the population ages, a key concern for many patients is the risk of bone fractures including hip and spine fracture. Melissa Cater and Pam Hinton explore the problem of low bone density and effective strategies to enhance bone density and strength. The common strategy to help patients with osteoporosis is pharmaceutical therapy designed to decrease bone resoprtion or increase bone formation. These drugs often have unpleasant side effects and have a low rate of compliance. They provide excellent evidence that weight bearing exercise with impact and resistance exercise are effective strategies to preserve bone mass and reduce the risk of fractures.

In our obesogenic environment, chronic inflammation arises in large part from white adipose tissue. Chronic inflammation may be a primary contributor to cardiovascular disease. Young-Min Park, Margo Myers and Victoria Vieira-Potter examine the evidence that indicates that physical inactivity is a direct cause of the inflammation associated with obesity and that physical activity can mitigate the inflammatory disturbances even without weight loss. A number of molecular mechanisms are outlined suggesting that exercise may reduce inflammation in white adipose tissue by a variety of pathways and mechanisms suggesting it is a simple an robust way to reduce chronic inflammation and the morbidity and mortality associated with chronic inflammation. MM

School of Medicine
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Linoleic Acid, Vegetable Oils & Inflammation

by Kevin L. Fritsche, PhD

Despite the consistency of favorable recommendations regarding dietary LA, the possibility that this fatty acid contributes to excess inflammation has received considerable attention.



Kevin L. Fritsche, PhD, is a Professor of Animal Sciences and Nutrition & Exercise Physiology at Missouri University in Columbia.
Contact: fritschek@missouri.edu

Abstract

Should we listen to warnings that linoleic acid (LA) promotes inflammation and that Americans would be healthier if they restricted their intake of LA (i.e., vegetable oils)? A recently published systematic review of 15 clinical trials failed to find any support for the "diet LA causes inflammation hypothesis." These findings support current recommendations that a diet with 5 to 10 energy percentage from polyunsaturated fatty acids, such as LA, is healthful and appropriate for most Americans.

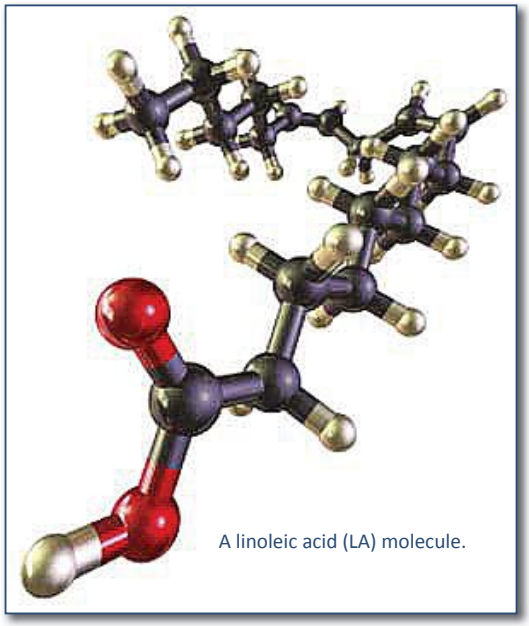
Introduction

On average Americans consume more than 40 grams (~3 tablespoons) of vegetable oil each day. Vegetable oils, such as those from soy, corn, or canola, are rich in linoleic acid (LA), an omega-6 fatty acid and an essential nutrient. Omega-3 fatty acids are also essential nutrients that can be obtained from soy, canola and flaxseed oils as well as certain cold-water fish, such as tuna, salmon, and herring. The relationship between and among the various members of these two families of essential nutrients has been the subject of much research and controversy. In this article, the focus will be on LA, from which all other omega-6 fatty acids can be derived.

The effects of dietary fats on cardiovascular disease (CVD) and other chronic health conditions have long been an important consideration in the development of dietary guidelines in the United States and around the world. The 2010 Dietary Guidelines for Americans[1] recommend that monounsaturated and polyunsaturated fats be substituted for saturated fats in the diet. There is currently much consistency among recommendations from government and professional organizations that both omega-6 and omega-3 classes of polyunsaturated fatty acids (PUFA) are desirable, and that LA as well as omega-3 PUFA consumption should be encouraged as a replacement for saturated fatty acids (SFA), trans fatty acids, and (in some cases) refined carbohydrates.

Since the 1970s researchers have known that linoleic acid (LA) reduces blood cholesterol levels and lowers the risk of heart disease. Thus, it is no surprise that a recent American Heart Association (AHA) Science Advisory[2] recommended that omega-6 PUFA make up at least 5 to 10% of total energy. In addition, a current Position Statement from the American Dietetic Association (i.e., Academy of Nutrition and Dietetics) and Dietitians of Canada[3] noted that the recommended range of intakes for omega-6 PUFA

(primarily LA) in the U.S. from the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH)[4], the Institute of Medicine (IOM)[5] ranges from 5 to 10% of energy.


A linoleic acid (LA) molecule.

Despite the consistency of favorable recommendations regarding dietary LA, the possibility that this fatty acid contributes to excess inflammation has received considerable attention. The primary basis of concern is that large amounts of LA will prompt excessive formation of arachidonic acid (AA) and subsequent synthesis of pro-inflammatory eicosanoids (e.g., prostaglandin E_2 (PGE_2), leukotriene B_4 (LTB_4) and thromboxane A_4 (TXA_2).[6-10] Elevated pro-inflammatory eicosanoid generation could drive up other biomarkers of inflammation (e.g., interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP)) that are associated with increased incidence of cardiovascular disease (CVD), cancer and other chronic diseases. In addition, the possibility that high LA intake will result in decreased elongation of ALA to eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA) due to competition for the Δ-6 desaturase is a frequently stated concern.[8,11] This competition, in turn, could reduce the formation of anti-inflammatory eicosanoids, including the newly discovered resolvins and neuro-protectins that are derived from these longer-chain omega-3 fatty acids.[12] The literature in this field is very complex and numerous narrative reviews have been published that have come to different conclusions with respect to the possible pro-inflammatory effects of dietary LA.[13-17]

What the field was missing was a systematic review of randomized controlled trials that examined the impact of dietary LA on biological markers of inflammation among healthy adults. Therefore, in 2010 a colleague and I set out to fill this void in the literature. We conducted a search of the English and non-English literature using MEDLINE, the Cochrane Controlled Trials Register, and EMBASE to identify relevant articles. Fifteen clinical trials (seven cross-over and eight parallel studies) met the inclusion criteria (e.g., randomized, placebo-controlled intervention studies in healthy humans greater than one year of age in which the only fatty acid other than LA that was allowed to differ substantially between the experimental and control diets was oleic acid). The most frequently reported biomarker of systemic inflammation was circulating CRP. Surprisingly, there was no significant impact of varying LA intake on circulating CRP in any of these trials.[18] Furthermore, dietary LA showed no effect on circulating concentration of various other inflammatory biomarkers, including: IL-6, TNF-α, ICAM-1, L-selectin, P-selectin, fibrinogen, PAI-1, platelet activity (fibrinogen load), tPA/PAI-1 complex, TXB_2, PGE_2, $PGF_{2\alpha}$.[18]

In addition to these results from RCT (the gold standard in biomedical research), there have been a number of well-designed observational studies that have explored the relationship between LA intake and inflammation in humans. For example, Ferrucci and colleagues[19] observed that total omega-6 PUFA plasma concentrations were inversely associated with serum CRP, IL-6, IL-6r, IL-1ra, and TNF-α and paralleled the associations observed for total plasma omega-3 PUFA in a cross-sectional analysis of 1,123 Italian adults. In addition, Pischon and colleagues[20] observed that the lowest levels of inflammation were found in subjects who had the highest consumption of both omega-3 and omega-6 PUFA among 405 healthy men and 454 healthy women from the Health Professionals Follow-Up Study and the Nurses' Health Study, respectively. Other observational studies reported inverse and/or no association between plasma or dietary LA and a variety of markers of chronic inflammation.[21,22] The results from these and other epidemiological studies illustrate the weakness of "omega-6/omega-3 ratio" as a meaningful parameter. A more complete discussion of the shortcomings of the omega-6/omega-3 ratio has been published previously.[23]

There are several limitations in the data available for this first systematic review of the relationship between dietary LA and inflammation. First, all of the RCT incorporated small numbers of subjects. The largest study had only 60 subjects that completed the trial. Three of

the 15 RCT were conducted in metabolic wards, which enhanced the control over the dietary intervention, but had only six to nine subjects enrolled. A second limitation is the uncertain clinical relevance of various biomarkers of inflammation being measured in clinical studies. Often researchers measure multiple biomarkers of inflammation in the hope that one or more of them will have predictive value relevant to clinical outcomes. Many inflammatory biomarkers are characterized by considerable intra- and inter-individual variability. This variability makes it difficult to detect subtle changes with small sample sizes and the possibility of false negative outcomes cannot be dismissed. No consensus exists regarding which biomarker is best, since each has advantages and disadvantages, however, the linkage between CRP or fibrinogen and CVD risk is quite strong.[24] A third shortcoming of these RCT is their relatively short duration. The shortest trial was two weeks and the longest was 40 days. Two weeks is about the minimum amount of time required for diet-induced modifications of circulating and tissue fatty acids to stabilize.[25] However, the time required for dietary lipids to affect inflammation-related processes is less well understood.

Based on the current evidence from RCT and observational studies there appears to be virtually no data available to support the hypothesis that LA in the diet increases markers of inflammation among healthy, non-infant humans. However, in light of the limitations of the evidence available, one cannot fully reject the "diet LA drives inflammation hypothesis" at this time. To do so, will require additional data from larger and longer studies with meticulous dietary control that include subjects from differing genetic endowments. Nevertheless, the outcome of this recent systematic review should provide the dietetic and medical community with a measure of reassurance regarding current dietary recommendations that emphasize optimal intake of both omega-3 and omega-6 PUFA.

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Disclosure

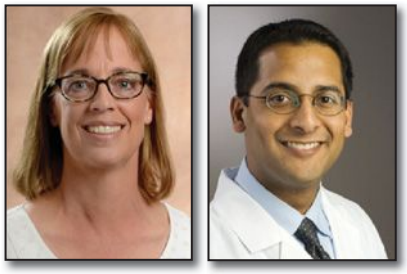
KF is currently serving as a scientific advisor for the lipids committee of the International Life Sciences Institute of North America (ILSI-NA) MM

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Children, Youth, and Parents: Screening for Obesity Risk With the Spectrum of Physical Activity

by Sara Gable, PhD & Aneesh K. Tosh, MD

Establishing healthy physical activity habits during childhood is key to a lifetime of well-being.



Sara Gable, PhD, (left), is Associate Professor and State Extension Specialist for the Department of Nutrition and Exercise Physiology. Aneesh K. Tosh, MD, MS, (right) is Associate Professor, in the Division of Adolescent Medicine, Department of Child Health. Both are at Missouri University School of Medicine.
Contact: gables@missouri.edu

Abstract

The current article reviews several practical approaches to screening for obesity risk among children and youth, with an emphasis on the spectrum of physical activity. We encourage physicians to utilize evidence-based strategies (e.g., 5-2-1-0), implement motivational interviewing techniques, and focus on "crunch time" (i.e., the period of day after school and before bedtime) when gathering information about physical activity type and intensity. The insights gained are useful for evaluating obesity risk and establishing goals for lifestyle interventions. Characteristics of successful interventions with youth are also discussed and include goal-setting, self-monitoring, and pedometers.

Introduction

About 29% of Missouri's young citizens carry excess weight. In 2009-2010, among Missouri children and youth ages 2 to 19, 14.4% were overweight ($\geq$ 85th - < 95th BMI percentile) and 14.4% were obese ($\geq$ BMI 95th percentile). [1] Childhood obesity tracks notably into adulthood, is associated with numerous medical complications, [2] and is linked with social, emotional, and scholastic difficulties. [3] Because of its potential for a range of detrimental consequences, the implications of pediatric overweight and obesity are profound for life-course human development and well-being.

To step-up prevention efforts, the American Academy of Pediatrics' Expert Committee recommends universal assessment of obesity-related behaviors and attitudes. [4] Meeting this goal requires identifying effective and efficient screening approaches for use in the clinical setting. This article presents several approaches to evaluating the lifestyle habits of children and youth, with a particular focus on the spectrum of physical activity (PA).

Recent surveys show that 27% of Missouri youth engaged in PA that increased their heart rate and made them breathe hard for at least 60 minutes on 7 days in the week prior to the survey. About 15% of youth surveyed did not achieve this level of PA on any day prior to being interviewed and 32% reported watching TV for 3 or more hours on a typical school day. [1] With attention to the full spectrum of PA, physicians will have access to more options when working with patients to set goals, motivate change, and chart progress.

A Time-Saving Strategy for Gathering Preliminary Information

While physicians recognize the importance of asking about lifestyle behaviors during patient encounters, most report low self-efficacy in addressing obesity management[5] and nearly one-half identify lack of time as a barrier.[6] Providers who are interested in a time-saving alternative to a lifestyle history may elect to implement a 5-2-1-0 behavior screening tool while patients are waiting to be seen. [7] The 5-2-1-0 approach targets four common daily lifestyle goals: 5 servings of fruits and vegetables; no more than 2 hours of screen time; 1 hour of moderate to vigorous physical activity; and, no sugared beverages. A yes/no question about the presence of a TV in the child's bedroom is also recommended. [8] Having a television in the bedroom is associated with 1.5 more hours of screen time daily and is a significant risk factor for obesity. After review of patient responses, health care professionals can make targeted suggestions to move patients and families closer to the 5-2-1-0 goals. They may also opt to delve further into the topic of physical activity during the universal assessment of obesity-related behaviors and attitudes.

Background: Motivational Interviewing Techniques

Motivational interviewing is gaining acceptance as an approach to physician-patient encounters that serves multiple outcomes. As shown in Table 1, motivational interviewing centers on patients and blends non-directive questions, active listening, and comparing patients' current health practices with their health-oriented values.[4] Providers who implement motivational interviewing strategies have been successful at improving BMI among their obese adolescent patients. [9] These techniques open communication channels, build physician-patient rapport, and support patient self-efficacy toward positive behavior change. This foundation is crucial when more difficult conversations are needed. Establishing oneself as committed to a patient's well-being is crucial when change in the family's lifestyle behaviors becomes imperative for a child's health. Furthermore, motivational interviewing presents the opportunity to acknowledge progress in lifestyle habits.

Where to Begin? "Crunch Time"

When asking patients about their PA, one strategy is to embed questions in periods of the day that allow discretion for children, youth, and parents. A time with great potential for healthy and not-so-healthy lifestyle behaviors occurs between 3:00 pm and bedtime. This "crunch time" often involves significant calorie consumption and sedentary behavior, which is permitted because parents believe that youngsters have already exercised sufficiently earlier in the day. [10] MO law currently requires 150 minutes per week of physical activity for elementary school students, no universal physical activity requirements for middle school and junior high, and 1 credit hour of physical education for high school graduation. Consequently, children and youth still need opportunities for PA outside of school. Determining a patient's actual discretionary time is a useful place to start the screening process. Questions can then follow about the patient's typical and preferred activities.

The Spectrum of Physical Activity: Intensity and Type

When asking about discretionary time use, the goal is to elicit enough specificity so that children's activities can be linked with general estimates of PA intensity. Because children and parents commonly underestimate the level and duration of exercise performed daily, it is important to consider the full range of how kilocalories can be expended.

As presented in Table 2, the physical activity spectrum begins with fully sedentary behavior, such as prolonged periods of sitting or lounging. A growing body of research indicates that in adults, extended periods of low energy activity are associated with increased morbidity.[11] In youth, sedentary behavior takes different forms and may be perceived as more or less productive (e.g., homework and reading versus screen time and phone/texting time) and more or less preferred. [12]

The spectrum then shifts to baseline or light intensity activity. These are the movements associated with daily life and are characterized as non-exercise activity thermogenesis (NEAT). NEAT activities include standing, pacing, walking between classes, fidgeting, gesturing, and meal preparations, such as cooking and setting the table, and may expend upwards of 350 kilocalories per day.[13] There is widespread concern that the accumulation of NEAT is declining because of domestic conveniences and less physical forms of employment and leisure and is being replaced by more very low intensity activities.[11, 13] For example, since 1999, youth engagement with media in the form of TV content, music, computers, video games, print, and movies has increased from an average of 6 hours and 19 minutes per day to 7 hours and 38 minutes,[14] with the majority of media activity involving TV (3:47 and 4:29, respectively).

Moderate- and vigorous-intensity are the next levels

Table 1
Motivational Interviewing Template for Physical Activity: For Parents and Adolescents

Goal	Sample Language
1. Gather Information	1. Your child's body mass index places him/her at a higher risk for medical problems including diabetes. Have you or any other caregivers had any concerns about your child's weight or level of activity? May I ask some questions about this? 2. Is your child in physical education at school? If so, how often and for how long? 3. What other forms of regular exercise do you/does your child receive? 4. In total, how many minutes of aerobic exercise do you/does your child receive daily? 5. What activities do you/does your child do during "crunch time," the period of time between 3pm and bedtime? 6. How much screen time do you/does your child view daily? Is there a television or other sources of screen time in the bedroom? What are your rules about screen time? Are you familiar with the American Academy of Pediatrics recommendations for daily recreational screen time (2 hours)?
2. Express Empathy	1. To the parent: we know that you are very busy and trying your best to take care of your family. 2. To the child: we know that you are busy and tired after a full day of school. 3. We are hoping to find fun ways to increase physical activity that works with your busy schedule.
3. Identify Discrepancy	1. On a scale from 1-10 (10 being the most important), how important is it that you/your child participates in the recommended amount of physical activity (60 minutes daily)? 2. Why that number, why not a lower number? 3. What are the benefits/negatives of exercising? What are the benefits/negatives of screen time?
4. Avoid Argumentation and Roll with Resistance	1. I understand that you are busy/tired during "crunch time", but since we have talked about the benefits of exercise, may we talk about some strategies to increase the amount of physical activity and exercise that your child is receiving? 2. Regardless of weight, children who exercise are healthier than those who don't. I am hoping we can find a fun activity you/your child can do that improves his/her health. May we explore some options?
5. Support Self-Efficacy	1. What are some possible activities you/your child would consider? (e.g. helping with yard work or housework, walking, swimming, biking)? 2. What barriers exist that prevent you/your child from exercising the recommended amount (screen time, child's motivation, safety, childcare, transportation, financial, equipment)? Can we work together to address some solutions to those barriers so we may improve your child's level of physical activity? 3. Would it be possible for your child to earn his/her screen time, for example, 30 minutes of exercise earns 60 minutes of screen time? 4. Would it be possible for someone (parent, sibling, friend) to exercise with your child? 5. How likely is it that you can remove the television and other types of screen time from the bedroom? 6. Can we set an exercise goal today, even if it is for a few minutes? It may help to track your progress on a chart or with a phone app. We can then review and build on our exercise goals at future visits.

Adapted from http://www.cdc.gov/physicalactivity/everyone/glossary/index.html and Levine et al 2006

of physical activity (MVPA). MVPA engages the cardio-respiratory systems and is typically achieved via aerobic activity and muscle and bone strengthening activities. These types of PA are recommended for all ages to maintain and improve physical health and fitness. Visit: http://www.cdc.gov/physicalactivity/everyone/guidelines/what_counts.html for age-appropriate examples of MVPA and different activities for children and youth.

Evaluation

Before evaluating patient discretionary time use and PA intensity and type, the information that is gathered must be contextualized. Factors such as patient age, gender, parent work schedules, family socioeconomic status, neighborhood characteristics, and community resources all contribute to how lifestyle habits develop and their potential for change. For instance, during the transition from early to

mid-adolescence, adolescent girls experience a significant increase in sedentary behaviors. [15] Additionally, preschoolers who live in neighborhoods perceived by mothers as unsafe are more likely to watch more than two hours of TV per day. [16] These considerations will likely influence provider suggestions.

Physical Activity

The Centers for Disease Control and Prevention recommend that children and youth accumulate 60 minutes or more of PA per day. Most of this activity should be aerobic and at the moderate to vigorous level of intensity. The CDC also recommends that young people engage in muscle and bone strengthening activities at least 3 times per week as part of their PA routine. Patients can also be advised to avoid prolonged periods of low energy expenditure, such as uninterrupted sitting. Although exact cut-points have yet to be determined, Dunstan et al reported that two-minute light intensity PA breaks every 20 minutes were beneficial for overweight and obese adults' glucose and insulin responses. [18]

The American Academy of Pediatrics recommends that children and youth over age 2 be allowed up to 2 hours per day of recreational screen time. [8] For children under 2 years of age, parents are encouraged to avoid all screen exposure. The AAP also advises that TVs not be placed in any bedrooms and that TV viewing near bedtime be limited.

In some instances, the screening process will reveal healthy PA habits. Providers can acknowledge patients' specific behaviors, articulate their benefits, and encourage patients (and parents) to keep up the good work. Conversely, the screening interview may reveal that a young patient is on a worrisome trajectory of low PA that could lead to weight problems. When this occurs, eliciting parent perspectives on the situation is essential. Table 1 presents sample questions to use for this purpose. In some instances, parents will not perceive any health-oriented problems and in others, parents will concur with providers and be open to strategies for change. For both outcomes, the objective is to assess parent readiness for change, efficacy and confidence, and, if possible, to work together on realistic, short-term goal setting. [7] The role of parents

Table 2
The Spectrum of Physical Activity: Intensity and Type

Physical Activity by Level of Intensity	**Definition**
Fully Sedentary/Lowest Intensity	The lowest intensity form of physical activity. Characterized by prolonged sitting. Burns fewer calories than standing, gum chewing, and fidgeting.
Baseline Activity/Light Intensity	The light intensity activities of daily life. Includes: standing, walking slowly, lifting objects, "puttering". A lifestyle that includes only baseline, or light intensity activity is considered inactive.
Moderate Intensity	Moderate intensity activity is 3.0 to 5.9 times more intense than the intensity associated with a fully resting state. On an individual scale from 0 to 10, moderate intensity activity is at about 5 or 6. A person's heart beats faster and breathing is hard.
Vigorous Intensity	Vigorous intensity activity is at least 6.0 times more intense than the intensity associated with a fully resting state. On an individual scale from 0 to 10, vigorous intensity activity is at about 7 or 8. A person's heart beats much faster and breathing is also much harder.
Types of Physical Activity	**Definition**
Non-Exercise Activity Thermogenesis (NEAT)	"NEAT is the energy expenditure of all physical activities other than volitional sporting-like exercise" (p. 731; Levine et al 2006).
Exercise	Exercise is physical activity that is planned, structured and repetitive. The goal of exercise is to maintain or improve health, physical fitness, and performance.
Aerobic Activity	Aerobic activity engages the large muscle groups for a sustained time period. It makes a person breathe harder and brings more oxygen to the body and is good for strengthening children's cardio-respiratory system.
Muscle Strengthening	Muscle strengthening activities increase skeletal muscle strength, endurance, and mass.
Bone Strengthening	Bone strengthening activities create an impact on bones that fosters bone growth and strength.

Adapted from http://www.cdc.gov/physicalactivity/everyone/glossary/index.html and Levine et al 2006.

in children's health-related attitudes and behaviors and the successful prevention and treatment of childhood weight problems cannot be overlooked.

Goal-Setting and Self-Monitoring

Interventions that successfully increase child and youth PA share several characteristics. Specifically, they attend to the full spectrum of PA and incorporate accepted behavior change strategies. For example, goal-setting and rewards for progress engage the full range of PA intensity and type. Providers can discuss strategies to minimize low intensity activity by advising against a television in the bedroom and recommending screen time limits. Further, linking predetermined amounts of NEAT and MVPA with time earned for highly-preferred, low intensity activities (e.g., video games, social media) is effective in PA-oriented behavior change plans. [12, 19] Even modest changes in activity intensity can have a marked effect on overall PA and kilocalorie expenditure.

A recent meta-analysis of pedometers and youth PA reported that pedometers, when combined with goal-setting and self-monitoring, are associated with increased PA. [19] Pedometers can be used to generate baseline step counts and set individualized behavior change goals. Self-monitoring can be accomplished with daily step count diaries. Both goal-setting and self-monitoring have been made easier due to the widespread availability of exercise monitoring smart-phone applications. Although 12,000 steps a day approximates the recommendation for 60 minutes of daily MVPA, [20] experts recommend introducing incremental goals for behavior change that emerge from baseline PA.

Modifying the physical environment and how "crunch time" is structured can also beneficially influence child and youth PA. Parents may want to consider creating screen-free zones in the house and establishing family time when everyone's mobile-, computer-, and TV-screens are shut down. Unless absolutely necessary, remote control devices can be minimally-used. And, instead of sitting in a restaurant and being served dinner, family mealtime preparations can be viewed as an opportunity for shared NEAT.

Conclusions

This paper outlines a PA-approach to screening for obesity risk among children and youth. We utilized "crunch time" as a period of the day with great potential for accumulating very low energy activity. By relying on the full spectrum of PA intensity and type, providers can work with children, youth, and parents to set realistic goals for behavior change. Establishing healthy PA habits during childhood is key to a lifetime of well-being.

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School of Medicine
College of Human Environmental Sciences
College of Agriculture Food and Natural Resources

Vitamin D Deficiency & Childhood Obesity: A Tale of Two Epidemics

by Catherine A. Peterson, PhD & Anthony M. Belenchia, MS

Physicians should routinely monitor the vitamin D status of obese children and adolescents and correct vitamin D insufficiency through dietary supplementation.



Catherine Peterson, PhD, RD, (left) is an Associate Professor in the Department of Nutrition and Exercise Physiology at Missouri University, and Anthony Belenchia, MS, is a doctoral student in the Nutritional Sciences Graduate Program MU.
Contact: petersonca@missouri.edu

Abstract

Obesity and vitamin D deficiency represent two of the most wide-spread health concerns in the United States, especially among children. There is a well-established inverse relationship between vitamin D status and obesity; however, it is unknown as to whether vitamin D deficiency contributes to, or is a consequence of obesity. Based on available research, the positive effects of correcting hypovitaminosis D in obesity seem to be primarily related to its action on glycemic control.

Introduction

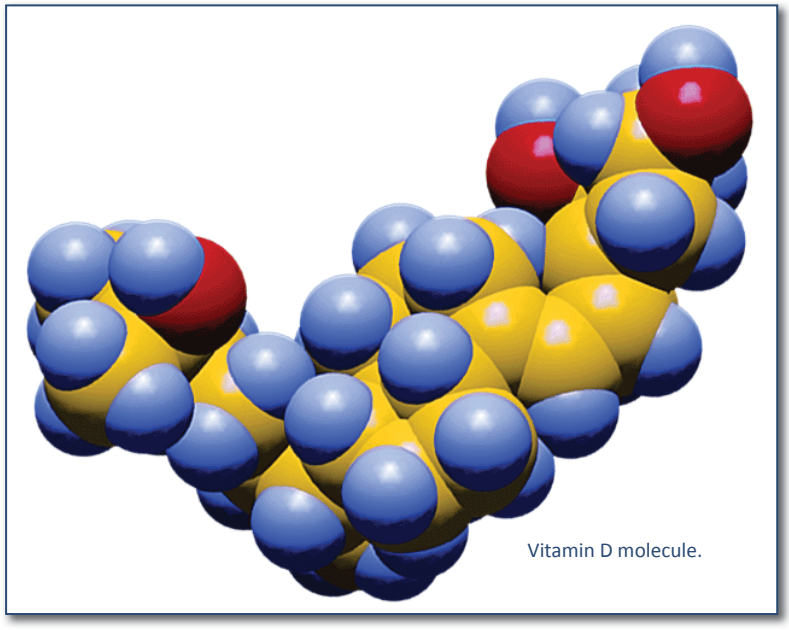
The classical and most widely understood biological functions of vitamin D involve calcium homeostasis and bone mineralization; however, vitamin D is also necessary for many other cellular processes and vitamin D receptor (VDR) has been identified in nearly every cell type.[1] Data accumulated over the last decade have lead researchers to speculate that the vitamin D deficiency epidemic may be a major contributor to many obesity-associated complications such as the metabolic syndrome and diabetes. Moreover, epidemiological and clinical studies show that the obese have lower vitamin D status; while other trials have indicated that obese individuals with better vitamin D status may respond to an energy-restricted diet more favorably (more body fat loss) than obese with poor vitamin D status.[2,3] The purpose of this review is to explore the recent advances in our understanding of the roles vitamin D may play in obesity and obesity-associated metabolic conditions with a particular emphasis on pediatric obesity.

Pediatric Obesity and Vitamin D Deficiency Defined

Obesity is defined as having excess body fat and the most common metric used in its assessment is body mass index (BMI, weight in kilograms divided by the square of height in meters). Although the diagnostic cut-offs are somewhat controversial, the Centers for Disease Control considers a BMI greater than or equal to the 95th percentile on the BMI-for-age growth charts to be indicative of pediatric obesity.[4]

Vitamin D status is assessed by measuring serum concentrations of 25 hydroxyvitamin D (25(OH)D). Traditionally, vitamin D deficiency, or hypovitaminosis D, has been defined as a 25(OH)D concentration of <20 ng/mL, however recently, an additional classification of "insufficiency" was proposed at a Vitamin D Workshop and elaborated by Grant and Holick; it is defined as 20-32 ng/mL (sufficient is defined as 33-100 ng/mL).[5,6]

Independently, both pediatric obesity and vitamin D deficiency have been classified as epidemics in the United States (U.S.) population. Data from the NHANES 2009-10 survey show the prevalence of obesity among children 6 through 11 years at 18% and among adolescents 12 through 19 years at 18.4%.[4] Likewise, data collected from NHANES 2003-06 indicate that approximately 21% of normal weight youth are vitamin D deficient whereas the prevalence of vitamin D deficiency in obese children rises as excess adiposity increases, up to 49% in the severe obese.[2]



Vitamin D molecule.

Vitamin D Primer

Vitamin D can be ingested as ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3); of these, D3 is thought to be the most potent, although a few studies challenge this assertion.[7] Only a few foods, such as fish liver oils and fatty fish, naturally contain vitamin D. In the U.S., vitamin D-fortified milk is the primary dietary source. Vitamin D can also be synthesized in human skin in response to sunlight exposure. Radiation with wavelengths 290-315 nm (UVB) are absorbed by epidermal and dermal stores of 7-dehydrocholesterol.[1] During exposure to ultraviolet radiation, 7-dehydrocholesterol is converted to previtamin D3 and then rapidly converted to vitamin D3. Once D3 is formed, it is sterically unacceptable and is ejected from the plasma membrane into the extracellular space. As vitamin D enters the circulation, it is bound to a group-specific protein known as vitamin D-binding protein (DBP). It is then transported to the liver where it undergoes its first hydroxylation on carbon 25, making 25(OH)D, the major circulating form of vitamin D in the body, yet biologically inert. For it to become active, it must undergo a second hydroxylation by 1α-hydroxylase in the kidney, producing 1,25 dihydroxyvitamin D (1,25 $(OH)_2D$) or calcitriol. However, it is known that numerous other tissues also possess enzyme systems capable of hydroxylating 25(OH)D to produce the active form 1,25 $(OH)_2D$ for autocrine/paracrine functions, notably cellular proliferation, growth, and differentiation.[1]

Ninety to 100% of most humans' vitamin D comes from exposure to sunlight;[5] while supplements containing vitamin D can also provide a substantial source. Furthermore, in one report of U.S. intakes, no child or adult in the study received the recommended vitamin D dose from food sources alone.[8]

In addition to dietary intake, several factors can affect vitamin D status. During winter months in temperate climates and year-round at high latitudes, the solar zenith angle is decreased, thus attenuating the atmospheric penetration of UVB radiation.[1] In Missouri, cutaneous synthesis occurs only between March and October, peaking in mid-summer. Another factor inversely associated with circulating 25(OH)D is the degree of skin pigmentation by melanin which functions as a natural sunscreen.[1] Likewise, even low-strength sunscreen lotions (≥SPF 7) are capable of inhibiting the majority of cutaneous synthesis. Other factors associated with increasing risk of vitamin D insufficiency include cultural clothing practices where little/no skin is exposed, fat malabsorption, and excess adiposity.

Relationship Between Adiposity and Vitamin D Status

Obesity is a risk factor for vitamin D deficiency. Studies of obese adults and children demonstrate that body fat mass is inversely correlated with serum 25(OH) D levels.[9] Regression analysis of adult data predicts that for every 10% increase in BMI percentile there is a 4.2% decrease in 25(OH)D concentration.[10] It is thought that this vitamin D insufficiency is likely due to the vitamin's preferred deposition in body fat compartments, making it unavailable to be converted to 25(OH)D. This hypothesis is supported by early studies demonstrating that obese individuals are only about half as efficient in converting

the vitamin, whether taken orally or through cutaneous synthesis following UVB exposure, to 25(OH)D.[9]

Experiments in humans confirm that adipose tissue is a major deposition site of vitamin D and its metabolites.[9] However, some recent investigations challenge the hypothesis that stored vitamin D is less bioavailable, concluding that circulating concentrations of 25(OH) D were simply more diluted in larger individuals.[11] Here, they show that when 25(OH)D concentrations are corrected for body mass, vitamin D bioavailability does not differ between normal-weight and obese individuals.



The increasing prevalence and severity of childhood obesity has been accompanied by troubling upsurges in the frequency of insulin resistance, impaired glucose tolerance and type 2 diabetes (T2D) among U.S. children and teens. Vitamin D deficiency has been linked to all of these diseases.

Vitamin D in Adipose Tissue

While there is a well-documented association between vitamin D status and obesity, there is confusion over whether vitamin D deficiency contributes to, or is a consequence of obesity.[9,12] This is perpetuated by the mixed results from studies investigating the effectiveness of supplementation to reduce body weight and adiposity, which have produced mixed results.[3,13] Data from animal and in vitro experiments, however, provide some insight into the complexity of the relationship. The latest findings show that adipose tissue is a direct target of vitamin D. The expression of VDR and 25(OH)D 1α-hydroxylase (CYP27B1) genes have been identified in both mouse and human adipocytes. There is also evidence that the active form of vitamin D, 1,25 $(OH)_2D$, may inhibit adipogenesis and reduce fat mass by suppressing the expression of key adipogenic transcription factors and reducing lipid accumulation during adipocyte differentiation.[14] Other reports indicate that vitamin metabolites also influence adipokine production and the inflammatory response in adipose tissue. Taken together, these observations provide mechanistic support for the assertion that vitamin D deficiency compromises the metabolic functioning of adipose tissue.

Vitamin D Status and Obesity-Associated Metabolic Complications in Children

The increasing prevalence and severity of childhood obesity has been accompanied by troubling upsurges in the frequency of insulin resistance (IR), impaired glucose tolerance (IGT) and type 2 diabetes (T2D) among U.S. children and teens. Nearly one-third to one-half of obese children and adolescents display some clinical symptoms of abnormal glucose metabolism.[15] The most alarming aspects of altered glucose metabolism in obese children are the implications for chronic disease and early death in adulthood.[16] Vitamin D deficiency has independently been linked to IR, IGT and T2D as well as shares similar risk factors including physical inactivity (i.e. decreased outdoor activity), non-white ethnicity and aging. More importantly, the mounting research evokes potential for the improvement of vitamin D status via supplementation to aid in the mitigation of these metabolic health problems.

The first observations linking vitamin D status to T2D in humans came from reports showing that both healthy and diabetic subjects have a seasonal variation in glycemic control.[17] Although not as well documented as in adults, several observational studies have since demonstrated that low serum 25(OH)D may be a risk factor for abnormalities in glucose homeostasis in children. For example, in a study of obese children and adolescents living in Wisconsin, serum concentrations of 25(OH)D were positively correlated with insulin sensitivity, which was mediated by fat mass, but negatively correlated with HbA_{1c}.[18] Significant hypovitaminosis D in obesity has even been observed in

children living at lower latitudes in the US (and thus greater opportunity for sun exposure) and has been negatively associated with assessments of IR (HOMA-IR and two-hour glucose from oral glucose tolerance test).[19] A recent analysis of data collected from a national survey of 5,867 children and adolescents (NHANES 01-06), revealed that, regardless of obesity, serum 25(OH)D was significantly associated with several cardiometabolic risk factors, including HOMA-IR and systolic blood pressure.[20] It's worth noting that subclinical vitamin D deficiency is particularly prevalent in obese African-American youth and it too is correlated with insulin insensitivity.[21] In contrast, a recent report exploring the relationship between vitamin D status and insulin resistance and cardiovascular risks in very young obese children (two to six years) saw no association.

While the associative link between vitamin D status and various glycemic variables is rather strong, the data from trials examining the effects of vitamin D administration on insulin resistance and glucose metabolism is somewhat conflicting. In 2012, a systematic review and meta-analysis of the evidence on vitamin D supplementation and glycemic control surveyed 15 randomized controlled trials (RCT) comparing vitamin D or analogues with placebo; only adult studies were included.[22] The results suggested a weak effect of vitamin D supplementation in reducing fasting glucose and improving insulin resistance in patients with T2D or impaired glucose tolerance. However, a major flaw of this meta-analysis is that the studies included used wide-ranging vitamin D forms and dosing regimens; in most trials where no effects were observed, the dose or duration of vitamin D supplementation were inadequate to increase serum 25(OH)D to sufficient concentrations, i.e. > 30 ng/mL. In the only known published double-blind RCT testing the effectiveness of supplementing obese adolescents, our lab found that 4000 IU per day of cholecalciferol safely increases their 25(OH)D concentrations to a level at which the impaired glucose metabolism and insulin resistance associated with obesity is attenuated.[13] Remarkably, the reduction in insulin resistance (as measured by HOMA-IR) that we observed was similar to results involving metformin and was independent of changes in body weight. In agreement with these results, two RCT of overweight adults with IR, found cholecalciferol supplementation doses of 2000 and 4000 IU were necessary to see significant clinical improvements in insulin sensitivity.[23,24] In all three of these RCT, vitamin D supplementation resulted in serum concentrations of 25(OH)D > 30 ng/mL.

The biological mechanisms by which vitamin D influences glycemic control in obesity are not well understood. The proposed mechanisms include enhancing glucose uptake through both direct and indirect means, regulation of glucose-mediated secretion of insulin by pancreatic beta cells, and reducing inflammation.[25]

Obesity is characterized by chronic low-grade inflammation. Various mechanisms involved in the acute-phase inflammatory response and the activation of the innate immune system have been implicated in the pathological processes underlying insulin resistance, T2D, and other metabolic complications.[17] Although several studies have demonstrated negative associations between circulating 25(OH)D and circulating concentrations of multiple inflammatory cytokines and adipokines, human trials investigating the impact of vitamin D supplementation on inflammatory biomarkers of patients with or at risk of developing T2D are scarce and contradictory.[17] Among the limited observational studies involving obese children, one showed that serum 25(OH) D was significantly correlated with adiponectin,[26] while another showed that hypovitaminosis D was associated with higher circulating concentrations of serum IL-6 as well as biomarkers of oxidative stress and endothelial activation.[27] In our RCT of obese adolescents, we did not find any significant effects of vitamin D supplementation on inflammatory markers, however the serum leptin to adiponectin ratio was significantly lower in the vitamin D group compared with the placebo.[13] Due to the wide variability in inflammatory marker measurements among individuals, however, it may be that some of the studies were not adequately powered to detect differences among treatment groups. Further research using larger sample sizes is warranted.

Practice Recommendations and Conclusions

In 2010, the Institute of Medicine's (IOM) Food and Nutrition Board (FNB) established new dietary reference intakes (DRI) for vitamin D. The recommended dietary allowance (RDA) for individuals from one to seventy years of age was set at 600 IU per day and the tolerable upper intake level (UL) was raised to 4,000 IU per day for all individuals nine years of age and older.[6] While many of these values are more than double previous recommendations, they are not without controversy. The new DRI are based solely upon optimizing bone health, which has led several experts in the field to question their adequacy and/or appropriateness. Moreover, they do not take into account the increased need of specific

populations, such as dark-skinned or overweigh/obese individuals.

Results from adults estimate that non-obese require a 100 IU intake to increase serum concentrations of 25(OH) D by ~1.0 ng/mL;[7] while obese require twice the dose to see an equivalent response. Indeed, findings from the RCT of obese adolescents conducted by our laboratory showed that 4000 IU of vitamin D3 per day produced a mean increase of 19.5 ng/mL or, 1 ng/mL for every 205 IU ingested.[13] Despite this documented inefficiency, current American Academy of Pediatrics (AAP) recommendations for the treatment of pediatric overweight obesity do not mention obesity's effect on vitamin D status.[28] In contrast, the latest vitamin D recommendations from The Society of Adolescent Health and Medicine do recognize obesity as a risk factor for vitamin D deficiency.[29]

Conclusion

Both vitamin D and obesity are wide-spread health problems in US children, sharing some of the same risk factors and associated comorbidities. Based on available epidemiological and clinical data, excess adiposity is linked with poor vitamin D status and the negative effects of vitamin D deficiency during obesity seem to be primarily related to its action on glycemic control. Thus, it appears that it would be prudent for physicians to routinely monitor the vitamin D status of obese children and adolescents. Moreover, correcting vitamin D insufficiency through dietary supplementation may be an effective adjunct to the standard treatment of obesity-associated IR, IGT and T2D.

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Disclosure

None reported.

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School of Medicine
College of Human Environmental Sciences
College of Agriculture Food and Natural Resources

Increased Dietary Protein as a Dietary Strategy to Prevent and/or Treat Obesity

by Heather J. Leidy, PhD

These data illustrate that a diet rich in protein appears to be an optimal strategy to prevent and/or treat obesity.



Heather J. Leidy, PhD, is Assistant Professor in the Department of Nutrition & Exercise Physiology at the School of Medicine at Missouri University.
Contact: leidyh@missouri.edu

Abstract

Obesity in America continues to be a major public health concern. Emerging scientific evidence suggests that a diet rich in high-quality protein is a beneficial dietary strategy to prevent and/or treat obesity. This paper provides a brief synopsis of the latest research regarding the effects of higher protein diets to improve body weight management and energy intake regulation. Specific focus on the effects of increased dietary protein on appetite control, satiety, and food cravings are also explored.

Overview

High protein diets have gained both support and criticism over the past decade when recommended as a dietary strategy to prevent and/or treat obesity. Although numerous studies have shown improvements in energy intake regulation and body weight management, others postulate reduced diet quality and harmful effects on bone and kidney function. This paper provides clinical evidence supporting the role of higher protein meals and/or diets in promoting overall health. The effects of increased dietary protein on appetite control, satiety, and food cravings are also explored.

Dietary Protein Requirements

Dietary protein is essential for human health, promoting growth and development and providing energy throughout the lifecycle. The recommended dietary allowance (RDA) for protein is set at 0.80g protein·kg^{-1}·d^{-1} for healthy adults to prevent deficiencies. This quantity equates to approximately 48g of protein/d for women, 56g of protein/d for men, and is roughly 10% of daily intake.[1] Although current NHANES data show that most Americans are meeting this quantity,[5] additional benefits might exist with increased dietary protein above the RDA. As discussed below, recent studies have examined the effects of protein intake that is higher than the RDA. Such higher protein intake remains well within the acceptable macronutrient distribution range (AMDR) which has been set by the Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences as 10-35% of daily intake as protein.

Body Weight Management

In a recent meta-analysis involving 24 randomized, controlled trials of 1,063 overweight and obese individuals, changes in body weight and body composition were examined following 12.1 ± 9.3 weeks of controlled, energy-restricted diets containing either higher protein or standard protein intakes. Specifically,

the higher protein diets included 1.07-1.60g protein·kg^{1}·d^{-1} (27-35% of caloric intake as protein), whereas the standard protein diets contained 0.55-0.88g protein·kg^{-1}·d^{-1} (16-21% of intake as protein).[25] The meta-analysis showed that, compared to the standard protein diet, the higher protein version led to greater reductions in body weight (mean difference: -0.79 kg; CI: -1.50, -0.08; $p<0.03$) and fat mass (mean difference: -0.87 kg; CI: -1.26, -0.48; $p<0.001$) with increased preservation of lean mass (mean difference: +0.43 kg; CI: 0.09, 0.78; $p<0.01$).[25] Another meta-analysis was also recently performed but included randomized controlled trials that contained prescribed isocaloric diets with and without energy restriction.[20] The diets contained either higher protein (16-45% of daily intake as protein) or standard protein (5-23% of daily intake as protein).[20] This meta-analysis showed that, compared to the standard protein diet, the higher protein version led to greater reductions in body weight (mean difference: -0.36 kg; CI: -0.56, -0.17; $p<0.001$), body mass index (BMI; mean difference: -0.37 kg/m^2; CI: -0.56, -0.19; $p<0.001$) and waist circumference (mean difference: -0.43 cm; CI: -0.69, -0.16; $p<0.001$).

A large number of studies to date have examined the effects of higher protein intake in the context of controlled-feeding trials. However, two studies exist which provide useful data within a free-living, ad libitum feeding approach. As shown in Skov et al.,[21] overweight and obese adults completed a six-month dietary intervention consisting of either a higher protein (25% of daily intake as protein) or standard protein (12% of daily intake as protein) diet. Although protein consumption was tightly controlled, the participants were permitted to eat ad libitum. Over the six-month period, the higher protein diet led to greater weight loss compared to the standard protein diet (-8.9 kg vs. -5.1 kg, respectively; $p<0.05$) and greater fat mass loss compared to the standard protein diet group (-7.6 kg vs. -4.3 kg, respectively; $p<0.05$). Similar findings were also shown in another free-living, ad libitum feeding study by Weigle et al.[23] This trial was a single arm, control trial. The volunteers completed two weeks of a weight maintenance standard protein (15% of intake as protein) diet followed by two weeks of a weight maintenance higher protein (30% of intake as protein) diet. For the remainder of the 12 weeks, the volunteers were permitted to eat ad libitum as long as protein intake remained at 30% of daily calories. The consumption of the higher protein diet containing 30% of intake as protein led to an average weight loss of 5 kg over a 12-week period, 76% of which was fat mass[23].

Another critical research question in this area of body weight management is whether increased dietary protein might be a key strategy to prevent and/or reduce weight re-gain following weight loss. As shown in Westerterp-Plantenga et al.,[24] the addition of dietary protein following an energy restriction diet leading to approximately 10% weight loss led to a smaller amount of weight re-gain (17% weight re-gain) over a three-month period compared to no additional protein (37% weight re-gain, $p<0.05$).[24] In fact, most of the weight that was re-gained with the addition of protein was fat free mass, whereas the weight re-gained when no protein was added was mostly fat mass.[24] Similar findings were also evident in a follow-up study extended to six months of weight maintenance.[19] Other studies which have extended out to even longer periods (i.e., 8-13 months) also report sustained weight and fat mass loss with higher protein diets compared to standard protein versions.[3, 12] Collectively, these data support the role of increased dietary protein to lead to greater loss of weight and fat mass loss and to support maintenance of that weight loss over the longer-term.

Protein Sources
The key is to mix different protein sources into your daily routine to satisfy your hunger, including animal and plant proteins.

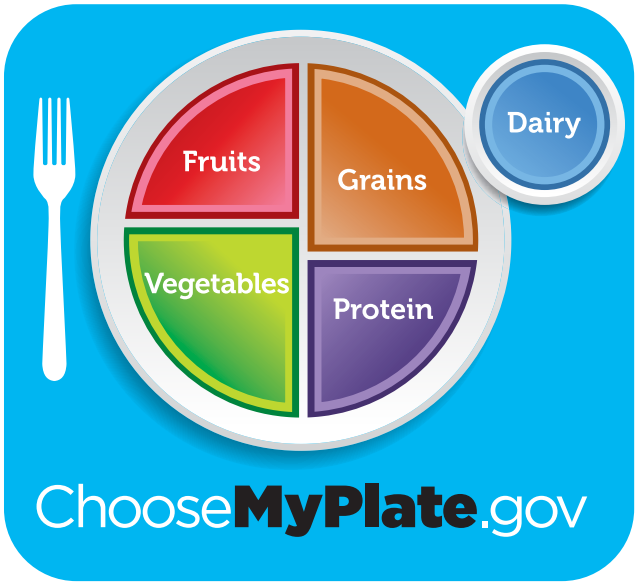


Regulation of Food Intake

The previous data illustrating greater weight loss during free-living, ad libitum feeding with increased dietary protein suggests an energy imbalance state potentially through spontaneous (i.e., voluntary) reductions in intake. Although the majority of previous studies incorporated controlled-feeding, Skov et al. and Weigle et al. allowed total intake to vary as long as protein intake was maintained.[21, 23] In both of these studies, increased dietary protein led to voluntary

MyPlate Icon

The new MyPlate Icon was introduced along with updating of USDA food patterns for the 2010 Dietary Guidelines for Americans with a different shape to help grab consumers' attention with a new visual cue. MyPlate illustrates the five food groups using a familiar mealtime visual, a place setting. The Icon serves as a reminder for healthy eating, and is not intended to provide specific messages.



reductions in total calorie intake of approximately 400 kcal/d.[21, 23] In most, but not all, acute controlled-feeding studies, the consumption of higher protein meals led to greater reductions in energy intake by as much as 600 kcal, at the subsequent meal, compared to normal protein meals.[2, 6] The substantial, spontaneous reduction in intake with increased dietary protein raises the question of the mechanism(s)-of-action supporting the improvement in energy intake regulation. Potential mechanisms include the improvements in appetite control and satiety frequently observed with increased protein consumption.

Appetite Control and Satiety

Physiological eating is a term used to describe eating in response to acute and/or chronic fluctuations in energy states such as fasting, meal omission, and weight loss. Physiological eating is typically assessed through markers of appetite control and satiety. These include perceived sensations of hunger and fullness (satiety) along with the key peripheral hormonal signals which initiate hunger (i.e., ghrelin) or satiety (i.e., CCK, PYY, GLP-1).

One of the first studies to identify the satiating effect of dietary protein included the consumption of 38 different foods, varying in macronutrient content.[8] Retrospective analyses identified a satiety hierarchy with the consumption of protein-rich foods leading to the greatest feeling of satiety followed by carbohydrate-rich foods and foods high in fat.[8] Since then, numerous acute, meal-related studies have been completed to compare higher versus standard protein meals on markers of appetite control and satiety.

Most, but not all, acute fixed-meal studies have illustrated significant postprandial reductions in perceived hunger and increased perceived fullness following the consumption of higher versus standard protein single meals.[6, 13] These responses have also been accompanied by hormonal responses including reductions in ghrelin and increases in plasma PYY and GLP-1.[13, 22] Other studies have also shown that increased dietary protein, provided at breakfast, lunch, and dinner, leads to immediate and sustained increases in perceived fullness and increased concentrations of plasma PYY, which occur throughout the day and into the evening hours.[14, 18]

Fewer studies have examined the effects of increased dietary protein during weight loss and/or weight maintenance (following weight loss) on markers of appetite control and satiety. During weight loss, higher protein, energy restriction diets led to greater perceived fullness (satiety) compared to standard protein versions.[10, 9, 15] Similar findings were also reported during weight maintenance following weight loss, such that increased dietary protein during weight maintenance led to greater perceived fullness compared to a standard protein diet.[24, 19] These data provide clear evidence supporting the role of increased dietary protein for improved appetite control and satiety.

Food Cravings

Physiological signals play a critical role in regulating energy intake during acute and/or chronic energy imbalance states. However, most Americans are driven to eat through hedonic, reward-driven signals triggered by the current obesogenic environment, which consists of free and easy access to highly palatable, energy-dense foods. Data from our lab has recently shown that higher protein meals can significantly impact reward-driven eating behavior. In these studies, overweight and obese individuals consumed either higher or standard protein meals. Using functional magnetic resonance imaging (fMRI), we identified the neural activation patterns in response to food stimuli prior to subsequent eating occasions. Compared to standard protein meals, the higher protein versions led to reduced activation in select cortico-limbic brain regions, including the insula, hippocampus, parahippocampus, and/or middle pre-frontal cortex.[16, 17] These regions are typically associated with food cravings, food reward, memories, thoughts and executive function. We also found that higher protein meals reduced unhealthy evening snacking on high fat and/or high sugar foods compared to standard protein

meals.[16,17] Although the data are limited, there is some indication that increased dietary protein positively impacts reward-driven eating behavior.

Increased Protein Quantity

Studies suggest that the amount of daily protein intake necessary to promote improvements in energy intake regulation and body weight management lies between 1.2-1.6g protein·kg^{-1}·d^{-1}, which is approximately 25-30% of intake as protein.[11,15] As previously stated, this is well within the acceptable macronutrient distribution range for protein and allows for the ability to meet the recommendations for other requirements. These include obtaining <30% of daily intake as fat and meeting the guidelines for fruits, vegetables, dairy, fiber. However, one point to consider is the fact that the majority of mechanistic data, particularly with appetite control, satiety, and protein synthesis (data not discussed), focuses on meal-specific quantities and not total daily intake. In these studies, approximately 30g of protein/eating occasion is required to elicit the biological changes associated with increased protein intake. Further research is needed to provide sufficient evidence to generate meal-specific recommendations.

Potential Harmful Effects of High Protein Diets

Although increasing evidence exists documenting the benefits of higher protein diets, there is concern for harmful effects of these diets primarily on bone and kidney health. Previously, high protein diets were suggested to increase bone resorption, increase urinary calcium, and increase the risk of fractures and osteoporosis.[7] However, as shown in Heaney, et al.[7] as well as the recent meta-analysis by Santesso, et al.[20] there is no effect of increased dietary protein on calcium metabolism and/or markers of bone health (i.e., bone mineral density in total body, lumbar, and spine; osteocalcium; and risk of fracture) in diets containing 1.0-1.96g protein·kg^{-1}·d^{-1} (16-45% of daily intake as protein). With respect to kidney function, high protein diets have been associated with kidney hypertrophy and increased glomerular hyperfiltration, which, over time, might lead to the development of chronic kidney disease. According to the meta-analysis by Santesso et al.,[20] two studies found slight increases in urinary creatinine (a marker of kidney health) with higher protein diets compared to standard protein versions and four studies showed no effect. Further, in a 24-month study, which is the longest protein-related study to date, Friedman, et al.[4] documented no harmful effects on indices of kidney function, including glomerular filtration rate, with the consumption of higher versus standard protein intakes. Although current research suggests that increased dietary protein within the recommended range appears to be a safe dietary strategy, additional long-term studies are warranted.

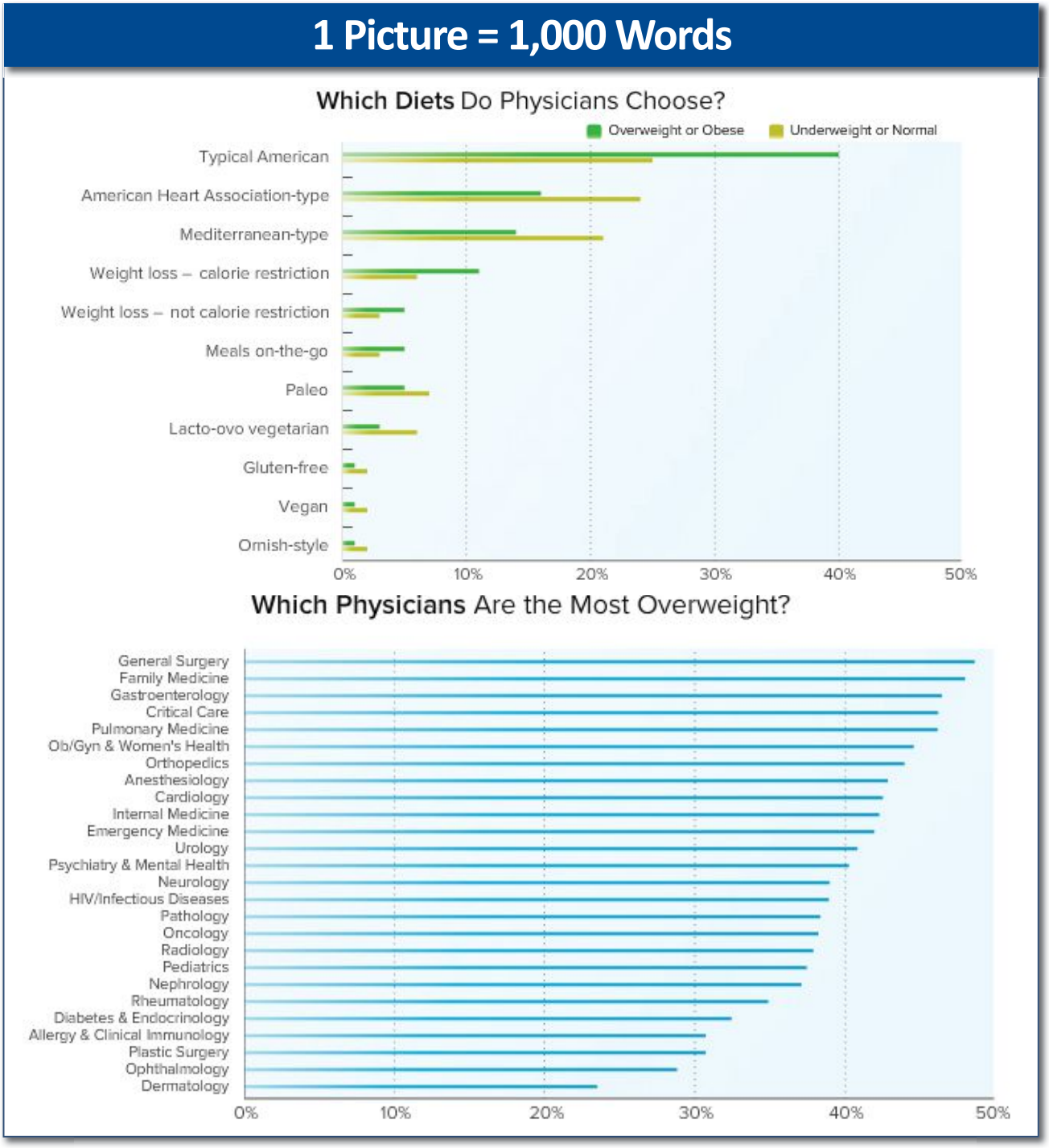
Summary

The consumption of higher protein diets, containing between 25-30% of calorie intake as protein, leads to significant improvements in body weight management, through voluntary reductions in energy intake, weight loss, and beneficial changes in body composition. One mechanism-of-action is due, in part, to improvements in appetite control, satiety, and reward-driven eating behavior. To date, the minimum amount of protein required to elicit these mechanistic responses is 30g of protein/eating occasion, which is approximately 1½ servings of high quality protein-rich foods. Further, no data exist suggesting that this quantity of protein consumption elicits any harmful effects on kidney and/or bone health. In summary, these data illustrate that a diet rich in protein appears to be an optimal strategy to prevent and/or treat obesity.

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1 Picture = 1,000 Words



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Disclosure

None reported.

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School of Medicine
College of Human Environmental Sciences
College of Agriculture Food and Natural Resources

Physical Activity and Bone Health

by Melissa I. Carter, MS & Pamela S. Hinton, PhD

Individuals who cannot tolerate high-impact modes of exercise should consider lower impact activities or progressive weight training that involves upper and lower body muscle groups.



Pamela S. Hinton, PhD, (left) is an Associate Professor and Director of Nutritional Sciences Graduate Studies, Nutrition & Exercise Physiology at Missouri University. Melissa I. Carter, MS, (right) received her Masters of Science in Exercise Physiology from MU.
Contact: hintonp@missouri.edu

Abstract

Osteoporosis and related fractures cause significant morbidity and mortality worldwide and result in enormous costs to affected individuals and society. Lifestyle choices across the lifespan impact osteoporosis and fracture risk. Physical activity is a viable strategy for the prevention and treatment of low bone mass.

Introduction: Osteoporosis

Osteoporosis, which is defined as "low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk",[1] is the most prevalent bone disorder. Currently, more than 75 million people in the United States, Europe, and Japan are diagnosed with osteoporosis, and over 4.5 million fractures occur annually in the United States and Europe.[2] Due to the increase in the aging population and the rise in life expectancy in recent years, the incidence of osteoporosis and related fracture risks are expected to increase.[3] According to the World Health Organization, osteoporosis is defined as a bone mineral density (BMD) that is two-and-a-half standard deviations or more below the average value for a young adult (T-score < -2.5).[2] Osteopenia is characterized as low bone mass, and is defined as a BMD that is between one and two-and-a-half standard deviations below the young adult mean (T-score between -1 and -2.5).[2] Low BMD is associated with increased risk of non-traumatic fracture; fracture risk is increased 1.5 to 3-fold or greater for each standard deviation decrease in BMD.[4]

Hip fracture is responsible for most of the mortality and morbidity associated with osteoporosis, and it is the leading cause of disability in the elderly.[1] It is well-established that the risk of death post-hip fracture is increased during the first three to six months after the injury.[5] Compared with women, men have a significantly greater risk for complications after a hip fracture, including increased morbidity, mortality, loss of independence, and rate of institutionalization.[5, 6] While hip fractures are associated with mortality, spine fractures are known to be a common source of pain, deformity, loss of height, and disability.[5] Among individuals with osteoporosis, a high proportion are bedridden with serious, life-threating complications.[2] Consequently, osteoporosis is a leading cause of mortality, morbidity, and medical expense worldwide,[2] as well as in the United States.[1]

Risk Factors for Fragility Fracture

Although BMD is an important determinant of fracture risk, non-traumatic fractures occur in individuals with normal BMD. In addition to BMD, there are other skeletal (e.g.,

abnormal rates of bone turnover) and non-skeletal (e.g., falling) risk factors for fragility fracture. Therefore, assessment of fracture risk should consider additional factors that predict risk independent of BMD.[7] Recently, a tool that evaluates fracture risk based on multiple clinical risk factors (See Table 1) was developed for assessment of fracture risk.[8, 9] FRAX® (www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture or a major osteoporotic fracture, which includes a clinical spine, hip, forearm or humerus fracture. The FRAX® tool more accurately predicts fracture risk than predictions based only on BMD.[8]

Table 1
Clinical Risk Factors for Fragility Fracture

- Age
- Sex
- Low body mass index
- Previous fragility fracture
- Parental history of fracture
- Glucocorticoid treatment
- Current cigarette smoking
- Alcohol use (>3 drinks/day)
- Rheumatoid arthritis
- Hypogonadism
- Physical inactivity, immobilization
- Thyroid disorders
- Diabetes

Treatment of Osteoporosis

There are two categories of drugs for the treatment of osteoporosis: anti-resorptives, which slow the rate of bone breakdown (resorption) and reduce fracture risk; and anabolics, which enhance bone formation, thereby lowering fracture risk. Although there is evidence supporting the efficacy of osteoporosis medications to improve bone health, the osteoporosis drugs are not without serious side effects. For example, the anti-resorptive bisphosphonates are associated with bone, joint or muscle pain, nausea, difficulty swallowing, heartburn, esophagitis, gastric ulcer, flu-like symptoms (intravenous bisphosphonates), osteonecrosis of the jaw, and spontaneous femur fractures (NOF). Estrogen therapy and estrogen plus progesterone therapy, which are used to prevent osteoporosis in women, may increase the risk of estrogen-sensitive cancers. In addition, some osteoporosis medications must be administered by injection or intravenously. Therefore, it is not surprising that drug treatments for osteoporosis have low rates of compliance and persistence, and most patients who stop taking their osteoporosis medication do not restart.[10]

Exercise-based interventions are an attractive alternative to medication due to the reduced cost, fewer serious side effects, and additional health benefits, including improved balance and fall reduction (See Figure 1).[11] Moreover, because osteoporotic fractures occur most frequently at the hip and spine, site-specific interventions to increase BMD are highly desirable. Physical activity allows for targeted strengthening of the hip and spine because sufficient skeletal loading stimulates net bone formation at the stressed skeletal sites.[12]

Prevention of Osteoporosis

Acquisition of at least 90% of peak bone mass occurs by age 18, with additional gains of 5% to 10% during young adulthood. Bone formation and bone resorption markers both decrease in pre-menopausal women and in men between the ages of 20 and 50, thus suggesting bone homeostasis.[13] Around age 50 in men and after menopause in women, bone resorption is significantly increased, thereby reducing bone mass.[13] Because bone mass declines with aging, maximization of peak bone mass has been recommended as one the most effective ways to prevent osteoporosis.[14] Nutrient deficiencies, endocrine disorders or physical inactivity during this critical period of skeletal growth can have lasting deleterious effects onbone health.[14] After acquisition of peak bone mass has occurred, minimizing the rate of age-related loss of bone mass and strength is the primary strategy for prevention of osteoporosis.



Figure 1
Exercise-based interventions are an attractive alternative to medication due to the reduced cost, fewer serious side effects, and additional health benefits, including improved balance and fall reduction.

Physical Activity

Physical inactivity is a modifiable risk factor for osteoporosis, and increasing physical activity at any point throughout the lifespan positively affects bone health,[15-19] while reductions in physical activity can result in bone loss.[20, 21] Cross-sectional and longitudinal studies have shown that the skeletal benefits of physical activity during adolescence persist into young adulthood, while activity-associated bone loading during young adulthood increases BMD in middle-age and older adulthood. In addition to increasing BMD, bone loading during adulthood increases bone size, cortical area and strength[22] and reduces hip fracture risk later in life.[18]

The American College of Sports Medicine recommends weight-bearing endurance activities, including those that involve jumping (such as tennis) and jogging, three to five times per week and resistance exercise two to three times per week to preserve bone health during adulthood.[23] Resistance training is recommended by the National Strength and Conditioning Association to increase BMD or to prevent age-associated reductions in BMD.[24] The Surgeon General's Report on Bone Health also recommends progressive resistance training, as well as daily jump-training and participation in weight-bearing recreational activities, for individuals who can tolerate high-impact activity.[1] However, there are no clinical trials that demonstrate the efficacy of these recommendations to decrease fracture incidence, and the effects of exercise-based interventions on BMD are mixed. Thus, the optimal exercise prescription (i.e., exercise mode, intensity, duration, and frequency) for bone health remains to be identified. The design of exercise prescriptions for bone health should be based on the mechanisms by which exercise affects bone and on the mechanical loading characteristics that result in the greatest increases in bone strength.

Exercise can affect bone via multiple mechanisms, including: muscle contraction forces, gravitational loading, and endocrine/paracrine effects. During physical activity, bone is subjected to mechanical forces exerted by muscle contraction and gravitational loading. At the cellular level, bone cells (osteocytes) perceive these mechanical forces as cell deformation, changes in extracellular fluid shear stress, pressure gradients and electric fields.[12] The osteocytes communicate with osteoblasts and osteoclasts to modulate bone formation and resorption thereby changing bone geometry and material properties.[25] Because most modes of physical activity involve both muscle contraction and gravitational loading, it is difficult to determine their relative effects on bone.

Muscle Contraction Forces

It is well accepted that bone adapts to the mechanical demands it is subject to, and muscle contractions contribute a portion of those demands.[26, 27] The importance of skeletal muscle contraction forces to bone mass is supported by the parallel changes in bone mass and muscle strength throughout the lifespan.[26, 28] Similarly, in states of muscular disuse that result in muscle atrophy, such as disease, inactivity, or paralysis, muscle contraction forces are severely reduced and there are site-specific reductions in bone mass and bone strength.[27] Infants born with intrauterine-onset neuromuscular paralysis exhibit normal bone length, but impaired cortical thickness and bone mass.[26] Because a fetus is exposed to a weightless environment in utero, the low bone mass and increased bone fragility observed in these infants can be attributed entirely to the absence of muscle contraction forces.

Site-specific differences in the relationship between skeletal muscle mass and BMD demonstrate the importance of muscle contraction to the preservation of bone mass. Studies of tennis players, in which the BMD of the dominant (i.e., racket) arm is compared to the non-dominant arm, demonstrate that the dominant arm has greater muscle and bone mass than the non-dominant arm.[28] Resistance training of the major muscle groups of the upper and lower body exerts muscle contraction forces on the arm and leg bones. In resistance-trained athletes, skeletal muscle mass is positively associated with BMD of the arms, legs, hip and lumbar spine.[29] In particular, the positive relationship between skeletal muscle mass and BMD of the arm—a non-weight-bearing skeletal site—suggests that muscle contraction forces make a significant contribution to skeletal muscle mass-associated increases in BMD. Cycling, unlike whole-body resistance training, results in repetitive exertion of muscle contraction forces on only the leg bones. Consequently, in cyclists, skeletal muscle mass is positively associated only with leg, but not arm, hip or spine, BMD.[29] Resistance-training intervention studies of either the upper body or unilateral resistance training of the lower body that resulted in increased muscular strength have shown mixed effects on BMD.[28, 30, 31]. However, we found that after 12 months of progressive, periodized resistance training, changes in arm skeletal muscle mass were positively associated with changes in upper body BMD.[31] Thus, there is considerable evidence that muscle contraction forces are important for bone strength.

Gravitational Loading

Gravitational loads are reactive loads resulting from contact between a weighted body (i.e., human) and a substrate (i.e., ground).[32] Gravitational loads are measured via ground reaction forces, which are determined by body mass and the acceleration/deceleration of the activity.[32] During high-impact activities, such as gymnastics, the ground reaction forces can be between 10 and 20 times body weight,[32] while low-impact, weight-bearing, activities



Figure 2
Athletes who play sports, which exert high-impact loading on the skeleton, such as soccer, volleyball, and gymnastics, have greater BMD and stronger bones.[2]

such as walking have ground reaction forces approximately equivalent to body weight.

Gravitational loading has a powerful influence on skeletal health,[32] which is evident by the marked loss of bone that occurs in a weightless environment. For example, during space flight, astronauts lose bone at a rate of up to 1% per week.[33] Although the astronauts are still actively using their muscles during everyday activities, the elimination of gravity and impact forces results in a dramatic loss of bone mass, which is greatest in weight-bearing skeletal sites.[33] Likewise, exercise in a weightless environment cannot prevent that bone loss that occurs in the absence of gravity.[34] Similarly, there is an accelerated rate of bone loss during bed rest.[35] Therefore, the findings from space flight and bed rest studies indicate that gravitational loading is necessary to preserveBMD at weight-bearing sites.[36]

As mentioned above, most modes of physical activity increase both muscle contraction forces and gravitational loading of the skeleton. Consequently, it is very difficult to isolate the effects of muscle contraction forces from those of gravitational loading, and it remains to be determined whether muscle contraction forces or gravitational loading is the dominant osteogenic stimulus.[32] Studies that compare athletes in sports that are non-weight-bearing, but load the skeleton via muscle contraction forces, with athletes in high-impact sports provide some insight into the relative importance of muscle contraction forces and gravitational loading to bone health.

Sports such as cycling and swimming involve muscle contraction forces on skeleton, but because body weight is supported, lack a gravitational loading component. Studies that have compared BMD of cyclists and swimmers to non-athlete controls and to weight-bearing-athletes consistently report that cyclists and swimmers have reduced BMD[37-42] and that differences persist when controlling for differences in body weight or lean body mass.[29, 37] A study comparing runners, cyclists, weight lifters, and non-athlete controls, showed that the cyclists and controls had similar BMD at all sites; whereas the weight lifters and runners had significantly higher BMD.[43]

Athletes who play sports, which exert high-impact loading on the skeleton, such as soccer, volleyball, and gymnastics, have greater BMD and stronger bones (See Figure 2).[27] Similarly, athletes who participate in the highest-impact sports (i.e. basketball and volleyball) have the highest concentrations of serum bone formation markers, as well as the greatest BMD when compared to athletes in moderate-impact sports (i.e. soccer and track), no-impact sports (i.e. swimming), and sedentary controls.[36] Athletes involved in non-impact sports have reduced hip BMD compared with athletes in high- and moderate-impact sports and did not differ from sedentary controls.[36] Thus, the stress associated with high-impact, weight-bearing sports may induce bone formation and enhance osteogenesis at weight-bearing skeletal sites.

Mechanical Loading Characteristics that Optimize Gains in Bone Strength

For well-over a century, it has been known that the stresses placed upon the bone determine its strength and architecture.[44] According to Wolff's Law, "Every change in the form and function of bone…is followed by certain

definite changes in the internal architecture, and equally definite alteration in their external conformation in accordance with mathematical laws."[45] In other words, the structural and material properties of bone change in response to mechanical loading. Studies in animal models allow identification of the characteristics of mechanical loading that induce the largest increases in bone strength. Mechanical loading, whether due to muscle contraction or gravitational loading, causes bone deformation. Strain is a measure of the magnitude of bone deformation in response to application of force. Strain magnitude, frequency, rate, and direction all impact bone's response to the applied force, as do the number of loading cycles and "recovery" between application of force.

Strain magnitude (i.e., amount of deformation) affects bone formation, with larger applied forces resulting in greater rates of bone formation. In the middle of the twentieth century, Frost determined that the stresses exerted on a bone must achieve a minimum effective strain before adaption occurs.[46] Thus, the bone deformation must reach a certain point before bone is added; likewise, if the stresses fall below a certain point, bone is lost.[27] Less than a decade later, it was found that the strain had to be dynamic (i.e., cyclic application and removal of external force), as opposed to static (i.e., constant application of external force), to induce an increase in bone strength.[44] More recently, it was determined that the frequency of the dynamic loading also influenced bone adaptions, with higher frequencies resulting in greater bone formation.[47, 48] The strain rate (i.e., the amount of deformation divided by time), which is related to strain magnitude and frequency, also affects the skeletal response to mechanical loading.[49]

Strain rates greater than habitual strain rate result in bone formation, while disuse-associated reductions in strain rate result in bone resorption. The strain direction also affects bone response, such that bone adapts to become stronger in the direction of applied force. For example, bones that are loaded in compression become stronger in compression, while those that are loaded in torsion are more resistant to fracture by application of torque. Thus, the skeletal response is specific to the strain direction, and the greatest bone adaptations happen with dynamic strains, at a magnitude or frequency that can be detected by the bone cells.[48]

In addition to strain characteristics, insertion of "rest" periods between loading cycles, bouts, and blocks enhances bone formation for a given number of loading cycles at a constant strain magnitude and frequency. For example, insertion of a 14-second rest between loading cycles resulted in a two-fold greater increase in bone formation compared with the response to loading with shorter rest intervals.[50] Longer bone-loading exercise bouts (i.e., more loading cycles) do not proportionally increase the bone formation response.[44] The detection of the mechanical signal requires that the bone cells be in a sensitive, receptive state.[48] After as few as 40-100 loading cycles, bone cells are desensitized to mechanical stimuli, such that additional loading, at a strain magnitude and frequency which would normally be osteogenic, has no effect on bone formation.[48] It appears that bone cells regain sensitivity to mechanical loading after ~ two hours and are fully sensitized after eight hours.[51] Likewise, insertion of a one-week rest block in a three-week "training" block resulted in nearly a two-fold greater increase in bone strength compared to three continuous loading blocks.[52]

Atypical stresses applied to bone drive adaptive changes.[44] The stresses that induce osteogenesis are not the numerous cycles of normal stresses that the bone experiences on a day-to-day basis; rather, the strains that induce bone formation are the atypical stresses to which the bone is not habituated.[44, 53] Thus, the bone cells become accustomed to the strains associated with repetitive activities, such as walking or running. However, activities, such as multi-directional jumping, that produce strains to which the bone is not habituated, enhance the bone formation response to increase bone strength.

Based on the our current understanding of the characteristics of mechanical loading that result in the greatest increases in bone strength, the "ideal" exercise prescription for bone health should include the following: load the skeletal sites of interest, high-impact activity, result in dynamic strain, be "unusual" and include rest between loading cycles (10-15 seconds), sessions (eight hours), and blocks (several days). In addition, when it comes to skeletal benefits of exercise, it is important to remember that more is not better—as few as 40-100 loading cycles per day is sufficient.

Practical Applications

The existing data from experimental animals, cross-sectional studies of athletic populations and from exercise-intervention studies support the exercise prescription of weight-bearing endurance exercise, activities that involve jumping, and resistance exercise that targets all major muscle groups for the preservation of bone mass. Ideal modes of activity are those that involve jumping and multi-directional movements, e.g., basketball or plyometrics. Thus, individuals who participate primarily in non-weight-bearing physical activities, such as cycling, swimming, or rowing, should be encouraged to add bone-strengthening

activities, including resistance training or jumping, to their training regimes. A simple, ten-minute program of physical activity that incorporates 50 three-inch, multi-directional jumps per day would meet these parameters.[1]

Likewise, resistance training, which increases skeletal muscle mass and strength, may benefit individuals whose primary mode of exercise does not involve impact forces. Individuals who cannot tolerate high-impact modes of exercise should consider lower impact activities or progressive weight training that involves upper and lower body muscle groups. For older adults, for whom falls are a significant contributor to fracture risk, physical activity should aim to improve muscle strength and balance. It is important to note that the maximal benefits of physical activity on bone health depend on adequate nutrient intake, in particular calcium and vitamin D intake, and on normal hormonal status.

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School of Medicine
College of Human Environmental Sciences
College of Agriculture Food and Natural Resources

Adipose Tissue Inflammation and Metabolic Dysfunction: Role of Exercise

by Young-Min Park, BS, Margo Myers, BS & Victoria J. Vieira-Potter, PhD

Obesity and physical inactivity are associated with chronic low-grade inflammation, which provides the common soil from which a myriad of metabolic diseases develop.



Young-Min Park, Margo Myers, and Victoria J. Vieira-Potter, PhD, are in the Department of Nutrition and Exercise Physiology, College of Human Environmental Sciences, at Missouri University.
Contact: vieirapotterv@missouri.edu

Abstract

Our current environment has led to a vicious cycle of physical inactivity, obesity, and chronic inflammation, creating the "perfect storm" for metabolic diseases. White adipose tissue (WAT) is the major source of obesity/inactivity-related inflammation; in turn, inflammation leads to insulin resistance and metabolic dysfunction. Inactivity, even in the absence of weight gain, disrupts WAT metabolism, while exercise mitigates WAT inflammation. The anti-inflammatory mechanism(s) of exercise require additional study. Two current hypotheses include: (1) exercise-mediated anti-inflammatory cytokine secretion, and (2) exercise-mediated improvements in adipocyte oxidative capacity.

Adipose Tissue Inflammation Leads to Metabolic Disease

Inflammation is an organism's multi-level response to protect itself from harmful stimuli and begin the healing process. Although in most cases inflammation is resolved quickly, when elimination of the initial trigger is not accomplished, or when the trigger is ongoing, acute inflammation becomes chronic. Obese individuals typically have a two to threefold increase in plasma concentrations of immune factors such as tumor necrosis factor (TNF)-α, Interleukin (IL)-6, monocyte chemoattractant protein (MCP)-1, C-reactive protein (CRP), and others. Such chronic low-grade inflammation is an underlying cause of cardiovascular disease (CVD), Type 2 Diabetes (T2D), some cancers, and many other metabolic diseases associated with obesity, inactivity, and aging.

Research over the past two decades has demonstrated that the major source of inflammation associated with obesity is the WAT. No longer considered an inert storage organ, the WAT is an active endocrine organ producing and secreting a plethora of cytokines, hormones and other factors collectively called "adipokines". When under metabolic stress, adipocytes produce inflammatory mediators and chemo-attractant molecules (e.g., MCP-1) that can both recruit and activate resident and nonresident immune cells. It is these immune cells, namely macrophages (Mϕ) and T-lymphocytes (i.e., T-cells), that perpetuate the inflammatory situation in the WAT. WAT Mϕ-derived inflammatory molecules such as TNF-α directly disrupt insulin signaling, leading to the development of insulin resistance (IR) and eventually T2D. Cytokine-mediated IR is one known mechanism

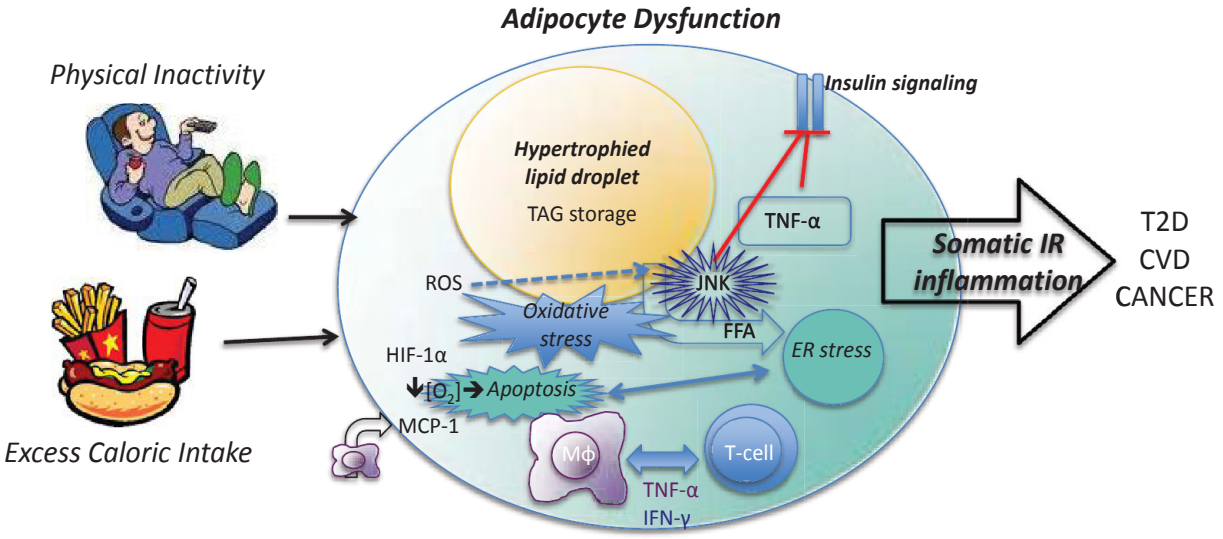


Figure 1

Physical inactivity and excess caloric intake lead to adipocyte dysfunction. Adipoycte hypertrophy results from excess TAG storage within lipid droplets. Excess FFA leads to adipocyte stress (e.g., ER stress) and the rapid expansion results in hypoxia and oxidative stress via activation of transcription factors such as HIF-1α. The "stressed" adipocyte expresses chemoattractant molecules (e.g., MCP-1) which help recruit Mϕ and T-cells; these immune cells become "primed" by inflammatory molecules (e.g., TNF-α, IFN-γ) produced both by the adipocyte as well as resident and recruited immune factors, some of which directly inhibit insulin signaling (e.g., TNF-α). Oxidative stress increases ROS which activate inflammatory transcription factors including JNK which directly inhibits insulin signaling. Under such metabolic stress, apoptosis may occur; dead adipocytes in turn recruit inflammatory Mϕ which exacerbate the inflammatory situation, leading to continued inflammation/IR both in the adipocyte and systemically. TAG = triacylglycerol; IR = insulin resistance; ROS = reactive oxygen species; HIF-1α = hypoxia inducible factor; MCP = monocyte chemoattractant protein; TNF = tumor necrosis factor; IFN = interferon; Mϕ = macrophage; FFA = free fatty acids; JNK = c-Jun activated protein kinase; ER = endoplasmic reticulum.

behind the strong relationship, evidenced by both human and animal studies, between WAT Mϕ infiltration and somatic IR.[1]

An important distinction that has emerged relatively recently is that obesity is associated with "classical" or "M1" Mϕ activation in WAT. When Mϕ take on an "M1" activation state, they secrete more inflammatory molecules such as TNF-α. It is speculated that these M1 Mϕ in turn activate T-cells to also secrete pro-inflammatory signals such as IFN-γ, and that these cytokines lead to Mϕ-T-cell cross activation. It is proposed that it is this immune cell/adipocyte cross-activation that leads to tissue specific and eventually systemic IR. Just as M1 Mϕ are inflammatory, alternatively activated "M2" Mϕ are anti-inflammatory and have been shown to mitigate IR. Similarly, T-cells can take on a more anti-inflammatory/regulatory role under certain environmental conditions. Thus, the metabolic dysfunction associated with WAT inflammation is not merely a consequence of immune cell infiltration per se, but of complex immune cell-adipocyte interactions that take place under specific environmental conditions.

Several mechanisms have been proposed to explain the etiology of WAT inflammation in obesity; however, the brevity of this review precludes a thorough discussion of these. Among the prevailing theories are: (1) increased adipocyte death secondary to hypoxia associated with adipocyte size expansion, (2) adipocyte-immune cell priming (as explained in a very simplified context above) and (3) intra-adipocyte metabolic stress. While the exact etiology of WAT inflammation remains unclear, inflammation arising from the WAT is the "common soil" that unites obesity, physical inactivity and metabolic disease (See Figure 1).

Obesity, Inflammation and Physical Inactivity – A Vicious Cycle

While physical inactivity and obesity tend to coexist, a growing body of evidence supports the concepts that: (1) physical inactivity is a direct cause of the inflammation and metabolic dysfunction associated with obesity; and (2) exercise training/physical activity can mitigate inflammatory and metabolic disturbances even in the absence of weight loss. Support for the first concept is that physical inactivity is associated with inflammation and metabolic dysfunction even in lean individuals. In a study of non-obese patients who exhibited low-grade systemic inflammation evidenced

by elevated plasma CRP and MCP-1, and lower insulin sensitivity, a brief period of complete inactivity exacerbated their inflammatory state, as indicated by a reduction in circulating adiponectin (an anti-inflammatory, insulin-sensitizing protein secreted from adipocytes) and increased abdominal WAT inflammation.[2] Even the healthy controls in that study exhibited an increase in gene markers of WAT inflammation after the inactive period. On the other hand, for any given body mass index, those who exercise regularly have lower levels of inflammatory markers.[3] This may help explain why ~20% of obese individuals are not afflicted with T2D, CVD, or various types of cancer traditionally associated with obesity.[4] In some cases, obese individuals who are physically active present a healthier metabolic profile than their inactive, yet leaner, counterparts. This is true across ages.

One study of overweight children showed that, compared to equally obese unfit children, aerobically fit children had lower systemic inflammation.[5] Another randomized controlled trial of overweight and obese asthmatics compared the effects of weight loss via diet, exercise, or the combination on asthma-related clinical outcomes.[6] While asthma control improved with each intervention, WAT reduction per se (assessed via Dual-energy X-ray Absorptiometry, "DXA") was associated with reduced airway inflammation. What's more, exercise per se was associated with a reduction in a specific subtype of bronchial inflammation. Those findings suggest that there are unique benefits of both fat loss and exercise training on inflammatory outcomes. A growing number of animal studies aim to determine the unique mechanisms behind exercise-related improvements in insulin sensitivity, ectopic lipid accumulation, systemic inflammation, and immune cell function. Many have demonstrated that the inflammatory and metabolic improvements occur in the absence of overall weight loss, suggesting that the mechanism goes beyond the obvious obesity-mitigating effect of exercise.[7,8] Our hypothesis is that exercise training may improve the overall health of the WAT, in part via anti-inflammatory mechanisms, and that such exercise-related improvements contribute to systemic metabolic improvements associated with exercise.

This is Your Adipocyte on Exercise: An Overview

Before a discussion of how exercise may reduce WAT inflammation, it is essential to provide a brief summary of exercise physiology pertaining to the adipocyte. Adipose

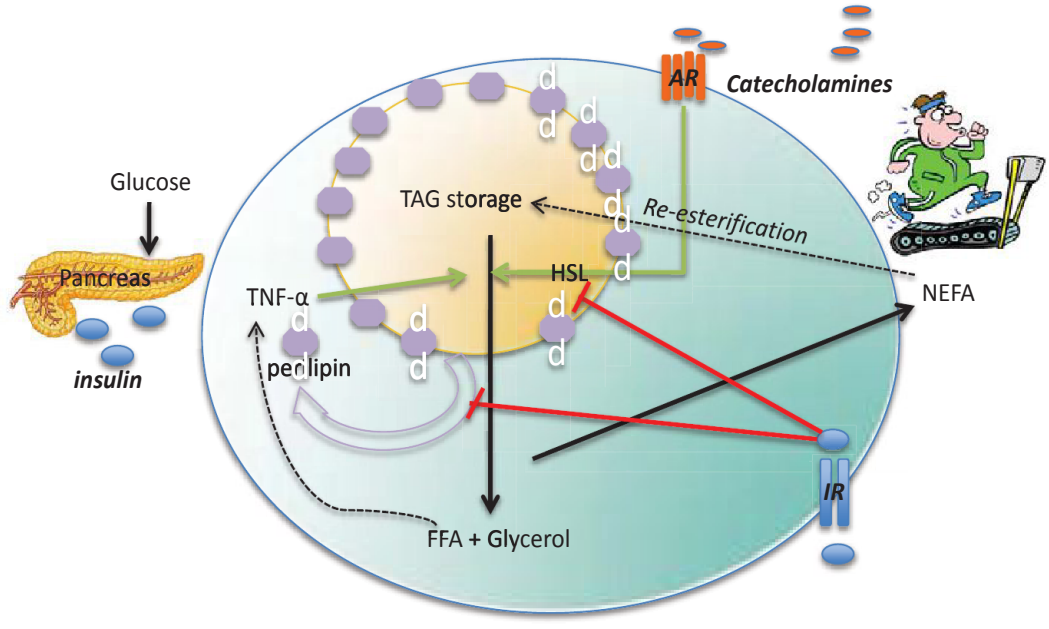


Figure 2
Adipocyte lipolysis is stimulated during exercise and inhibited by insulin. Catecholamines released during exercise bind to adrenergic receptors (AR) on the cell surface of adipocytes which ultimately phosphorylate (i.e., activate) lipases such as hormone sensitive lipase (HSL) allowing for TAG breakdown into FFA and glycerol. Lipid droplet proteins including perilipin are phosphorylated allowing them to dissociate from the lipid droplet surface; together these events allow for NEFAs to leave the adipocyte and enter the circulation where they are taken up by exercising skeletal muscle. Insulin inhibits this process while inflammatory cytokines (e.g., TNF-α) activate it. In the presence of high blood glucose, NEFAs are not taken up and therefore get re-esterified and re-enter the storage depot. Under IR conditions, insulin-mediated inhibition of lipolysis is diminished leading to a dyslipidemic blood profile as well as exacerbated inflammation within the adipocyte.

tissue is the body's largest energy reserve, storing upwards of 80,000 kilocalories of potential energy. With positive energy balance, adipocytes enlarge as they fill with lipid in the form of triacylglycerol (TAG); [9] excess energy storage over time leads to obesity and adipocyte dysfunction/inflammation, in part via mechanisms described above and illustrated in Figure 1.[10] Given its huge supply of stored energy, it is not surprising that adipose tissue is immensely affected by exercise, especially endurance exercise, which requires much more energy than that stored as glycogen in skeletal muscle and liver.[10] With negative energy balance, fatty acid utilization increases to meet energy demands and adipocytes shrink. As blood glucose levels become limited (e.g., during endurance exercise), WAT lipolysis increases as the body relies more on fatty acid oxidation.[11] Net whole body fat oxidation is determined by many factors that regulate both WAT lipolysis and skeletal muscle oxidative capacity. WAT lipolysis and skeletal muscle fatty acid oxidation are tightly linked such that WAT lipolysis increases plasma non-esterified fatty acid (NEFA) concentration, and NEFAs are taken up by exercising muscles in a concentration-dependent manner. NEFA oxidation is dependent on both the intensity and the duration of the exercise.[12]

Adipocyte lipolysis is stimulated strongly by catecholamines (e.g., epinephrine/norepinephrine released during exercise) and potently inhibited by insulin, as illustrated in Figure 2.[13] Briefly, catecholamines bind to adipocyte cell surface adrenergic receptors, triggering intracellular signaling events culminating in the phosphorylation of hormone sensitive lipase (HSL) by protein kinase A; phosporylated HSL mediates the hydrolysis of TAG resulting in the release of NEFAs and free glycerol from the adipocyte.[14,15] Lipid droplet proteins such as perilipin are also important regulators of lipolysis and, when active, allow for the hydrolysis of lipid droplets within adipocytes. Other important players in the stimulation of lipolysis are adipose triglyceride lipase (ATGL) and CG158. ATGL is a TAG hydrolase and the rate-limiting enzyme that promotes the catabolism of fat in both adipose and non-adipose tissues. Efficient ATGL activity requires activation by CG158, and upon stimulation of ATGL, release of fatty acids is increased.[16,17] On the other hand, insulin (which decreases during exercise) de-activates both HSL and lipid droplet proteins thereby inhibiting lipolysis.

Insulin Resistance (IR), Lipolysis and Exercise

WAT IR is associated with dysregulated lipolysis; meaning, insulin's ability to suppress lipolysis is reduced. What's more, inflammatory cytokines produced and secreted by the WAT stimulate lipolysis, thus leading to hyperlipidemia and a vicious cycle of inflammation, IR, and adipocyte dysfunction (See Figure 2). As adipocytes enlarge, they themselves become IR and resilient to further lipid accretion, an insulin-dependent process. This failure to store fatty acids leads to ectopic lipid accumulation in various tissues including skeletal muscle, liver, and pancreatic islets. Moreover, FFAs themselves induce IR via the activation of serine kinases, including c-jun N-terminal kinase (JNK), which disrupt downstream insulin signaling; this is referred to as lipotoxicity.[18-21]

One of the best-known metabolic effects of regular physical activity is increased whole body insulin sensitivity. It is well appreciated now that insulin-stimulated glucose uptake increases in the immediate post-exercise period; this is true in humans and rodents. The mechanism(s) by which exercise acutely enhances insulin sensitivity are not completely defined, although evidence has demonstrated improvements in skeletal muscle insulin signaling (i.e., enhanced expression of insulin signaling proteins including insulin receptor, insulin receptor substrates (e.g., IRS-1), and Akt phosphorylation) after acute exercise in both humans and rodents.[22,23] Such insulin-signaling improvements have been related to a reduction in skeletal muscle JNK activation, suggesting an anti-inflammatory mechanism by which acute exercise improves insulin signaling.[22]

Another mechanism by which exercise has been associated with improvements in skeletal muscle IR is through amelioration of de novo lipogenesis.[24] Obesity and inactivity are associated with ectopic lipid storage in liver and skeletal muscle, which contributes to systemic IR. Exercise training, by increasing both WAT lipolysis and skeletal muscle NEFA oxidation, may reduce the proportion of FFAs towards detrimental pathways, such as ectopic storage of fatty acid metabolites.[25] Since intramuscular triglyceride (IMTG) is an important source of fuel for skeletal muscle during high-intensity, exhaustive endurance exercise, training increases IMTG synthesis and storage, especially when NEFA accessibility is high-- this is known as the "athlete's paradox".[26] This metabolic paradox is likely explained by the fact that it is not the size of the IMTG pool, but rather the balance between fatty-acid availability, uptake, and oxidation, which determines IR. That is, by improving the balance between skeletal muscle FA uptake and oxidation, exercise may prevent the development of skeletal-muscle IR.[27]

Similar to the effects in skeletal muscle, exercise improves insulin sensitivity in the WAT. While the mechanism(s) behind exercise-mediated improvements in WAT insulin sensitivity are not fully understood, some work has shown improvements in insulin signaling, similar

to what happens in skeletal muscle with exercise training. Effects of exercise (i.e., two 3-hour bouts of moderate exercise) on insulin signaling in WAT (i.e., increased insulin-induced tyrosine phosphorylation of the insulin receptor and IRS-1; serine phosphorylation of Akt) have also been documented in rodents.[28]

Another possibility is that exercise improves IR in WAT by decreasing endoplasmic reticulum (ER) stress (i.e., increased expression of mutant proteins disrupt protein folding in the ER, activating a signaling network called the unfolded protein response which may ultimately trigger cell death). ER stress is triggered by obesity and/or cellular metabolic dysfunction and is associated with inflammation via activation of the JNK signaling pathway.[22] In one study, exercise training reduced phosphorylation of eukaryotic translation initiation factor 2-alpha kinase3 (PERK) and eukaryotic initiation factor 2 (eIF2), two markers of ER stress, in WAT and hepatic tissue of rats fed an high fat diet (HFD), which was associated with an improvement in insulin signal transduction and an inhibition of JNK activity.[22] Similarly, in another rat study, eight weeks of swim training resulted in JNK suppression and improvements in insulin signal transduction in WAT.[22] In summary, it is well understood that adipocyte physiology is intimately affected by exercise and exercise training; the effects of exercise go far beyond the regulation of lipolysis.

WAT as a Target Tissue for the Anti-inflammatory Effects of Exercise

A number of human trials and animal studies have demonstrated an inverse relationship between systemic inflammation (e.g, circulating CRP) and exercise training.[29,30] The mechanism driving this anti-inflammatory effect of exercise is not known, but may involve direct anti-inflammatory effects in the WAT. Certainly, by way of reducing total visceral adipose tissue, exercise serves to counter obesity-related WAT inflammation, since the visceral adipose tissue depot is most metabolic and inflammatory.[31] However, it appears that the anti-inflammatory effects of exercise go beyond simply reducing visceral adiposity.

Weight loss-independent, exercise-mediated reductions in WAT inflammation have been documented in humans[32] and rodents.[7,33] One study investigated the effects of a 15-week exercise intervention (i.e., 2-3 hours of moderate intensity walking, swimming, or aerobics, five days per week) on weight loss, insulin sensitivity, and inflammation (systemic, as well as gene expression in WAT and skeletal

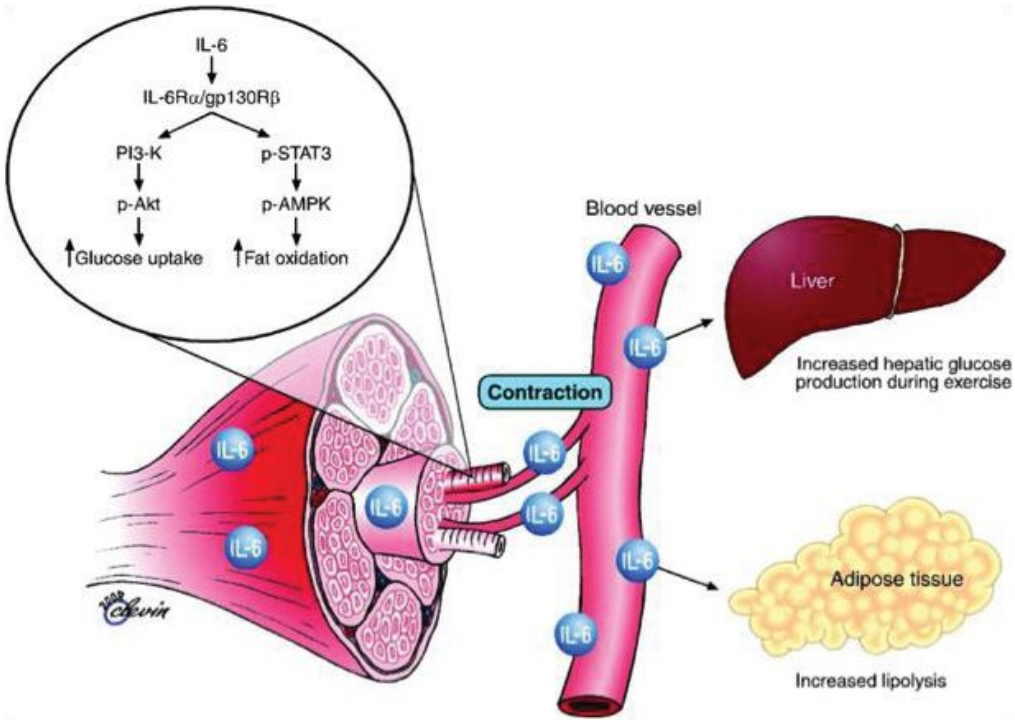


Figure 3. Biological role of skeletal muscle-contraction induced IL-6. Figure from Pedersen et al. 33 In response to muscle contraction, the myokine IL-6 exerts its effects both locally within the muscle through activation of AMPK, and peripherally in several organs in a hormone-like manner. IL-6 acts in an autocrine or paracrine manner to signal through a gp130Rβ/IL-6Rα homodimer, contributing to activation of AMPK and PI3 kinase to enhance glucose uptake and fat oxidation.

muscle biopsy samples) in severely obese subjects.[32] Those subjects experienced improvements in insulin sensitivity (as indicated by HOMA) and reduced systemic inflammation (e.g., decreased CRP, MCP-1; increased adiponectin).[32] Importantly, that study also found that WAT inflammation decreased with exercise, an effect that was not found in the skeletal muscle. In a similar study with animals, a reduction in WAT gene expression of CD68 and CD14 (Mϕ markers) and TNF-α were observed in morbidly obese rats exposed to acute swimming exercise for 12 weeks.[28] Similarly, in obese mice, moderate exercise training (6 or 12 weeks of treadmill running) lowered systemic and as well as WAT inflammation, anti-inflammatory effects that predicted improvements in IR and hepatic steatosis.[7] Another group showed that 6 weeks of voluntary wheel running exercise decreased WAT inflammation in obese mice, even in the presence of HFD.[33] Likewise, in genetically-obese rats, endurance exercise training in combination with the drug, metformin positively altered WAT secretion and plasma concentrations of leptin and IL-10, shifting the WAT toward an anti-inflammatory phenotype.[34] In another study using HFD-fed mice by Kawanishi et al., exercise training resulted in a marked reduction in WAT inflammation despite not weight-reducing effect of exercise.[35] Those authors went on to show that exercise was associated, not only with a reduction in total WAT Mϕ content, but an M1-M2 Mϕ phenotype switch.

Acute exercise has also been reported to have anti-inflammatory effects in WAT: a mild-moderate 3-h exercise bout reduced inflammation in the epididymal WAT (a major visceral fat depot) of rats as indicated by decreased mRNA levels of TNF-α, IL-1β, and MCP-1. Similar to the study by Kawanishi et al., there was also a switch in Mϕ phenotype from pro-inflammatory "M1" to anti-inflammatory "M2" phenotype in that study, suggesting that the mechanism may involve the acute hormonal/physiological/immunological changes associated with exercise.[28]

Cytokine-Mediated Effect of Exercise: A Possible Anti-inflammatory Mechanism

One hypothesis by which exercise improves WAT inflammation is via the secretion of myokines, which are cytokines released from exercising muscle cells. Similar to adipokines, myokines have been shown to exhibit their effects both locally and peripherally. IL-6 is one such recently identified myokine that has shown potential in possessing a protective metabolic role. IL-6 may exert beneficial metabolic effects via enhancement of lipolysis and mitigation of the inflammatory response in WAT (See Figure 3). Interestingly, IL-6 is commonly secreted by enlarged adipocytes and has been associated with reduced insulin action in WAT and systemically.[36] However, the identification of IL-6 as a myokine has brought a renewed interest in this cytokine.

Pedersen et al.[36] were the first to demonstrate that IL-6 is markedly produced by exercising muscle cells and released into the circulation during and after exercise. Plasma IL-6 levels increase exponentially with exercise and is related to exercise intensity, duration, mass muscle recruited, and endurance capacity of an individual. Produced by both type I and II muscle fibers, IL-6 acts to regulate glucose and lipid metabolism. In skeletal muscle, IL-6 activates AMPK and PI3 kinase to enhance glucose uptake and fat oxidation, and also exerts effects in a hormone-like fashion affecting other tissues such as liver (e.g., hepatic glucose production) and WAT (e.g., enhanced lipolysis). Additionally, IL-6 lessens circulating TNF-α levels, implying an anti-inflammatory role. Starkie et al.[37] used a model of low-grade inflammation established with a low dose of E.coli endotoxin administered to healthy individuals. The TNF-α response induced by endotoxin was totally blunted by a 3h bout of cycling exercise or an infusion with recombinant human IL-6. Consistent with these multiple beneficial effects, mice with IL-6 deficiency develop obesity and IR, effects that are reversed with IL-6 administration.[38] Thus, provocation of an increase in muscle IL-6 secretion may help explain some of the metabolic and anti-inflammatory effects of exercise.

Similar to anti-inflammatory effects of myokine during exercise, adipocyte-released adiponectin levels, which are inversely proportional to abdominal fat mass and IR, significantly increase with both acute and short-term aerobic exercise training.[39] Adiponectin inhibits nuclear factor κB (NFκB), an essential transcription factor for the expression of inflammatory and stress related proteins.[40] What's counter-intuitive is that adiponectin has been shown to stimulate rapid TNF-α secretion in human and mouse Mϕ. This, in turn, stimulates IL-10, an anti-inflammatory cytokine, thus creating tolerance to further LPS stimulation.[41] In summary, regular exercise training may protect against chronic low-grade systemic inflammation as well as adipocyte inflammation via the increased secretion of immuno-modulatory factors such as adiponectin from adipocytes, and IL-6 produced by skeletal muscle cells.

Exercise Makes Fat 'Fit': Role of PGC1-α

Transcriptional co-activator PPAR-γ co-activator-1 α (PGC1-α) can mediate many biological programs associated with energy metabolism, and has been shown to modulate oxidative metabolism via mitochondrial biogenesis. PGC-1α is highly expressed in brown fat tissue (BAT) and

up-regulated with cold exposure. Unlike WAT, which is used mostly for energy storage, BAT increases energy expenditure via heat generation due to inefficient fatty acid oxidation. This function of BAT is attributed to its greater mitochondrial content combined with its capacity to uncouple respiration and ATP production, via up-regulated uncoupling protein (UCP)-1.[42] This thermogenic capacity of BAT allows mammals to live below thermo-neutral conditions without shivering. Moreover, animals with abundant natural or induced BAT are resistant to obesity.[43]

In one study, mice with up-regulated PGC-1α were not only resistant to obesity and diabetes, but also had a prolonged life-span.[44] Human white adipocytes transfected with PGC-1α present increased levels of UCP-1, suggesting PGC-1α can remodel WAT into BAT; this is called "browning" of WAT.[45] Exercise up-regulates skeletal muscle PGC1-α, which is linked to mitochondrial biogenesis, angiogenesis, and fiber-type switching. In individuals with T2D, skeletal muscle PGC-1α mRNA levels are reduced [46] whereas the attenuated levels are restored by various types of exercise ranging from acute to chronic endurance.[47] Sutherland et al.[48] demonstrated that two hours of daily swimming exercise training for a month led to increases in markers of WAT mitochondrial biogenesis such as cytochrome-C oxidase (COXIV) and Core1 expression and citrate synthase activity, which are all driven by increased PGC-1α and mitochondrial transcription factor A (Tfam). Recently, a newly identified "exercise hormone", irisin, has received much attention due to its potential browning effect on WAT. The Fndc5 gene stimulated by PGC-1α in exercising muscle forms irisin, which is secreted into the circulation, and stimulates a biological program making WAT more like BAT via up-regulated PGC-1α and UCP-1 expression. Spiegelman and Bostrom[44] demonstrated that exercise (i.e., voluntary wheel running and swimming) in mice drives the subcutaneous and visceral fat pads into a thermogenic gene program (e.g., enhanced mitochondrial content and increased levels of UCP-1 gene expression) via triggering an increase in circulating irisin.

Exercise-related improvements in WAT mitochondrial function (i.e. enhanced PGC-1α) have been associated with reductions in visceral adiposity through greater lipolysis. What's more, enhanced WAT browning is associated with reduced inflammation, offering a hypothetical mechanism by which exercise is anti-inflammatory. A possible mechanism between browning and suppressed inflammation may be that PGC-1α directly suppresses reactive oxygen species (ROS) in WAT.[49] ROS are often associated with obesity-associated diseases; they increase oxidative stress and trigger inflammatory cytokine production (Figure 1).[49] Anti-inflammatory effects of PGC-1α have been demonstrated in vitro using skeletal muscle cell lines. That is, enhanced expression of PGC-1α in C2C12 myotubes suppressed inflammatory cytokine production.[50] It is possible that, via up-regulation of PGC-1 in WAT, exercise may reduce WAT inflammation thus constituting another possible anti-inflammatory mechanism.

Summary/Conclusions

Obesity and physical inactivity are associated with chronic low-grade inflammation, which provides the common soil from which a myriad of metabolic diseases develop. The main source of this inflammation is WAT, an active endocrine organ largely responsive to changes in physical activity and metabolism. An emerging body of evidence suggests that physical inactivity may directly and adversely affect the WAT, therefore leading to local and systemic inflammation. Exercise mitigates both systemic and WAT inflammation, an effect likely independent of exercise's obesity-reducing effects. That is, exercise training may reduce inflammation both by reducing total body fat, and by fat loss independent mechanisms. While the mechanism(s) by which exercise reduces WAT inflammation are not completely defined, there are convincing data to support several specific molecular pathways. Exercise may trigger immune-mediated cross-talk between adipocytes and skeletal muscle cells via exercise-mediated myokine secretion, enhance the metabolic capacity of adipocytes via increasing mitochondrial function/capacity, or directly affect immune cells (e.g., promote M2 Mϕ activation, decrease inflammatory cytokine production) within WAT.

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Disclosure

None reported.

MM

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Asymptomatic Coronary Artery Disease in Type II Diabetes

by Paramdeep S. Baweja, MD, Pratik B. Sandesara & M. Javed Ashraf, MD

Individuals with diabetes are at increased risk of asymptomatic Coronary Artery Disease, and Coronary Artery Disease is the leading cause of morbidity and mortality.



Paramdeep S. Baweja MD, Pratik B. Sandesara, and M. Javed Ashraf, MD, MPH, (above), MSMA member since 2014, are in the Department of Medicine, Cardiology Division at the Truman Medical Center, and the University of Missouri - Kansas City School of Medicine.
Contact: mjaved_ashraf@yahoo.com

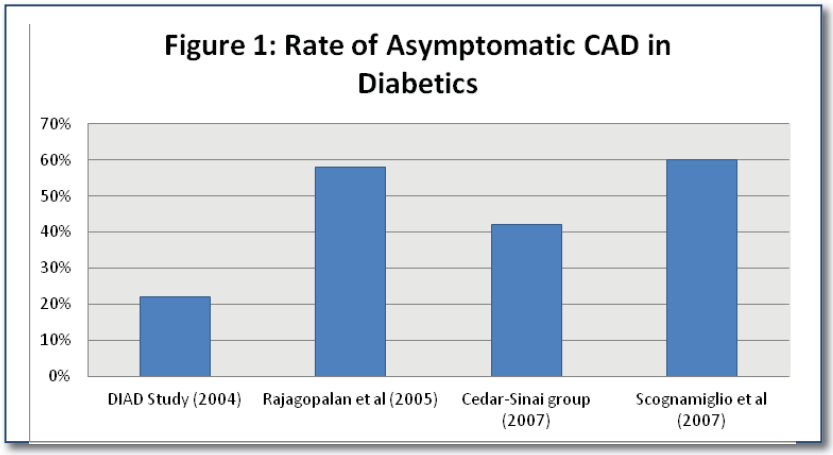
Abstract

Coronary artery disease is a major cause of morbidity and mortality in patients with diabetes mellitus and remains one of the largest burdens on health care resources. Prevalence of asymptomatic CAD in this population is high and poses a diagnostic challenge due to lack of overt clinical complaints. At this time there is no clear algorithm to screen for silent myocardial ischemia in diabetics. In this article we review various diagnostic tools available for assessment and propose a step wise approach for risk stratification in these patients.

Introduction

Currently, almost 11 percent (>25 million) of the adults in the United States have diabetes and 90-95 percent represents type II Diabetes (DMII).[1] The epidemic of diabetes is on an exponential rise as by the year 2030, 4.4 percent (366 million) of the world is projected to have diabetes from an estimated 2.8 percent (171 million) in 2000.[2] Coronary artery disease (CAD) is a major cause of morbidity and mortality and the biggest contributor to direct and indirect costs of diabetes.[3] Individuals with DMII have increased risk, faster progression and greater extent of CAD compared to non-diabetics.[4] Diabetes is considered a CAD risk equivalent, as the risk of myocardial infarction (MI) in a diabetic patient without prior history of MI is similar to the risk of re-infarction in a non-diabetic individual with a previous infarction.[5, 6] This confers a greater than 20 percent risk per 10 years for major coronary events, which is considered the highest risk category 5. The age of transition to high-risk category in DMII occurred approximately 15 years earlier for both men (at age 41) and women (at age 38) compared to non-diabetics.[7] Individuals with diabetes also have higher incidence of multi-vessel CAD (66 versus 46 percent) and a greater number of diseased vessels compared to non-diabetics.[8]

Cardiovascular death is the most common cause of death in diabetes and outcomes of coronary artery disease are worst in diabetics. The Multiple Risk Factor Intervention Trial (MRFIT) showed that over 12 years, cardiovascular disease caused 9.7 percent of the deaths in diabetic men compared to 2.6 percent in non-diabetic men and this difference was independent of age, ethnic group, cholesterol level, systolic



blood pressure, and smoking history.[9] Post-myocardial infarction, diabetes patients have twofold increase in 30-day and five-year mortality.[10, 11] In addition to the increased cardiovascular risk, one of the biggest concerns in diabetic patients is the high prevalence of asymptomatic CAD.

Prevalence of Asymptomatic CAD in Diabetes

An important aspect of cardiovascular disease in diabetes is the prevalence of asymptomatic CAD. Diabetics have increased incidence of silent ischemia and myocardial infarction that has been attributed to prolonged anginal perception threshold due to autonomic neuropathy involving sympathetic fibers innervating the heart. [12, 13, 14] Figure 1 illustrates the rates of asymptomatic CAD detected in several studies summarized here. In the Framingham Heart Study, diabetic men had almost twice the rate of clinically unrecognized infarctions compared to non-diabetic men (39 percent versus 18 percent).[15] In the Detection of Silent Myocardial Ischemia in Asymptomatic Diabetics (DIAD) study, 22% of the asymptomatic patients with type II diabetes had evidence of ischemia on stress myocardial perfusion imaging.[13] Another study reported 58% of asymptomatic diabetics had an abnormal positive stress single-photon emission computed tomography (SPECT) scan.[16] The Cedar-Sinai group reported in 42% abnormal SPECT scan with no differences between patients with angina and asymptomatic disease.[17] In a retrospective observational study by Scognamiglio et al., 60% of asymptomatic diabetic patients had an abnormal myocardial contrast echocardiography (MCE) and follow up coronary angiography was abnormal in 65 percent of the patients with an abnormal MCE.[18]

It is important to note that the difference in the prevalence of asymptomatic CAD in these studies can be attributed to selection bias in study design and the fact that retrospective studies showed higher prevalence than prospective studies. Even with the wide range in prevalence of asymptomatic coronary artery disease (20-60%), we can deduce that asymptomatic CAD has a high prevalence in individuals with DMII. These observations support the argument for screening for asymptomatic CAD in diabetic patients. In the remainder of this paper we will review the current data and guidelines on screening for CAD in diabetic patients.

Studies on Screening for Asymptomatic CAD in Diabetics

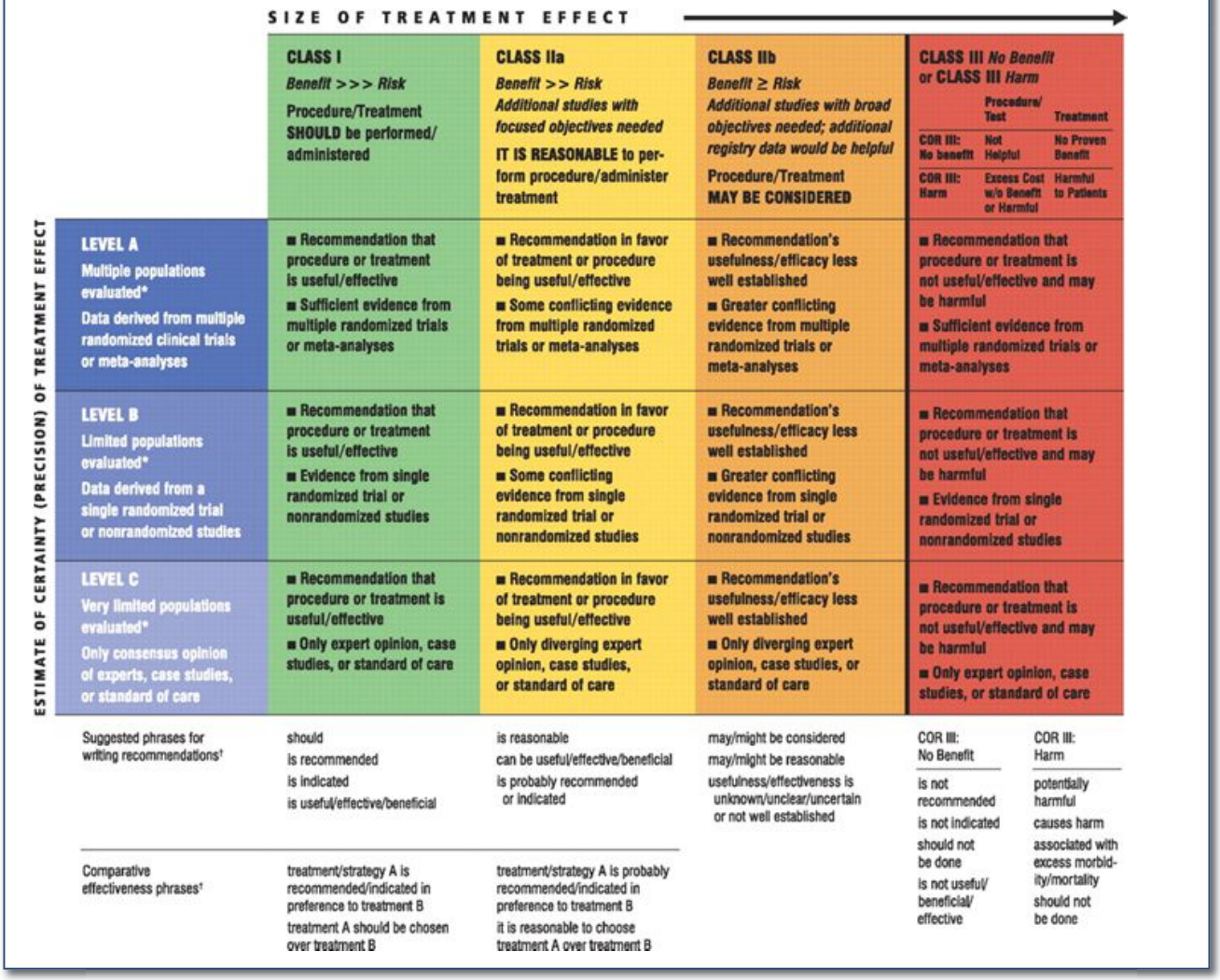
The DIAD study was a prospective, randomized, multicenter trial investigating the screening of CAD in asymptomatic diabetics.[13] In this study, 22% had myocardial perfusion defects with 6% of cohorts comprising moderate or large perfusion defects. This study also showed that the conventional risk factor screening approach recommended by the ADA did not predict an abnormal MPI.

The second part of the DIAD study showed that myocardial ischemia may reverse over time. In 56 (79%) of the 71 individuals (out of 358) with initial MPI abnormalities had resolution of ischemia at three-year follow-up and 10% of the individuals with normal initial MPI had abnormal MPI.[19] These changes were attributed to intensive risk factor reduction with increased use of ACE inhibitors, statins and aspirin in the group that demonstrated resolution of ischemia.

The third part of the study looked at effect of screening on cardiac event rates.[20] The overall cardiac event rate was 2.9 % at five years and did not differ significantly between the screened versus non-screened groups. The presence of perfusion defects predicted outcomes as individuals with moderate or large defects had 2.4% per year adverse event rate compared to 0.4% per year in the normal to mildly abnormal MPI. Even though there was no difference in clinical outcomes in the screened versus non-screened individuals, it is important to realize that this was a low risk group of patients.

Another prospective study used coronary artery

Figure 2: ACCF/AHA Applying Classification of Recommendations and Level of Evidence 22



ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT →			
	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	**CLASS IIa** *Benefit >> Risk Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	**CLASS III** *No Benefit* or **CLASS III** *Harm* (Procedure/Test: COR III: No benefit — Not Helpful; COR III: Harm — Excess Cost w/o Benefit or Harmful. Treatment: No Proven Benefit; Harmful to Patients)
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†	should; is recommended; is indicated; is useful/effective/beneficial	is reasonable; can be useful/effective/beneficial; is probably recommended or indicated	may/might be considered; may/might be reasonable; usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended; is not indicated; should not be done; is not useful/ beneficial/ effective — COR III: Harm: potentially harmful; causes harm; associated with excess morbidity/mortality; should not be done
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B; treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B; it is reasonable to choose treatment A over treatment B		

calcium (CAC) score and SPECT MPI to determine the rate of silent ischemia in DMII.[21] It concluded that coronary calcium score was a better predictor of silent ischemia and short-term cardiovascular events than established cardiovascular risk factors. In addition, CAC and MPI can be used synergistically to predict adverse cardiovascular events but the effect on clinical outcome of patients is unknown.

These two studies do not make a strong argument for screening asymptomatic diabetics for CAD due to failure to show improved outcomes from screening for silent ischemia. However, it is important to note that the patients in the DIAD study were at a low risk for cardiovascular events and the sample size was relatively small.

Various Screening Modalities

As noted earlier, individuals with diabetes are at increased risk of asymptomatic CAD and CAD is the leading cause of morbidity and mortality. With the incidence of diabetes rising at an epidemic proportions, it is important to risk stratify individuals to better manage cardiovascular outcomes. In the following sections we review the various modalities available to screen for CAD.

Exercise Electrocardiography

Exercise Electrocardiography (ECG) stress test offers good prognostic value. Poor prognosticators include poor exercise ability (<5 METS), exercise induce angina, low peak BP, fall in BP during exercise, chronotropic incompetence and ventricular arrhythmias.[22] Patients might not be able to satisfactorily perform a standard treadmill

test due to reduced exercise capacity or presence of peripheral artery disease. ECG abnormalities might occur late in the ischemic cascade leading to lower accuracy of exercise ECG. ECG stress testing has 50% sensitivity and 80% specificity and it may be considered for CV risk assessment in intermediate-risk asymptomatic adults.[23]

Myocardial Contrast Echocardiography

Several studies have shown prevalence of ischemia using myocardial contrast echocardiography (MCE) in diabetic individuals.[18, 24] Sixty percent of asymptomatic diabetic patients had abnormal MCE that was irrespective of the number of risk factors and 65 % of them had CAD on angiography.[18] This study showed that significant CAD existed in asymptomatic diabetics that were independent of the risk factor profile. Patients with two or more risk factors had higher rate of three-vessel disease, diffuse disease and vessel occlusion indicating more severe disease.[18] MCE has an overall sensitivity and specificity of 89% and 52% respectively for detection of CAD in diabetic patients. [24]

Coronary Artery Calcium Score

Coronary Artery Calcium (CAC) score can be measured via Electron-Beam Computed Tomography (EBCT) and Multi-Slice Computed Tomography (MSCT) as noninvasive quantification of coronary atherosclerosis burden to identify asymptomatic patients at high risk for CAD. Several studies have shown that CAC measurement can be used a predictor of cardiovascular events in asymptomatic diabetic patients and can extend beyond conventional risk factors.[21, 25, 26, 27] In 10,377 individuals (903 diabetic patients), Raggi et al., concluded that diabetics had a higher CAC and mortality (3.5% versus 2.0%) compared to non-diabetics over a five year follow-up.[25] Mortality increased in proportion to screening CAC in asymptomatic diabetic patients. Interestingly, with a CAC of zero, the survival rates for diabetics and non-diabetics were similar.

In a study by Anand et al., one-third of the patients had a coronary calcium score of >400 and 28 percent of those had inducible ischemia.[21] The Diabetes Heart Study showed that CAC was an independent predictor of mortality with the risk of mortality increasing with increased level of CAC.[26]

CAC score can be used as an initial screening test in high-risk individuals at risk for inducible ischemia, but is less predictive in patients with renal insufficiency and the elderly even though they have high prevalence of coronary calcification, limiting the diagnostic value.[28] To optimize screening of asymptomatic diabetic patients, those with CAC score >400 should be further evaluated using other imaging modality to assess myocardial perfusion or wall motion abnormalities.[28] According to the ACCF/AHA guidelines for assessment of cardiovascular risk in asymptomatic adults, CAC score measurement can be used for cardiovascular risk assessment in asymptomatic diabetics >40 years of age (class IIa, level of evidence B. Check Figure 2 for details on the classification).[23]

Myocardial Perfusion Imaging

Myocardial Perfusion Imaging (MPI) defects as a marker for CAD can be analyzed via single-photon emission computed tomography (SPECT) and Positron Emission Tomography (PET) scan. Stress SPECT has been shown to be useful in detection of asymptomatic CAD in DMII patients. Studies have reported[22, 33, 42] and 58 percent abnormal SPECT rates in asymptomatic diabetics.[13, 29, 16, 17] In addition, several studies have confirmed that stress SPECT provides incremental prognostic value to achieve adequate risk stratification in diabetics.[30, 31, 32] SPECT has similar sensitivity and specificity in diabetic and non-diabetic individuals. Kang et al., reported a sensitivity and specificity of 86 and 56 percent in 138 diabetic patients, which is similar in non-diabetics.[33]

More recently, the J-ACCESS 2 investigation evaluated the prognostic value of gated myocardial perfusion imaging on asymptomatic Japanese DMII patients.[34] The study showed that patients with summed stress scores greater or equal to 9 had 1.9-fold increase in rates of cardiovascular events or death, hence abnormal MPI may have high prognostic value to predict increased risk of CV disease in asymptomatic diabetic patients.

One prospective randomized trial (DIAD study) has concluded that initial screening with stress MPI did not affect the five-year outcomes in screened versus non-screened asymptomatic diabetic patients as mentioned earlier. [20]

Although stress SPECT scan has been shown to have prognostic value it does have some drawbacks. One of the concerns is that the extent and severity of perfusion abnormalities exceeds that predicted by coronary angiography in diabetic patients. For example, in the study by Rajagopalan et al., 40% of the patients with high-risk MPI had mild angiographic CAD.[16] Normal stress SPECT is associated with higher risk in diabetic compared to non-diabetics.[17, 31, 35] SPECT and PET scans expose patients to

Table 1: ADA Guidelines for diagnosis of CAD in Diabetic Patients
Typical or atypical cardiac symptoms
Resting EKG suggestive of ischemia or infarction
Peripheral or carotid occlusive arterial disease
Sedentary lifestyle, age >35 years, and plans to begin a vigorous exercise program
Two or more of the risk factors listed below (a–e) in addition to diabetes
a) Total cholesterol >240 mg/dl, LDL >160 mg/dl, or HDL <35 mg/dl
b) Blood pressure >140/90 mmHg
c) Smoking
d) Family history of premature CAD
e) Positive micro/macroalbuminuria test

ionizing radiation and should only be used in those whom the benefits outweigh the risks. One way to enhance the yield of stress SPECT in asymptomatic DMII patients is to combine it with CAC score. As mentioned earlier, Anand, used coronary artery calcium (CAC) score and SPECT MPI to determine the rate of silent ischemia in DMII. Myocardial ischemia was detected on SPECT MPI in 48 and 71.4 percent of diabetic patients with CAC >400 and >1000 respectively.[21] They concluded that CAC and MPI can be used synergistically to predict adverse cardiovascular events but the effect on clinical outcome of patients is unknown. It is also important to consider that diabetics have a faster progression of atherosclerosis as cardiac events can occur two years after a normal stress MPI.[35] According to the ACCF/AHA guidelines for assessment of cardiovascular risk in asymptomatic adults, stress MPI may be considered for CV risk assessment in asymptomatic diabetics and those with CAC >400 (Level of evidence: C).[23]

Coronary Computed Tomography Angiography

Coronary Computed Tomography Angiography (CCTA) provides a morphologic examination of the coronary arteries. CCTA has sensitivity and specificity of 85-95% and a negative predictive value of >98%.[23,36] A study of 140 asymptomatic diabetic patients who underwent CCTA concluded that the prevalence of CAD is higher in DMII patients compared to nondiabetics resulting in three-fold higher rate of cardiac events (1.8% versus 0.5 percent per year) and that CCTA can provide predictive value in addition to traditional risk factors in diabetics.[36] Choi, et al. concluded that a significant number of diabetics with normal ECG, SPECT and no peripheral artery disease had evidence of occult CAD on CCTA.[37] The drawbacks of CCTA include the risk of contrast nephropathy, radiation exposure, lack of information concerning ischemia and sub-optimal view of vessel distal bed. CCTA is not recommended to assess need for revascularization as MPI provides better functional assessment compared to CCTA. Current ACCF/AHA guidelines do not recommend CCTA for CV risk assessment in asymptomatic adults (Class III, Level of evidence: C).[23]

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) can be used as a non-invasive coronary angiogram and can also provide functional (myocardial perfusion) and anatomical (ventricular function, wall motion) information without radiation exposure. MRI is less accurate than CT for diagnosing coronary stenosis especially in vessel distal bed analysis. In a prospective trial of 752 patients cardiovascular magnetic resonance imaging (CMR) was superior to SPECT in detection of clinically significant CAD with higher sensitivity (86.5 versus 66.5 percent), specificity (83.4 versus 82.6 percent) and positive (77.2 versus 71.4 percent) and negative predictive values (90.5 versus 79.1 percent).[38] MRI has the potential to provide information on atherosclerosis plaque vulnerability to identify individuals at high risk for acute

coronary syndrome.[39] Coupling of non-invasive imaging of coronary arteries with pharmacological stress test to assess the intensity and location of ischemia could make MRI the gold standard for CAD detection. Although the above study showed positive results for the use of MRI, further studies are needed in asymptomatic individuals, especially diabetics. Current ACCF/AHA guidelines do not recommend use of MRI for risk assessment in asymptomatic adults (Class III, Level of evidence: C).[23]

Should We Screen Asymptomatic Patients?

Studies have shown the prevalence of asymptomatic CAD to be 20-60% in diabetics providing a rationale for screening this population. Before screening can be recommended, certain criteria should be met: the prevalence of CAD in the population should be high, screening test should accurately differentiate between low and high risk patient, identification of individuals with disease should lead to treatment with better outcomes and the screening strategy must be cost-effective.[40] There is lack of evidence of improved outcomes in asymptomatic diabetic patients to supports screening for silent ischemia at this time.

Current Recommendations & Guidelines on CAD Screening

The 1998 ADA guidelines for diagnosis of coronary artery disease in patients with diabetes are shown in Table 1.[41] Since the 1998 guidelines, several studies have shown that the risk stratification according to the number of risk factors has not been shown to be effective in asymptomatic diabetics.[13,16,18] A recent post hoc analysis of the high-risk participants in DIAD study found that annual cardiac event rate was not altered by routine screening for silent ischemia. [42] With the currently available evidence, one must question the cost effectiveness of indiscriminant screening. It is unclear what the implications are beyond risk stratification. The American Diabetes Association does not recommend routine screening for CAD in diabetic patients, as it does not improve outcomes as long as the cardiovascular disease risk factors are treated. [3] In our opinion a stepwise screening with CAC score followed by SPECT, if necessary, is reasonable and may allow for optimal risk stratification of asymptomatic diabetics based on currently available data.

Medical Interventions

Since diabetes is already established as a CAD risk equivalent, screening for CAD will not alter medical treatment as it already warrants optimal medical therapy. The ADA guidelines recommend cardiovascular risk assessment annually and treatment of these abnormal risk factors (risk factors include dyslipidemia, hypertension, smoking, coronary disease and presence of micro- or macro-albuminuria).[3] Patients with known CAD should be treated with Angiotensin Converting Enzyme (ACE) inhibitor, aspirin and statin to decrease risk of cardiovascular events.

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial did not show a reduction in the risk of death, myocardial infarction, or other major cardiovascular events with PCI in addition to optimal medical therapy.[43] Diabetics comprised 33 percent of the patients in this study but they had stable coronary artery disease.

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study showed that compared to intensive medical therapy alone, prompt coronary revascularization in addition to intensive medical therapy did not reduce all-cause mortality or the composite of death, myocardial infarction or stroke.[44] COURAGE and BARI 2D trials shown that optimal medical therapy is comparable to revascularization in diabetic patients diagnosed with stable CAD.

Conclusion

Coronary artery disease is a major cause of morbidity and mortality in patients with diabetes mellitus. The rate of asymptomatic CAD in this patient population is high. There is a lack of evidence to support screening for silent myocardial ischemia in diabetics and the ADA guidelines do not recommend screening for asymptomatic CAD. After reviewing the data, we feel that stepwise screening with CAC score followed by SPECT MPI if necessary is a reasonable option for risk stratification in diabetic patients. Future prospective trials are needed to provide better guidelines on this issue.

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Disclosure

None reported.

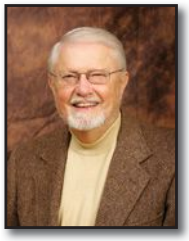
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Nicotine Addiction Treatment: A Review

by Donald A. Potts, MD & John S. Daniels, MD

Nicotine is powerfully addictive, and cigarette smoking is the greatest preventable cause of premature death in the United States.





Donald A. Potts, MD, (left) MSMA member since 1977, is Emeritus Associate Professor, UMKC School of Medicine; he is certified in tobacco treatment and received The Surgeon General's Award for tobacco use prevention. John C. Daniels MD, MSMA member since 1979, is the *Missouri Medicine* Editorial Board member in Internal Medicine. He practices in St. Louis.
Contact: PottsD@umkc.edu

Abstract

Tobacco use in the United States has decreased by almost 50 percent since 1965, although the decline over the past few years has stalled. In the high school student population the smoking rates have not only plateaued over the past several years but have even increased. This paper will discuss the pathophysiology of tobacco addiction and treatment options for smoking cessation.

Introduction

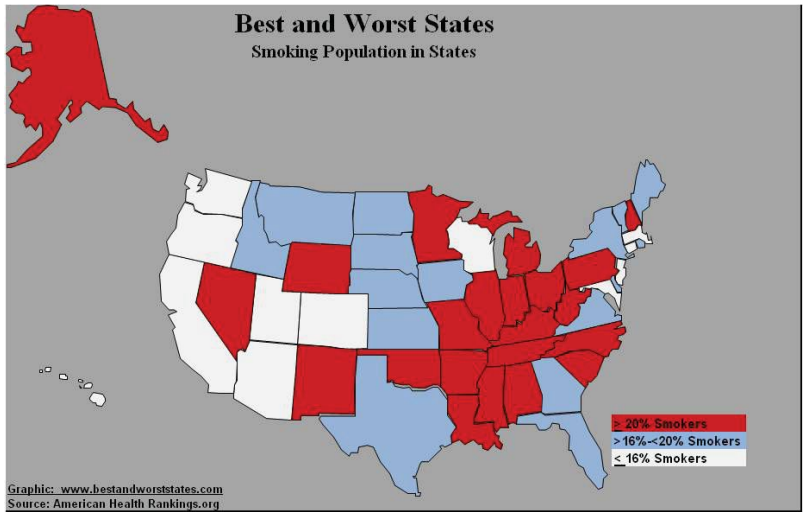
Cultivation of tobacco began in the Americas by the Mayan Indians several hundred years B.C. Tobacco was first cultivated by European settlers in Virginia in the early 1600s, and Sir Walter Raleigh has been credited by some for introducing tobacco in England in the 1580s. The use of cigarettes became widespread in the 1900s with the advent of modern day advertising. By the 1960s over 40 percent of the adult United States population smoked cigarettes. Today approximately 20 percent of adults and high school students smoke cigarettes.[1] (See Figure 1)

By the 1930s reports of a marked increase in lung cancer prevalence began to emerge and many physicians attributed this increase to the use of cigarettes. The tobacco industry fought these reports until the 1964 Surgeon General's report which clearly linked the use of cigarettes to the development of lung cancer, emphysema, and chronic bronchitis.[2] Only since the 1980s have the majority of Americans been convinced that tobacco use is the cause of these fatal lung diseases.

According to the National Institutes of Health, nicotine is powerfully addictive and cigarette smoking is the greatest preventable cause of premature death in the United States. Cigarette smoking accounts for one out of five deaths, 87 percent of lung cancer deaths, and at least 30 percent of all cancer deaths each year in the U.S. Individuals who quit smoking prior to the age of 50 reduce by half their risk of dying in the next 15 years.[3] (See Figure 2.)

Of the 7,000 compounds that are produced when tobacco is burned, only nicotine seems to be truly addictive. At least 69 of these compounds have been shown to be carcinogenic, and many others are known toxins such as arsenic, formaldehyde, polonium 210, benzene, cadmium, nitrosamines, and hydrogen cyanide.

Figure 1
Best and Worst States / Smoking Population in the U.S.



Because it is the nicotine present in all tobacco products that is responsible for the addiction, most smoking cessation programs have paradoxically utilized nicotine in the treatment of tobacco addiction. The role of e-cigarettes in tobacco treatment is rapidly evolving (See sidebar page 82) Physicians are in a unique position to counsel their patients about the hazards of tobacco use and prescribe steps in aiding smoking cessation.

Pathophysiology of Nicotine Addiction

Addiction is defined as a continued repetition of a behavior despite adverse consequences, and can include (but is not limited to) addiction to drugs such as nicotine or narcotics, and addiction to behaviors such as overeating, sex, exercise, and gambling. Physiological addiction is characterized by tolerance to a substance and withdrawal symptoms when the substance is reduced or discontinued. Withdrawal symptoms include anxiety, irritability, intense craving for the substance, headaches, and many others.[4]

Nicotine produces its mood altering effects by activating nicotinic acetylcholine receptors located in the brain's mesolimbic reward system. These dopaminergic neurons release the neurotransmitter dopamine, giving rise to the pleasurable effects of nicotine which include a mild pleasurable rush, mild euphoria, increased arousal, decreased fatigue, and relaxation. Experimental studies clearly demonstrate the importance of dopamine in producing these pleasurable effects of nicotine. In addition, it has been shown that dopamine transmission is decreased during withdrawal of nicotine. Several treatment strategies are based upon this dopaminergic neuronal transmission and will be discussed later in this paper.[5]

According to the National Institutes of Health, most smokers use tobacco regularly because they are addicted to the nicotine. It is well documented that most smokers identify tobacco use as harmful and express a desire to reduce or stop using it. However, for the 35 million Americans who attempt to quit smoking each year, 85 percent relapse usually within the first week of withdrawal. The irritability, craving, depression, anxiety and sleep disturbances that usually begin within a few hours after the last cigarette and peak within the first few days of smoking cessation are too much for most individuals to overcome. Even those abstinent smokers who are successful in the short term remain vulnerable to relapse for months or even years after cessation of tobacco use. As with other addictive drugs, relapse occurs upon exposure to environmental stimuli that individuals associate with the rewarding effects of the nicotine.[6]

Nicotine Cessation Treatment Options

Physician Intervention

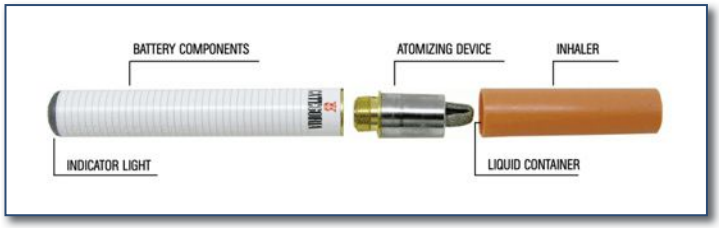
Recently it was reported that only slightly more than half of United States physicians asked their patients whether they used tobacco. Yet there is good evidence that physician intervention results in improved outcome in smoking cessation attempts. First physicians should



Electronic Cigarettes: 'Safe' or a "Pack of Lies"?

by John C. Hagan, III, MD

Electronic (E)-cigarettes have a heating element powered by a small battery. Most of these are the size and shape of a king-size cigarette. When activated they have a LED glow on one end. Through the other end, the user inhales vaporized nicotine from a cartridge in the device and exhales (usually glycerol or propylene glycol) a reasonable facsimile of tobacco smoke. Besides the physiological addictive effects of nicotine, the user has the tactile feeling, oral gratification and psychological sense of a real cigarette. These secondary properties may be an important part of the habituation to the use of tobacco products especially cigarettes.



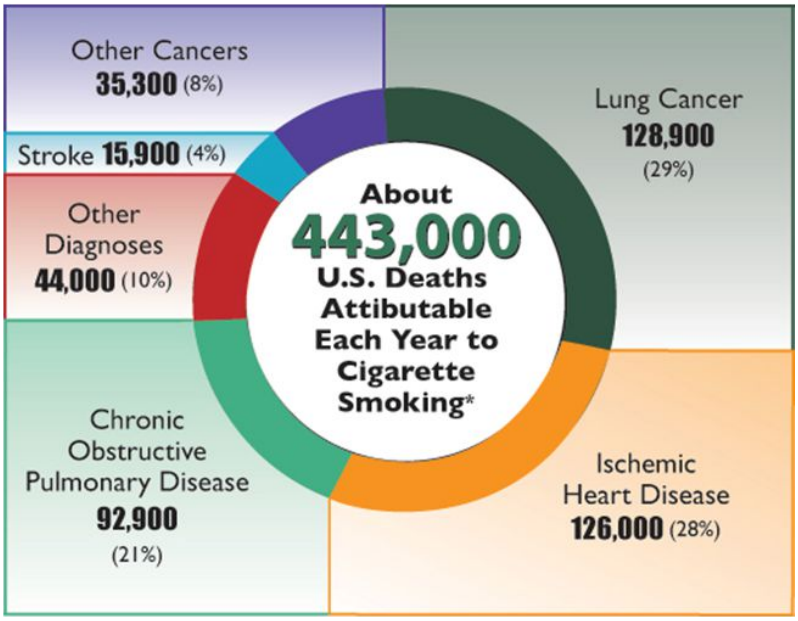
E-cigarettes are a nicotine delivery device. When "smoked" the user absorbs a significant dose of nicotine. Until recently nicotine and some of its analogues were the main ingredients of insecticides. Nicotine is an addictive poison deadlier than heroin or cocaine as measured by estimation of the LD50.

E-cigarettes are advertised as safer than tobacco smoking and/or as a means of smoking cessation. These claims should bring them under regulation and study by the Food and Drug Administration. E-cigarettes cause an increase in airway resistance very similar to tobacco smoke. Long term exposure may cause permanent changes in lung function as in tobacco smokers. E-cigarettes may be more effective for tobacco cessation than some of the methods described in the accompanying article. For cigarette users that have no wish or intention to stop smoking it may be that switching to E-cigarettes is less toxic. Further study is needed on the effectiveness of E-cigarettes in smoking cessation. Also whether for chronic use they are less toxic and carcinogenic than regular cigarettes.

Several countries have banned the sale of e-cigarettes, including Brazil, Finland, Lebanon, Malaysia, Mexico, Argentina, Israel, Panama, Canada (those containing nicotine), Jordan, Turkey, and Australia.

E-cigarettes will be the subject of a *Missouri Medicine* article in a future issue. Source: Wikipedia MM

Figure 2
Deaths Attributable Annually to Cigarette Smoking



ask all patient about tobacco use, not only at a first visit but at all subsequent visits. Physicians should discuss with each patient any health problems that have been directly or indirectly caused by tobacco use, and the risks that the individual faces for continued tobacco use in terms of current health issues as well as a risk factor for other possible future problems. For example, the individual with diabetes, hypertension, and hyperlipidemia should be warned that tobacco use dramatically increases the risk for cardiovascular disease including stroke and myocardial infarction. Educating each patient regarding their specific risks for continued tobacco abuse and expressing strong support in aiding the patient in smoking cessation is motivational for most individuals and increases the chances for a successful attempt in smoking cessation. Patients can be referred to smoking cessation support groups, and many hospitals have smoking cessation programs that offer psychological support for individuals going through the withdrawal process. Physicians should seek the resources available in their communities and utilize those resources when appropriate. Finally, physicians have a variety of medications that can be used to assist the individual in smoking cessation attempts.[7]

Medications

Medications, both nonprescription and prescription products, that have been shown the be effective in smoking cessation attempts. Nicotine replacement therapy relieves the withdrawal symptoms of smoking cessation and is available in slow-release transdermal patches or rapid acting transmucosal delivery systems. Table I shows current nicotine replacement therapies.

Buproprion has been approved by the Food and Drug Administration as a smoking cessation medication. As mentioned previously, dopamine has been demonstrated to be responsible for the pleasurable effects of nicotine use and a decrease in synaptic dopamine is associated with the withdrawal symptoms resulting from cessation of nicotine use. Bupropion acts by blocking the uptake of synaptic dopamine, thus alleviating the effects of smoking withdrawal such as depression, difficulty in concentrating, and irritability. Buproprion may have other beneficial effects at the cellular level, including blocking of norepinephrine uptake at the synapse. The combination of a nicotine replacement product with bupropion has been shown to be more effective in outcome than either product alone.

Varenicline has been approved by the Food and Drug Administration as a smoking cessation drug and has been demonstrated to be very effective in increasing success rates in controlled trials. The mechanism of action is complex, and involves its action as a partial agonist of a subunit of the nicotinic acetylcholine receptor that results in attenuation of the aversive effects associated with nicotine withdrawal; in addition it blocks the reinforcing effects of nicotine by blocking nicotine binding to the receptor. [8, 9, 10]

Considerable research is ongoing in the development of drugs that affect glutamate metabolism. Glutamate is released in the brain's mesolimbic reward system in response to the binding of nicotine to glutamate receptors on dopaminergic neurons. The increase in glutamate results in dopamine release and the resultant pleasurable effects of nicotine. Animal studies have demonstrated the beneficial effects of glutamatergic drugs in nicotine withdrawal by blocking the reinforcing effects of nicotine and by blocking the withdrawal symptoms associated with abstinence from nicotine. [11]

Finally, Gamma-Aminobutyric Acid (GABA) is the major inhibitory neurotransmitter in the mammalian nervous system. It has been demonstrated that animals with

Table 1
Nicotine Products to Aid in Cessation of Smoking

NICOTINE PRODUCT	DOSAGE	FDA STATUS
Transdermal Patch	7mg, 14mg or 21mg patch; dosage depending upon body habitus and smoking habits	Non-prescription
Nicotine Gum	2mg and 4mg pieces; dosage depending upon smoking habits; maximum dosage 24 pieces daily	Non-prescription
Nicotine Lozenge	2mg and 4mg lozenges; dosage depending upon smoking habits; maximum dosage 20 lozenges daily	Non-prescription
Nicotine Inhaler	Each cartridge contains 4mg nicotine in 80 inhalations; recommended dosage 6 to 16 cartridges daily	Prescription
Nicotine Nasal Spray	Each spray is 0.5mg of nicotine and each dose is one spray in each nostril; recommended dosage is once or twice hourly with a maximum of 40 doses daily	Prescription

chronic nicotine exposure have reduced levels of GABA in the mesolimbic reward system. Drugs that inhibit GABA breakdown or activate GABA receptors have been shown in animals to decrease the reinforcing effects of nicotine and prevent nicotine seeking behavior.[12]

Conclusion

Cigarette smoking continues to result in significant morbidity and mortality in the United States. Significant progress in our understanding of the mechanisms of nicotine addiction is resulting in the development of more effective pharmaceutical agents With these improved pharmacological agents and more aggressive physician and health care intervention, a resumption in the decline of smoking prevalence can be anticipated.

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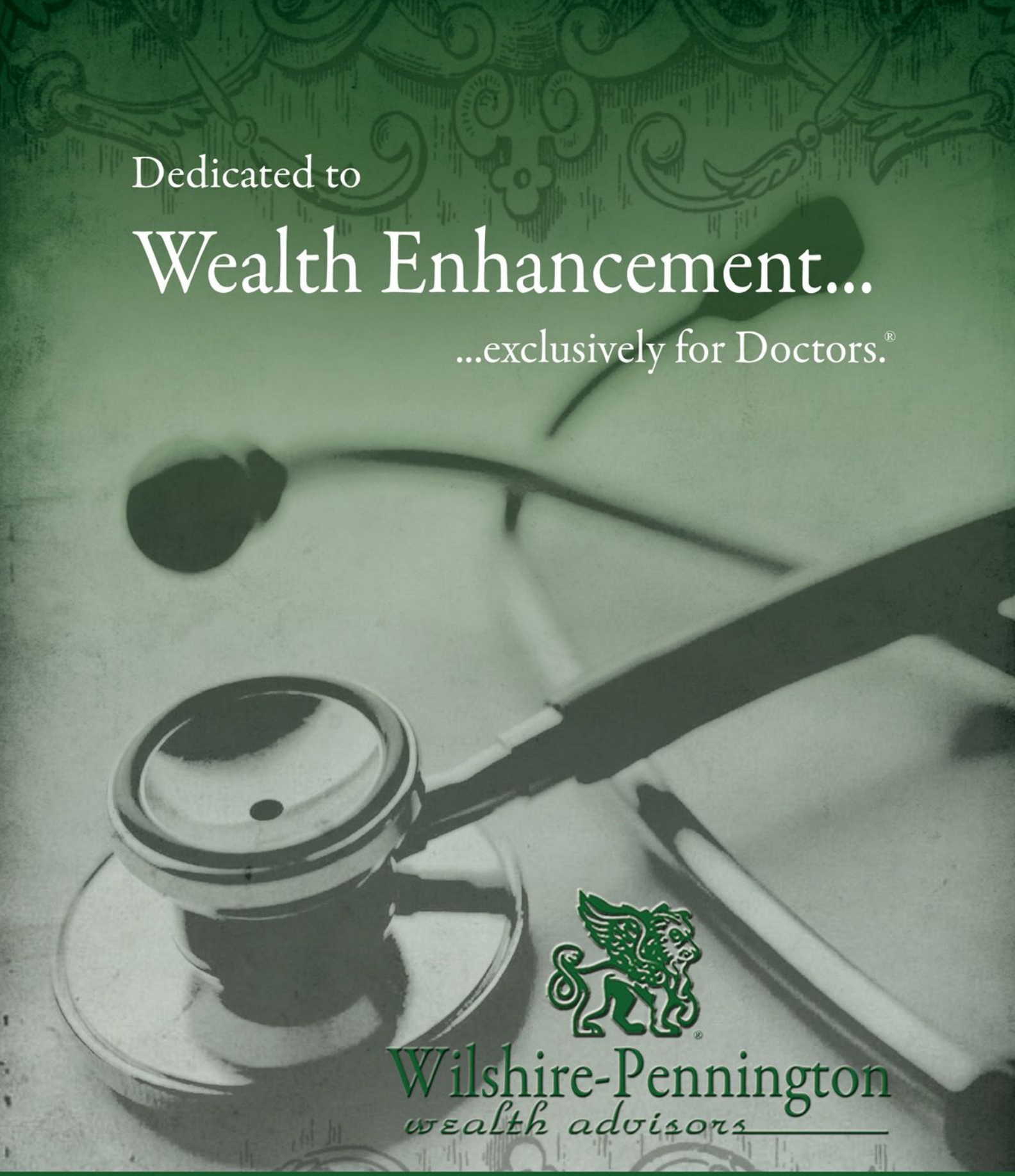
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None reported.

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(800)264-5815 • OFFICE:(405)751-8600 • FAX:(405)751-8898
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