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Literature Review

Artificial intelligence in medicine: What is it doing for us today?☆

Aliza Becker*

The College of Professional Studies, The George Washington University, Alexandria, VA, United States

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ABSTRACT

With its origins in the mid- to late-1900s, today, artificial intelligence (AI) is used in a wide range of medical fields for varying purposes. This review first covers the early work regarding AI in medicine, then aims to elucidate some of the most current applications of machine learning in medicine according to the following four specific categories: (1) its use in assessing the risk of disease onset and in estimating treatment success; (2) its use in managing or alleviating complications; (3) its role in ongoing patient care; and (4) its use in ongoing pathology and treatment efficacy research. Lastly, this paper clarifies some of the potential drawbacks, concerns, and uncertainties surrounding the use of AI in medicine and briefly discusses some of the efforts being made to prepare the health care industry for the implementation of AI.

Early work

According to the history books, the earliest applications of artificial intelligence (AI) in the medical field occurred predominantly in the 1960s and 1970s (the term itself having been coined by John McCarthy in 1955 [1]). On a broader scale, early theorists like Alan Turing [2] first questioned whether or not computers could be made to operate in a manner similar to that of the human brain (i.e., "to think"). Application of early machine learning principles came with the introduction of the Polish "bomba" and British "bombe" machines used to decipher the Germans' Enigma machine codes during World War II [3]. The development of the first AI program (i.e., the Logic Theory Machine) said to be capable of mimicking some aspects of humans' problem-solving abilities is often attributed to Herbert Simon, Allen Newell, and John Shaw in the mid-1950s [4,5], though several researchers in the same decade also explored the possibility of developing chess- and checkers-playing programs [6–8], including Arthur Samuel, who is believed to have introduced the term "machine learning" [8]. Joseph Weizenbaum at the Massachusetts Institute of Technology held a similar role in early artificial intelligence application work with his ELIZA language processing program, which mimicked a human therapist by incorporating key words or phrases input by the user to produce a response [9].

With the eventual revelation that AI could perhaps be used to specifically solve or clarify complex biomedical problems, interest in its potential grew exponentially. In 1961, Warner et al. published a study on the use of an automated diagnostic system for diagnosing congenital heart disease, in which data were drawn from 1035 patients referred for cardiac catheterization and analyzed [10]. MYCIN, a computer program developed by researchers at Stanford University in the 1970s, was used to diagnose and recommend treatment—specifically antibiotics, with the dosage adjusted according to each individual patient's body weight—for serious infections by identifying the bacteria in question causing the infection [11]. An earlier initiative conducted at the same institution, the Dendral project, had aimed to study hypothesis formation and discovery in science, specifically via assisting organic chemists in elucidating the structure of unknown organic molecules [12]. GUIDON, an intelligent computer-aided instruction program that uses AI techniques to represent both subject material and teaching strategies [13] was developed in the late 1970s for teaching infectious disease diagnosis to medical students through the use of case presentations. Other systems like INTERNIST-1 and its successor, Quick Medical Reference, were developed and put into play to assist health care professionals in patient diagnosis: these systems relied on a knowledge database of 570 diseases, which clinicians could reference when presented with a patient, while the latter system could also generate or refine hypotheses in complex cases [14]. Kulikowski and Weiss discussed the CASNET and EXPERT projects in the 1980s; the former was used in the context of glaucoma care, while the latter was established to help build models for reasoning in rheumatology and endocrinology [15]. As far back as 1959, an article in *Science* postulated how computers might fit into the process of patient diagnosis, acknowledging that

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* Correspondence to: 322B Barton Run Blvd., Marlton, NJ 08053, United States.
E-mail address: arbecker1@gmail.com

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"before computers can be used effectively … we need to know more about how the physician makes a medical diagnosis,"[16] with subsequent research aiming to elucidate this process in the context of computer operation [17].

In later years, research turned towards evaluating computer-aided diagnosis in comparison with the abilities of human physicians. A controlled, prospective, unselected real-time comparison study involving 304 patients with abdominal pain conducted in the early 1970s found that the computing system's overall diagnostic accuracy was higher than that of even the senior member of the clinical team [18]. A follow-up multicenter trial involving eight centers and more than 16,737 patients and 250 physicians, respectively, considered diagnostic accuracy using a baseline diagnosis method (human diagnosis) in comparison with computer-aided diagnosis; importantly, improvements in diagnosis, decision-making, and patient outcomes were noted with use of the latter [19]. Other research efforts attempted to utilize computers to generate new or more efficient methods of diagnosis not previously available through the compilation and use of standardized records, [20–23]; to improve the detection and classification of lesions in areas such as the vascular system, skin, lungs, or breasts via image analysis, [24–28]; and to elucidate biological mechanisms that may have previously been unknown [29,30]. Computer systems also began to find applicability in preventative medicine [31].

Today, AI is used in a wide range of medical fields for varying purposes. This review aims to discuss some of the most current applications of machine learning in medicine with respect to recent research published and products released, while also clarifying some of the potential drawbacks, concerns, and uncertainties surrounding its use. How the industry is preparing for the incorporation of this technology is also explored.

Current research

For the purposes of this section of the paper, which aims to act as a record of the various trends emerging in AI in medicine today, a PubMed literature search was conducted to identify relevant manuscripts published no earlier than 2015. Keywords included "artificial intelligence" AND "medicine" and "machine learning" AND "medicine." Only original research studies, case reports, or reviews that drew new conclusions from the studies they surveyed with available abstracts and which had been published on the subject of AI in medicine were included. Papers published in languages other than English without an available English translation were excluded. Once trends were identified, a broader Internet search using the same keywords was conducted to identify any other relevant studies that may have been overlooked, though the findings from this search were limited.

From this literature survey, it became apparent that AI is being employed in the medical space in at least four distinct ways: (1) in the assessment of risk of disease onset and in estimating treatment success prior to initiation; (2) in an attempt to manage or alleviate complications; (3) to assist with patient care during the active treatment or procedure phase; and (4) in research aimed at elucidating the pathology or mechanism of and/or the ideal treatment for a disease. The following presents specific study examples of these four categories and discusses their significance.

In evaluating the risk of disease onset and potential treatment outcomes

The cardiovascular space represents one area of medicine in which AI has been largely influential. In a study published in *Medicine,* Li et al. developed an artificial neuron network (ANN)—a computational model constructed similarly in form to that of a biological neural network that "learns" based on information that it is given—to predict the risk of congenital heart disease (CHD) in pregnant women, and found that the model was helpful in identifying those patients at high risk of developing CHD early on in pregnancy [32]. An ANN was also used in a multicenter comparison study evaluating whether the use of an ANN-based diagnostic system and conventional quantitation were comparable in diagnosing coronary artery disease [33]. Additionally, in a cohort of more than 370,000 patients free from cardiovascular disease, the use of machine learning was found to be beneficial in that it improved the accuracy of cardiovascular disease risk prediction through identifying patients who could benefit from preventative treatment, while also ruling out those in whom treatment would be unnecessary [34]. Jeganathan et al. evaluated the use of AI in mitral valve analysis, which is typically completed manually to diagnose patients with mitral valve disease. Their findings indicated that good reproducibility with minimal user intervention could be achieved via automated diagnosis [35]. Dawes et al. found that a machine learning model that uses three-dimensional cardiac motion was able to predict outcomes independently of conventional risk factors in patients with newly diagnosed pulmonary hypertension [36].

Machine learning has also been proven to be advantageous in assessing and identifying patients at risk for other diseases. One study by Kind et al. found that its use was beneficial in flagging individuals at high risk for colorectal cancer based on electronic medical records, including those with no visible clinical signs or symptoms [37]. Another employed machine learning to construct pretest models for predicting whether a patient would test positive for a particular respiratory virus [38]. Researchers at the Massachusetts Institute of Technology have developed a neural network model to identify depression from human speech patterns, regardless of what the speaker tells their physician [39]. Along this line, several papers also detail work being done to translate brainwaves into decipherable speech, which could eventually benefit those patients who are unable to talk [40]. Additionally, the use of AI in the diagnosis of melanoma [41], dementia [42], diabetic retinopathy [43], tuberculosis [44], and glaucoma [45] has also been investigated, as has its employment in predicting the outcome of radiation therapy [46], the occurrence of acute respiratory disease events and mortality in smokers [47], the success of substance abuse disorder treatment [48], the onset of diabetes [49,50], HIV transmission patterns [51], and the findings of breast cancer [52] and depression [53] in breast cancer patients, respectively. Assistance from AI to define certain subgroups within a patient population, such as individuals in the intensive care unit with similar clinical needs [54], or those patients with certain temporal bone abnormalities [55], has also been relied upon. Furthermore, while not representing an investigation on disease, per say, Stonko et al. were able to use an ANN to successfully predict trauma volume, the number of emergent operative cases, and average daily acuity at a level 1 trauma center by integrating temporal and weather data [56]. Ryynänen et al. considered the use of an AI method based on causal Bayesian networks to compare different treatment alternatives and identify patients who would benefit from treatment [57]. Though they evaluated the approach's application in continuous positive airway pressure treatment of sleep apnea, they acknowledge that it may be applicable in other conditions as well [57]. Other researchers at IBM Research (Yorktown Heights, NY, USA) and Google (Mountain View, CA, USA) are focusing on the prediction of emergency room visit [58] and hospital outcome [59] trends using machine learning as well.

To alleviate or reduce complications

In addition to its uses prior to or at the time of disease onset, AI may also be useful in mitigating progression or further adverse events of a disease. In a study by Dente et al., machine learning algorithms were used to identify predictive profiles of bacteremia and pneumonia in patients with combat wounds treated at the Walter Reed National Military Medical Center between 2007 and 2012 [60]. The researchers suggested that the implications of this study should also be considered in civilian trauma patients as well. Machine learning was also employed in the European Union-funded MOSAIC project to develop predictive models of type 2 diabetes mellitus complications such as retinopathy, neuropathy, and nephropathy using electronic medical records data [61]. Additionally, Wise et al. evaluated preoperative factors independently associated with prolonged postoperative ventilation in patients undergoing coronary artery bypass grafting, and aimed to optimize the identification of patients at risk before surgery using an ANN [62]. AI has also been used to estimate neurosurgical outcomes in focal epilepsy patients [63] and in predicting ischemic stroke and thromboembolism in patients with atrial fibrillation [64]. It may be beneficial in mitigating renal transplant rejection [65]. Furthermore, on the administration side, Hu et al. employed machine learning to better identify common complications in electronic health records data, as part of an effort to collect data for secondary purposes including research [66].

In ongoing patient care

With respect to its use during active treatment, AI predominantly appears to be beneficial in augmenting physicians' work. A study evaluating the use of computer-aided detection (CAD) of brain metastasis on radiologists' diagnostic performance in interpreting three-dimensional brain magnetic resonance imaging (MRI) scans found that CAD assistance helps radiologists to improve their diagnostic performance [67]. Researchers also employed AI to assess whether patients would tolerate major surgery or chemotherapy by analyzing their body morphometric age via muscle quantification [68], as well as in bone age assessment in the evaluation of patients with endocrine and metabolic disorders, respectively [69]. Other investigations indicate that AI may also have implications in intraoperative pathological diagnosis [70], the clinical management of patients undergoing echocardiographic evaluation [71], in collagen proportional area extraction during liver biopsy [72], in reducing the number of false-positive results when detecting nodules in chest radiographs [73], and in evaluating neurological deficit in stroke victims [74]. AI may also have some use in predicting long-term individualized disease progression [75], in evaluating childhood malnutrition [76], and in the analysis of breath samples to determine a patient's health status [77].

In clinical research and drug development

AI is also further expected help expedite clinical diagnosis and research. Researchers in Japan employed AI in the sequencing of cancer genomes to better identify patients with hematological malignancies and determine applicable drug information [78]. Additionally, a separate study by Heinson et al. on the use of machine learning indicated its applicability in distinguishing bacterial protective antigens (BPAs) from non-BPAs in reverse vaccinology, which could eventually assist in the development of new vaccines [79], while one by Romeo-Guitary et al. employed a systems biology approach and AI to identify a neuroprotective agent for the treatment of peripheral nerve root avulsion [80]. Researchers more recently published a proof-of-concept study on a computer system that can teach itself to design new drug molecules from scratch with certain desirable physical properties [81].

AI may also help to reveal new avenues for the diagnosis or monitoring of diseases that may ultimately simplify the task: in one study, Beck et al. used a machine-learning algorithm in the prediction of breast cancer prognosis and identified stromal morphologic structure as a previously unrecognized prognostic determinant for breast cancer [82], while researchers in a separate study used retinal fundus images to predict cardiovascular risk factors they report were not previously thought to be present or quantifiable in retinal images, including age, gender, smoking status, and major adverse cardiac events [83]. Other applications of AI in the medical research setting include as part of a recent study aiming to generate accurate classification models using machine learning techniques that could be used to identify insulin-degrading enzyme modulators, which the researchers hope will lead to an effective treatment for Alzheimer's disease [84]. A study considering the use of machine learning in the development of membranolytic anticancer peptides reported that, of 12 sequenced, 10 were active against cancer cells [85]. Some researchers have also suggested that AI may be a solution to answering fundamental questions in the drug development pipeline, including who to recruit and what outcomes to measure in clinical drug trials [86], as well as the potential drug responses that could present [87,88]. Lastly, AI may change the manner in which animal testing as part of drug development and clinical trials is performed: in a study published in the journal *Toxicological Sciences*, the training of an AI interface to predict what the toxicity effects of thousands of unknown chemicals might be using data on the outcomes of previous animal tests showed an accuracy comparable to that obtained using live animal tests [89].

Concerns

Despite these applications, however, there are still a number of concerns surrounding the adoption of AI into medicine. First and foremost, ethical concerns have been voiced, in particular with respect to the use of artificial intelligence in the care of elderly patients [90]. It is largely understood that the AI movement in medicine is represented by two separate branches: the virtual and the physical [91]. The virtual branch is best characterized by the use of mathematical algorithms that induce learning through experience, while the physical branch encompasses most predominantly the use of robots. Though these robots are being used in the surgical setting to improve procedural outcomes [92–94], there is also a growing interest in their use in the care of elderly individuals. Here is where many of the ethical concerns surrounding the use of AI stem from. Sharkey et al. highlighted a number of such in their article, including (1) the potential for a reduction in the amount of human contact; (2) increased feelings of objectification and the loss of control as well as deception and infantilization in the elderly; and (3) a loss of privacy, personal liberty, and the existence of conflict regarding the circumstances in which elderly people should be allowed to control robots [95]. However, despite these thoughts, it has been suggested that, overall, the use of robot technology in elder care is beneficial [96], though more research on the subject is ultimately needed [97]. With respect to the former branch, there may be racial bias that could arise as a result of the data provided to the AI system: Char et al.[98] cite the example of the fact that data from the Framingham Heart Study used in nonwhite populations led to both the overestimation and underestimation of cardiovascular disease risk [99]. More broadly, Char et al. further stress that bias could possibly introduced into health data in three ways: via human bias; as bias that is introduced either by accident or on purpose (e.g., by the manufacturer) into the AI system's design; and as bias in the ways in which health care systems use the data (e.g., as a result of physicians' tendencies to possibly avoid patients with certain diagnoses, AI systems may designate these diagnoses as being always fatal and may adversely adjust treatment protocols in response) [98].

There is also lingering concern that AI might one day replace medical technicians or physicians, especially those in medical disciplines in which diagnosis is based on pattern recognition. Indeed, one recently published article asked radiologists, “are you working with AI or being replaced by AI?”[100] In an editorial published in the *Archives of Pathology & Laboratory Medicine*, Granter et al. hypothesize that, based on the recent success of Google’s (Menlo Park, CA, USA) AI computer program, AlphaGo, in beating the world’s best player of Go, a complex board game with ancient roots, that it is likely that AI may eventually replace the human microscopist [101]. A follow-up editorial by Sharma et al. refutes Granter et al.’s argument, but acknowledges that, in time, it is likely that human clinicians’ “cognitive lead” over AI will narrow [102]. Char et al. note that AI could represent a boon as clinical medicine moves progressively toward a shift-based model and the number of clinicians who see a patient from presentation to the end of treatment decreases, but may also gather unintended levels of power as the only consistent observer of the patient’s progression [98]. Other reports, however, while they have called to mention the potential threat of AI, have suggested that it will likely augment, rather than hurt, physicians’ work [103–105].

Even if AI does not replace physicians, reliance on its capabilities may lead to the deskilling of medical professionals, or to inadequate or incorrect computer-aided diagnosis. In a study by Anh et al., of 2298 electrocardiograms (ECGs) characterized as atrial fibrillation by a computer algorithm, 442 ECGs from 382 patients were deemed to represent incorrect diagnoses by two electrophysiologists who reviewed the scans [106]. Southern et al. detailed the presentation of a 62-year-old female who was mistakenly diagnosed via computer interpretation of her ECG with acute ischemia, and used the case report as the basis for a study evaluating the effects of incorrect computer diagnosis on medical resident decision-making [107]. Hakacova et al. found that automated systems were not on average significantly better than nonexpert physicians in diagnosing cardiac rhythm disorders based on ECG scans, and that automated systems can be incorrect in cases in which physicians are incorrect as well, leaving open the potential for misdiagnosing a patient [108]. Komorowski et al. also noted concern regarding the possibility of AI use resulting in the dissemination of too much patient data, leading diagnosis to become more complex than necessary [109].

Lastly, there are also concerns regarding the compilation of data associated with electronic medical records. Even as far back as 1960, patient data were being collected via electronic systems, and there were both advantages and disadvantages to such noted [110]; one paper from 1964 acknowledged “it appears that the most difficult and controversial subject is the handling of medical records,” due in part to the fact that no protocols were yet in place regarding what should be collected and how it should be maintained, despite the fact that collection of some sort was already ongoing [111]. With the increase in the complexity of computer systems, concern over patient data collection and storage as well as the efficacy of associated security measures has only grown [112,113]. As technology continues to advance and devices become more connected, patient privacy will become an increasingly larger, more worrying, and more complicated issue [131,114]. Also adding complexity is the idea that patient medical records represent a potential significant source of data to use in breakthrough research [115]; indeed, Char et al. suggest that data gathered about specific patients’ health, diagnostics, and outcomes will likely become part of large datasets and may be incorporated in future published literature or clinical trials without the patient’s consent or knowledge [98]. In such a situation, many have asked—who really owns the data? [116] In light of this, practitioners should perhaps strive to keep their patients as informed as possible regarding how their medical records might be used and to obtain informed consent where they believe it might necessary.

Market offerings

At this time, there are a small but growing number of AI health care products on the market. Most current offerings appearing to be for use in patient diagnosis, and many seem specifically to supplement the abilities of existing imaging modalities. One example is the IDx-DR software program (IDx, LLC, Coralville, IA, USA) recently approved by the United States Food and Drug Administration (FDA), which uses an AI algorithm to analyze images of the eye taken with a retinal camera to spot symptoms of diabetic-related vision loss [117,118]. 20/20NOW similarly announced the release of its Eyelogic AI technology to assist in the diagnosis of retinal diseases [119]. Separately, the Viz.ai system (Viz.ai, Inc. Palo Alto, CA, USA), which connects to a hospital computed tomography scanner to alert the stroke specialist that a suspected large vessel occlusion stroke has occurred by relying on machine learning, was granted de novo classification by the FDA [120], while Imagen Technologies (New York, NY, USA) also obtained FDA approval to market its OsteoDetect computer-aided detection and diagnostic software, which employs an AI algorithm to analyze two-dimensional X-ray images for signs of distal radius fracture in adult patients [121]. Bay Labs (San Francisco, CA, USA) also recently received 510(k) clearance from the FDA for its EchoMD AutoEF software for the fully automated clip selection and calculation of left ventricular ejection fraction [122], with previous research having already demonstrated its good accuracy as compared with human cardiologists [123]. Butterfly Networks has received FDA clearance for the application of its Butterfly iQ® for iPhone AI-powered ultrasound imaging system in 13 clinical applications [124]. Subtle Medical has received both 510(k) clearance from the FDA and the European CE mark for its SubtlePET AI platform, which enhances the quality of images taken during positron emission tomography scans performed at a quicker pace [125], enabling an overall faster completion of patient imaging procedures. Similarly, HeartVista’s AI-driven, one-click autonomous MRI acquisition software can purportedly drastically cut the length of cardiac MRI scan procedures while simultaneously monitoring image quality [126]. Arterys, another manufacturer of an AI solution to supplement cardiac MRI, has added a number of enhancements to its original Cardio AI^{MR} platform [127]. Aidoc and MaxQ AI have additionally received FDA clearance for their respective AI technology offerings designed to assist with patient triage by flagging intracranial hemorrhage cases in head computed tomography scans [128,129]. Bayer and Merck have also jointly received a breakthrough device designation from the FDA for their chronic thromboembolic pulmonary hypertension AI pattern recognition software for use in conjunction with computed tomography pulmonary angiography [130]. QView Medical offers QVCAD, an FDA-approved AI system for concurrent reading of automated breast ultrasound scans [131].

Regarding other AI products that do not necessarily supplement the abilities of existing imaging systems, AliveCor has been busy in the realm of AI with the approval of their Kardia Pro AI-enabled monitoring platform for the early detection of atrial fibrillation [132] as well as the organization of a partnership with the Mayo Clinic for the development of tools for medical and non-medical personnel to easily screen for long QT syndrome through the combination of the company’s AI technology and the clinic’s patented algorithms [133]. A separate collaboration that yielded the KardiaK Platform, which screens for elevated levels of blood potassium without requiring any blood from the patient, has also received the FDA’s “Breakthrough Device” designation [134]. Another offering in the cardiology space that grew out of a collaboration between iRhythm Technologies and Stanford Medicine yielded a AI-powered algorithm capable of diagnosing a variety of arrhythmias through single-lead electrocardiograms at a level similar to a human cardiologist; the algorithm recently received 510(k) clearance from the FDA [135].

Conversely, some AI applications support ongoing patient care after a diagnosis has been made. Beta Bionics, Inc. (Boston, MA, USA), a medical technology company working to incorporate AI into the world's first autonomous bionic pancreas, was previously granted investigational device exemption approval, allowing the company to move forward with the recruitment of both adults and children for home-use studies to test its iLet™ Bionic Pancreas System [136]. AliveCor has previously touted the release of medical research highlighting the potential use of the company's AI technology as a potential alternative to surgically implanted heart monitors, although this indication has not yet been FDA-approved [137]. VRHealth offers Luna, a virtual reality AI therapist trained with evidence-based psychological protocols that aims to reduce the physical and psychological effects of hot flashes in users [138]. Notal Vision is also moving forward with efforts to introduce an AI-enabled optical coherence tomography system for monitoring wet age-related macular degeneration at home in the elderly [139].

In some cases, manufacturers are focusing on how AI could support physicians directly. Amazon has launched its Comprehend Medical service, a HIPAA-eligible service that uses machine learning to identify patient diagnoses, symptoms, medical test findings, treatments, and other relevant medical data for easier review from "unstructured" medical text such as doctor's notes [140]. AiDoc and SaferMD have also announced a partnership aimed at improving the Medicare reimbursement of AI radiology procedures [141].

Reflection

Overall, while AI has come a long way since its infancy in terms of its incorporation into medicine, it still has a long way to go—and, it may never, in fact, reach a point at which it will be totally independent of a human physician. Considering whether AI is on par with physician assessment, a letter by van Smeden et al. [142] in response to a study evaluating the use of deep learning algorithms for the detection of lymph node metastases in women with breast cancer [143] cautioned that certain criteria must be standardized and employed to ensure fair comparison—something that, at this time, a human must develop and "feed" to the AI system.

Still, AI's possible uses in diagnosis, treatment, and clinical research remain numerous, and the industry on some levels is beginning to prepare for the inevitable through the establishment of working groups, guidelines, frameworks, and the like [144–147]. Only several months ago, for example, the American Medical Association passed its first policy guidelines on "augmented intelligence," detailing five tasks that the organization will strive to perform [148]. In the image of the first workshops held in conjunction with the birth of modern AI [149], in more recent years, webinars, lecture series, and even entire conferences dedicated to the topic of AI in medicine have begun to spring up en masse [150–153]. Schools, too, on the subject of AI in health care are being established [154].

Furthermore, similar to how technology as a whole has become more readily adopted by younger individuals, AI's possible implications have begun to be considered more strongly in the education of the next generation of physicians [155]. One study by Uemura et al. suggested based on the findings of a study that employed an AI-based measure to analyze the hand movements of expert and novice surgeons that such could be used to provide feedback on surgeons' current skill levels and/or to inform them of areas in which they need to improve in [156]. Indeed, other research suggests that the majority of medical students agree that AI will improve certain medical disciplines (i.e., radiology) and that there is a need to include AI in medical training [157].

Considering all of the above, more studies must be completed in a preparatory manner so as to further elucidate the potential of AI. Physicians must educate themselves on the advantages of this new technology as well as the pitfalls. Formal guidelines and regulations must be established with regard to not only determining the situations in which AI should or can be used or not but also with respect to the handling of patient data and company oversight; this is especially of importance in the wake of revelations from exposed internal company documents that IBM Corp.'s (Armonk, NY, USA) Watson supercomputer gave physicians inaccurate cancer treatment advice, with company medical specialists and customers reporting "multiple examples of unsafe and incorrect treatment recommendations" [158,159]. Thorough testing of AI systems in development [160] should also be completed against human clinicians so as to quantify and define the technology's abilities and limitations. The social, legal, and ethical implications of using AI in medicine must also be considered thoroughly [98,161]. The completion of these steps and others will ensure a smoother and more effective integration of AI into medicine.

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Ethical approval

Not required

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Know Your Nutrient

Vitamin K

by Aliza Becker, BA, MPS

Vitamin K is the generic name for a family of fat-soluble compounds that share a common 2-methyl-1,4-naphthoquinone ring structure. Vitamin K is naturally present in some foods or available as a dietary supplement.[1] Its existence was first reported in the 1930s by Danish biochemist Henrik Dam, who observed that chicks fed a low-fat diet free from sterols as part of research on cholesterol metabolism tended to develop subcutaneous and intramuscular hemorrhages;[2] subsequent research led to the discovery of an "anti-hemorrhagic factor" designated as vitamin K (with the "K" standing in for the German word *koagulationsvitamin*).[3] Dam was later awarded the Nobel Prize in Physiology or Medicine in 1943, sharing with Edward Adelbert Doisy, an American biochemist, for their discovery of vitamin K and its chemical structure, respectively.[4]

SOURCES AND DOSING

Two forms of vitamin K exist in the United States (US) food supply.[1] Vitamin K1 (phylloquinone [PK]) is found in green, leafy vegetables, such as collards, spinach, and broccoli, as well as in soybean oil and canola oil.[5] In contrast, vitamin K2 (menaquinone [MK]) is found variably in certain animal-based foods and is mainly produced by bacteria and archaea. Notably, at least 15 types of MKs exist that are distinguishable by the number of isoprene units in their side chains. In a study of the US diet, Elder et al[6] reported that chicken, cheddar cheese, and egg yolks contained the highest amounts of MK-4, while Fu et al,[7] following a similar analysis of the US food supply, found that all processed pork products and fresh pork cuts contained MK-4, MK-10, and MK-11. Vermeer et al[8] reported that many cheeses contain MK-4 through MK-9, with levels depending on factors such as fat content, age, and country of origin. Meanwhile, among the vegetables they assessed, only the two fermented ones, natto and sauerkraut, contained MK8; the latter, a Japanese dish made from fermented soybeans, is considered a good source of MK-7.[9] Certain gut bacteria, such as *Escherichia coli* (*E. coli*) and *Bacteroides* species, may also produce MK.[10]

According to US dietary guidelines, the recommended daily amount of vitamin K for adults over the age of 19 years is 90µg/day for women (including pregnant or breastfeeding women) and 120µg/day for men.[11] Children require anywhere from 2 to 75µg/day, depending on their age.[11]

Although the U.S. population largely meets the recommended daily intake for vitamin K, certain populations are at risk for deficiency.

Newborns are typically given oral and/or intramuscular prophylactic vitamin K after birth to prevent hemorrhagic disease of the newborn,[12,13] which can occur soon after birth due to the limited placental transfer of this vitamin during gestation and their sterile gut or later in infancy when coupled with insufficient vitamin K in breast milk.[14] Although some research has previously suggested a link between intramuscular vitamin K and childhood leukemia,[15] later reports have since argued against this connection.[16] Individuals with disorders characterized by the malabsorption of fat, such as cystic fibrosis, chronic pancreatitis, and inflammatory bowel diseases, as well as those who have undergone certain surgical procedures, such as total pancreatectomy, small-bowel resections, or bariatric surgical procedures, may also benefit from vitamin K supplementation.[17] Patients on hemodialysis may also present with a poor vitamin K status,[18] and individuals taking drugs that interfere with vitamin K metabolism are similarly at risk of deficiency.[19]

EFFECTS IN THE BODY

For several decades after its discovery, vitamin K was thought to be used only for the synthesis of four blood-coagulation factors in the liver. In more recent years, however, researchers have expanded their focus, elucidating possible roles of vitamin K in the transportation of calcium to bone and the reduction of vascular calcification via the carboxylation of osteocalcin and activation of matrix Gla protein, two vitamin K–dependent proteins (VKDPs), respectively.

Effects on bone health. Sim et al[20] reported that increased dietary intake of PK-rich green leafy vegetables for four weeks in a population of middle-aged healthy men and women led to improved osteoblast function, which is thought to be due to vitamin K's role in increasing osteocalcin entry into the bone matrix and improving the material properties of bone (e.g., toughness). Moore et al[21] found that the serum PK concentration was significantly lower in their study group of postmenopausal women with prior fractures compared to the no-fracture group and was independently associated with fracture risk. Cheung et al[22] also suggested that daily PK supplementation may protect against fractures in postmenopausal women with osteopenia. Torbergsen et al[23] also observed that low serum concentrations of PK and 25-hydroxyvitamin D were significantly associated with risk of fracture in elderly patients hospitalized for hip fracture, implicating a synergistic effect between these two vitamins in addition to their independent roles.

Effects on cardiovascular health. Beulens et al[24] reported that high dietary MK intake, but probably not PK, may limit coronary calcification. Geleijnse et al[25] reported that MK intake was inversely related to all-cause mortality and severe aortic calcification, while PK intake did not correlate with any of their study outcomes. Vissers et al[26] noted that a high intake of MKs was associated with a reduced risk of peripheral arterial disease, at least in participants with hypertension, but a high intake of PK was not associated with the same. Gast et al[27] suggested that a high intake of MKs, especially MK-7, MK-8, and MK-9, could protect against coronary heart disease. However, PK may not be without its benefits: Shea et al[28] reported that PK supplementation slowed the progression of coronary artery calcification in healthy older adults with pre-existing coronary artery calcification. In patients with blood-clotting disorders, vitamin K antagonists (e.g., warfarin) are used to prevent stroke in patients with atrial fibrillation as well as venous thromboembolism, while PK itself is given to reduce the anticoagulant effects of such drugs.[29] Of note, vitamin K antagonists have been linked to higher levels of coronary artery and vascular calcification,[30,31] but the coronary-calcification effect appears absent with the use of newer non-vitamin K antagonist oral anticoagulants.[31]

Other effects on health. Vitamin K may also lower the risk of type 2 diabetes mellitus,[32] and research is ongoing concerning its potential in the treatment of cancer, particularly with regard to the effects of MKs on cell-cycle arrest and the inhibition of cell differentiation, apoptosis, autophagy, and invasion.[33] More generally, vitamin K may act as an anti-inflammatory[34] and an antioxidant,[35] and it has been associated with the inhibition of cognitive decline[36] and the prevention and treatment of neurodegenerative diseases, such as Alzheimer's.[37]

Most recently, research has reported that levels of dephosphorylated-uncarboxylated matrix Gla protein, a marker of vitamin K deficiency,[38] was greater in patients with COVID-19 relative to healthy controls,[39] with higher levels present in those with more severe disease.[40]

Editor's note: Vitamin K can lessen the effectiveness of Warfarin, a commonly prescribed blood thinner. Consult with your doctor to determine which vitamin K regimen is best for you.

QUICK GUIDE TO DIETARY SOURCES OF VITAMIN K

Green leafy vegetables
- kale
- spinach
- turnip greens
- collards
- Swiss chard
- mustard greens
- parsley
- romaine
- green leaf lettuce

Other vegetables
- Brussels sprouts
- broccoli
- cauliflower
- cabbage

Animal-based foods
- fish
- liver
- meat (chicken, pork)
- eggs
- cheese

Grains
- fortified cereals

Fats
- canola oil
- soybean oil

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CREAMED WINTER GREENS

Servings: 6

Ingredients

- 1 15oz can chickpeas, rinsed and drained
- Cooking spray
- 2 tablespoons chopped almonds or pine nuts
- 1 to 2 tablespoons olive oil
- One small onion, minced (~3/4 cup)
- 1 to 2 cloves garlic, minced
- 1 large bunch fresh greens, such as collards, kale, and/or spinach
- 1/2 cup coconut milk
- 1/4 teaspoon nutmeg
- 1/4 teaspoon salt
- 1/8 teaspoon pepper
- 1 teaspoon tapioca or cornstarch, optional

Directions

1. Thoroughly rinse the greens under running tap water and dry in a salad spinner or with clean paper towels. Remove the stems and tear the leaves into small pieces (you should end up with ~6 to 7 cups of prepared greens).
2. Heat olive oil in a large pot over medium heat. Add the onion and sauté for about 5 minutes or until translucent. Add the garlic and sauté a minute or two.
3. Add the greens a handful at a time while you continue to stir them around until all have been added and they have wilted a bit. Then stir in the coconut milk, nutmeg, salt, and pepper, and cook for 3 to 4 minutes more, until hot.
4. To thicken the sauce, mix the tapioca or cornstarch with a small amount of cold tap water. Mix until lump free and then to the greens and cook until thickened.
5. Top with toasted chickpeas and almonds or pine nuts

Nutrition Facts (per serving)

Calories: 388; Total Fat (g): 14.9; Saturated Fat (g): 5.5; Cholesterol (mg): 0; Sodium (mg): 144; Total Carbohydrate (g): 51; Dietary Fiber (g):14.3; Total Sugars (g): 9.3; Protein (g): 16.3; Calcium (mg): 150; Iron (mg): 6; Potassium (mg): 969 NHR

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About the Author

Ms. Becker is the managing editor of *The Journal of Innovations in Cardiac Rhythm Management*. She also works as a freelance editor and as a teaching assistant for the George Washington University's Master of Professional Studies in Publishing program.

VETERANS NEWS

Veterans Health Administration (VHA) increases care provided under MISSION Act

The 2018 Maintaining Internal Systems and Strengthening Integrated Outside Networks (MISSION) Act allows eligible vets to receive care from non-VHA healthcare providers. The program has vastly expanded in the last several years—33 million veteran community care appointments were completed in fiscal year 2021.

Access full story: https://thehill.com/opinion/healthcare/582583-veterans-health-administration-increases-care-provided-under-mission-act

Smoking rates steadily trend down among veterans receiving VA care

Cigarette use continues to decline nationwide, and the number of veterans enrolled in VA healthcare who identified as smokers has dropped nearly 20% in 21 years, from 33% in 1999 to 13.3% in 2020.

Access full story: https://www.va.gov/opa/pressrel/pressrelease.cfm?id=5742

Veterans exposed to burn pits will get expanded healthcare support, White House says

The Biden administration recently announced a series of new support options for veterans who have been exposed to "contaminants and environmental hazards," such as burn pits, while serving.

Access full story: https://www.cnn.com/2021/11/11/politics/military-exposure-burn-pits-biden-administration/index.html

Nutrition Basics

SUGAR

and the Human Body

by Aliza Becker, BA, MPS

Sugar, together with fruits, vegetables, fibers, and legumes, falls under the umbrella term of *carbohydrates*, which is one of the three macronutrients—alongside protein and fat—present in the human diet.[1] Sugar may be categorized in several different ways. First, there are simple sugars, known as monosaccharides, which are considered the most basic, fundamental units of a carbohydrate. Examples of simple sugars include glucose, galactose, and fructose.[1] In addition, there are compound sugars, called disaccharides, which contain two monosaccharides. Examples of compound sugars include sucrose and lactose.[1]

An oligosaccharide is any carbohydrate formed using 3 to 10 monosaccharide units, examples of which include raffinose and stachyose (found in legumes). A polysaccharide contains more than 10 monosaccharide units, and includes starches, glycogen, and fiber, such as pectin and cellulose.[1,2] Monosaccharides and disaccharides are known as simple carbohydrates, whereas oligosaccharides and polysaccharides are considered complex carbohydrates.[1] All carbohydrates, including sugars, contain carbon, hydrogen, and oxygen atoms in varying numbers arranged in different ways.[1]

SUGAR IN THE BODY

Healthy sugar processing in a healthy body. Carbohydrate digestion begins in the mouth, where an enzyme in saliva, salivary amylase, breaks the bonds between the monomeric sugar units of more complex carbohydrates. Digestion of carbohydrates continues by mechanical means in the stomach; however, carbohydrate digestion is most extensive in the small intestine, where pancreatic amylase from the pancreas and enzymes secreted by intestinal cells that line the villi initiate further breakdown of any remaining larger carbohydrate chains; the resulting monosaccharides are subsequently absorbed into the bloodstream and transported to the liver.[1,3]

Upon the arrival of monosaccharides, the liver then works to convert galactose to glucose and to break fructose into smaller carbon-containing units, either storing glucose as glycogen or returning it back to the blood.[3] In the latter case, the resultant increase in blood glucose prompts cells in the pancreas to secrete insulin, which triggers other cells throughout the body to transport glucose from the blood into different organ cells to use as fuel.[1,3] As this process occurs and blood glucose levels are reduced, other pancreatic cells release glucagon, which signals the liver to break down stored glycogen and release it into the blood as glucose, thus ensuring that blood glucose levels remain within the target range.[1,3]

Dysfunctional sugar processing in the body. *Lactose intolerance.* In individuals with lactose intolerance, an inadequate amount of the enzyme lactase leads to subpar breakdown of lactose in the small intestine. This results in undigested lactose continuing to the large intestine, where bacteria digest it, generating gases that cause diarrhea, bloating, and abdominal cramps.[3]

Hypoglycemia and hyperglycemia. Hypoglycemia occurs when the blood glucose level is too low, often defined by a plasma glucose concentration of less than 70mg/dL,[4] and is most commonly the result of medications taken to control diabetes, although other medications, critical illness or organ failure, a reaction to carbohydrates, an insulin-producing tumor in the pancreas, and some types of bariatric surgery can also trigger this state. In contrast, hyperglycemia may be diagnosed when the blood glucose is too high (i.e., greater than 125mg/dL while fasting or greater than 180mg/dL 2 hours after a meal). Hyperglycemia may result from damage to the pancreas, endocrine disorders that cause peripheral insulin resistance, the use of certain medications, total parental nutrition and dextrose infusion, or following surgery or trauma.[6] Although hyperglycemia can be a symptom of diabetes, it does not necessarily warrant a diagnosis of diabetes when presenting alone.[6]

Prediabetes and diabetes. A diagnosis of prediabetes is typically based on the individual having a fasting (i.e., having nothing to eat or drink for at least 8 hours other than water) plasma glucose level of 100 to 125mg/dL, a hemoglobin A1c concentration (i.e., the amount of glucose attached to hemoglobin) of 5.7 to 6.4 percent, or a two-hour postload glucose level of 140 to 199mg/dL. A diagnosis of diabetes is typically based on having a fasting plasma glucose level of at least 126mg/dL, a two-hour plasma glucose level of at least 200mg/dL during a 75g oral glucose tolerance test, or a hemoglobin A1c concentration of 6.5 percent or higher.[7]

Three primary types of diabetes exist—namely, Type 1, Type 2, and gestational diabetes. Type 1 diabetes, also known as insulin-dependent diabetes, immune-mediated diabetes, or juvenile-onset diabetes (although it can occur at any age), results from cellular-mediated autoimmune destruction of β-cells in the pancreas, leading to limited or no secretion of insulin.[8] Type 2 diabetes, also known as noninsulin-dependent diabetes or adult-onset diabetes, in contrast, occurs in individuals with insulin resistance or a relative (rather than absolute) insulin deficiency.[8] Type 2 diabetes may be clearly differentiated from Type 1 diabetes by its lack of autoimmune destruction of β-cells in the latter.[8] Given the autoimmune component, patients with Type 1 diabetes are also not generally overweight/obese, while those with or at risk for Type 2 diabetes typically are overweight or obese. Excess carbohydrate intake contributes both to weight gain and higher

SUGAR— NOT ALL THAT BAD?

Although sugar functions as a source of energy for the body, in special cases, it may also provide additional benefits.

- Sucrose and glucose have been shown to be effective analgesics in newborns undergoing heel-lancing, venipuncture, or intramuscular injection.[1]
- Sugar may be useful in wound healing by promoting a low-moisture environment that inhibits bacterial growth.[2]
- Hossain et al[3] suggested that the anti-hyperlipidemic effect of D-allulose, a no-calorie sweetener, in combination with its anti-inflammatory actions on adipocytes may be beneficial in the prevention of both obesity and atherosclerosis.
- Hayashi et al[4] noted that D-allulose suppressed the postprandial blood glucose elevation primarily in borderline diabetes cases.
- Soterakis et al[6] observed that the rate of alcohol removal from the blood was increased after ingesting fructose or sucrose compared to glucose.

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levels of sugar in the blood, and obesity increases the amounts of substances involved in the development of insulin resistance.[9] Gestational diabetes, on the other hand, occurs or is first identified during pregnancy,[8] although the International Association of Diabetes and Pregnancy Study Groups recommended in 2009 that high-risk women found to have diabetes at their initial prenatal visit should receive a diagnosis of overt (i.e., pre-pregnancy) diabetes rather than gestational diabetes.[10] Women at higher risk for developing gestational diabetes during pregnancy include those with marked obesity, a personal history of gestational diabetes, glycosuria (too much sugar in the urine), or a strong family history of diabetes.[8] As a general rule, therefore, diabetes can be either a result of dysfunction in the body's ability to process sugar or due to taking in more sugar than the body can properly process.

It has been recommended by the American Association of Clinical Endocrinologists and American College of Endocrinology that all adults aged 45 years and older be screened for prediabetes and diabetes regardless of their perceived risk,[11] while the United States Preventative Service Task Force (USPSTF) has suggested screening individuals with overweight or obesity who are 40 to 70 years of age.[12] According to the USPSTF, asymptomatic pregnant individuals should be screened for gestational diabetes no earlier than 24 weeks of pregnancy.[13]

HEALTH EFFECTS OF SUGAR CONSUMPTION

Natural vs. refined. Sugars as a group may be divided into two main types: natural and processed (or refined) sugars. While some sugar, such as glucose, fructose, and lactose, can be found in plants, fruits, and milk, others (e.g., high-fructose corn syrup) are created by way of heavy processing of certain natural sources such as sugar cane, sugar beets, and corn and are known as processed or refined sugars.[14] Certain sugars, such as sucrose, may also be defined as natural or processed depending on their source.[14]

Although natural and processed sugars are essentially metabolized in the body the same way, different effects can be observed among the different types of sugars.[15] Natural sugars are typically consumed in more limited quantities along with other nutrients, such as fiber and protein; as a result, natural sugars tend to be digested more slowly than added/refined sugars, ensuring the metabolism remains more stable over time.[15] In contrast, refined/processed sugars are typically added to foods in variable, sometimes significant, quantities,[15] resulting in variable processes of breakdown and variable amounts released into the bloodstream.

In a study that compared of the effects of different amounts of glucose, sucrose, or fructose added to tea to differing portions of carbohydrates in white bread (containing sucrose) on plasma glucose and insulin responses, Lee et al[16] found that the mean postconsumption glycemic and insulinemic index values of glucose were greater and those of fructose were smaller, respectively, in tea than those of the bread.

Evans et al[17] reported following a systematic review and meta-analysis that substituting fructose for glucose or sucrose in food or beverages lowers both peak postprandial blood glucose and insulin concentrations.

Yunker et al[18] concluded from their study that sucrose is less efficient at signaling postprandial satiation than glucose.

Finally, Teff et al[19] contended that, because fructose does not stimulate insulin secretion as glucose does, meals high in fructose likely result in lower concentrations of the hormone leptin, which is regulated by insulin-mediated glucose metabolism and is responsible, along with insulin, for long-term regulation of energy balance.As such, chronic consumption of diets high in fructose could facilitate persistent reductions in both insulin and leptin, leading to increased caloric intake and weight gain.

Cardiovascular disease (CVD). Persistently increased amounts of sugar intake, which can raise the blood sugar level, have been linked to a number of adverse health effects. Malik et al[20] reported that the consumption of sugar-sweetened beverages, collectively considered to be one of the most significant contributors to added sugar intake in the United States,[21] was positively associated with CVD in a dose-response manner.

In a meta-analysis and systematic review of 5,301 articles, Yin et al[22] narrowed the effect further, observing that a one serving-per-day increment of sugar-sweetened beverages was associated with an eight-percent higher risk of both CVD and mortality.

According to the results of a study by Kim et al,[23] a one serving-per-day increment of sugar-sweetened beverages was also associated with a similarly heightened risk of hypertension.

In a Swedish population-based prospective cohort study, Janzi et al[24] found that more than eight servings a week of sugar-sweetened beverages was associated with an increased risk (19%) of stroke.

Swaminathan et al[25] reported that systolic and diastolic blood pressure values were higher in study participants with a greater intake of refined grains, which include fewer nutrients and may be processed more rapidly in the body, leading to a greater increase in postprandial blood glucose concentrations as a result of the refinement process. Along these lines, Musa-Veloso et al[26] also documented an association between the consumption of intact oat kernels and a significant reduction in postprandial blood glucose levels compared to the consumption of refined grain.

In a meta-analysis, Meng et al[27] reported that increased intake of both sugar-sweetened and artificially sweetened beverages was associated with increased risk of Type 2 diabetes, CVD, and all-cause mortality.

Kidney and liver disease. The kidneys are also adversely affected by excess sugar in the blood. While the kidneys normally help to filter most glucose out from the blood for reabsorption, when the blood glucose level reaches at least 180mg/dL, such as in those individuals with uncontrolled diabetes, the kidneys begin excreting sugar into the urine in larger amounts (≥25mg/dL)—a condition known as glycosuria.[28] In patients with diabetes, diabetic nephropathy may emerge as a result of hyperglycemia,[29] leading to chronic kidney disease and end-stage renal failure.[30] Excess consumption of fructose may also be associated with gout as a result of the former's propensity to increase uric acid levels.[32] Fructose consumption has also been reported as a risk factor for nonalcoholic fatty liver disease.[31]

Compromised immunity. High blood sugar levels may also render individuals more susceptible to frequent and/or serious infections.[33] Both Type 1 and Type 2 diabetes have been found to significantly increase the risk of experiencing more severe complications from COVID-19 infection.[34]

Oral disease. Research suggests sugar consumption also has a direct relationship with oral health, specifically pertaining to the formation of dental caries, as the presence of sugars—especially sucrose,[35,36] which is fermentable—disrupts the pH in the mouth, resulting in an oral environment more favorable to those bacteria that produce dental biofilm.

Mood and cognitive dysfunction. Knüppel et al[37] documented an adverse effect of sugar intake on mental health, particularly noting an increase in incident mood disorders in men.

Seetharaman et al,[38] using data from the Swedish Adoption/Twin Study of Aging, found that high blood glucose levels correlated with poorer overall performance in perceptual speed as well as greater rates of cognitive decline in general, perceptual mental speed, verbal ability, and spatial ability scores. The same study reported that diet-based glycemic load was correlated with poorer overall performance in both perceptual speed and spatial ability.

Francis et al[39] found that a diet high in fat and refined sugar (HFS) was associated with poorer performance on hippocampal-sensitive memory tasks; a second experiment clarified that this effect is specific to hippocampal functioning and does not extend to measures of prefrontal cortex function. Also, in a laboratory-based test of food intake, the HFS-rich diet groups were less accurate when attempting to recall what they had previously eaten and demonstrated reduced sensitivity to internal signals of hunger and satiety.[39]

Cancer. Some research has attempted to discern sugar's role in cancer formation. In a French study, Debras et al[40] noted that consumption of diets with a higher glycemic load (e.g., those containing bread), which is a measure of how rapidly a specific carbohydrate food raises blood sugar, was associated with a higher overall risk for cancer, specifically postmenopausal breast cancer.

Sieri et al[41] reported similar results, finding that diets with a higher glycemic load appeared to inflate the risk of breast cancer, especially in premenopausal women and

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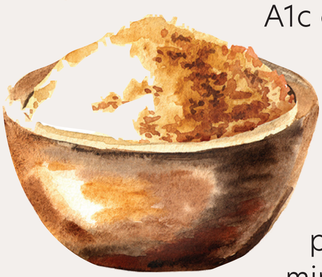
SWEET NEWS FOR PEOPLE WITH DIABETES

While the sugar content, whether naturally occurring or added during food processing, of many foods can increase blood sugar levels in the body,[1] this is not true in every case. For example, **monk fruit**—a small, round fruit grown in southeast Asia—contains natural sugars such as fructose, but it primarily gains its sweetness from mogroside V, a type of glycoside, which can be extracted for use as a food additive.[2] Though glycosides are compounds in which sugar is bound to another functional group by way of a glycosidic bond,[3] some research in diabetic rats indicates that monk fruit extract may have an antihyperglycemic effect[4] and may limit diabetic complications associated with oxidative stress.[4,5] Ban et al[6] similarly reported that diabetic rats fed yogurt sweetened with monk fruit showed greater blood glucose regulation and a significant reduction in both insulin resistance and glycosylated hemoglobin concentration compared to those fed yogurt sweetened with sucrose.

Stevia gains its sweetness from the actions of an enzyme, uridine diphosphate-dependent glucosyltransferase, which catalyzes the addition of branched glucosides to compounds (primarily stevioside and rebaudioside A) known as steviol glycosides.[7] According to Lee et al,[8] both steviol glycosides and their glucosylated derivatives demonstrate antihyperglycemic effects by activating glucose-induced insulin secretion. Chang et al[9] reported that oral administration of stevioside improves insulin sensitivity in rats. Research has also indicated that stevia may also have preferential effects in people with diabetes; for example, Gregersen et al[10] found that stevioside reduced postprandial blood glucose levels in individuals with Type 2 diabetes, and Rashad et al[11] observed that stevioside supplementation for 24 weeks improved glycemic control, fasting plasma glucose, two-hour plasma glucose, fasting serum insulin, Homeostasis Model Assessment of Insulin Resistance score, and hemoglobin A1c concentration in people with diabetes.



In addition, at least seven **naturally occurring "sweet" proteins** are known to exist—thaumatin, monellin, mabinlin, pentadin, brazzein, curculin, and miraculin.[12] These proteins may be sourced from various fruits in Africa and Asia,[12] and commercialization efforts are ongoing.[13]

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those with body mass index values of less than 25mg/m^2.

Laguna et al[42] linked simple sugar intake in drinks and fruit juice with an increased risk of both overall cancer incidence and mortality and all-cause mortality.

Finally, a 2017 report based on internal documents from a research project funded by the Sugar Research Foundation in the 1960s revealed that sucrose consumption was associated with elevated levels of beta-glucuronidase, an enzyme previously associated with bladder cancer in humans.[43]

Artificial and sugar alcohol sweeteners. Of note, the aforementioned studies focused on natural and processed sugars and did not include artificial (also known as no- or low-calorie) sweeteners (e.g., aspartame, sucralose) or sugar alcohols, (e.g., xylitol, maltitol, erythritol), which have their own health effects. Artificial sweeteners, which impart sweetness without the calories, could initially facilitate a modest amount of weight loss,[44] but over time may lead to weight gain by disrupting the brain's association between sweetness and caloric intake.[45] Artificial sweeteners have also been linked to shifts in the gut microbiota, which may promote antibiotic resistance[47] or even render certain bacteria pathogenic.[47]

Sugar alcohols are a kind of carbohydrate that raises the blood sugar less significantly than traditional sugars, potentially making them a good alternative; Mohsenpour et al[48] reported that a mixture of sugars and a sugar alcohol (lactose, fructose, sucrose, and erythritol) led to improved blood glucose levels compared to the same amount of glucose or sucrose, without any significant adverse effects. However, sugar alcohols have been linked to irritable bowel syndrome.[49]

GUIDELINES AND MOVING FORWARD

Both the 2020 to 2025 Dietary Guidelines for Americans[50] and the World Health Organization[51] recommend that consumption of added sugar should compose no more than 10 percent of an adult's daily calorie count. The American Heart Association[52] recommends limiting the amount of added sugars to not more than half of one's daily discretionary calorie allowance(i.e., no more than 100 calories per day for women and no more than 150 calories per day for men [or ~6 and ~9 teaspoons per day, respectively]). However, although Powell et al[53] documented a notable decline in calories from added sugars between 2003 and 2012 following a significant increase between 1977 and 2003, no further decline occurred from 2003 to 2012, and added sugar intake levels remained above the recommended level of 10 percent of the total energy intake as of 2016. Indeed, the 2020 to 2025 Dietary Guidelines for Americans[50] suggest that 80 percent of men and 77 percent of women in the United States still exceed the recommended 10 percent limitation for added sugar intake.

Key Takeaways

- Sugar, as a type of carbohydrate, provides energy to the body, and it may be found in both simple or complex and natural or processed (added) forms.
- Dysfunction in the body's processing of sugars as a result of disease, genetics, medication, or injury leads to blood sugar levels that are too low or too high, which may lead to further complications.
- Excess sugar intake, which can overwhelm the body's processing efforts, can also lead to disease.
- It is recommended that added sugars compose no more than 6% to 10% of an adult's daily calorie count.
- Sugar consumption in the United States remains too high, although it has decreased from decades ago.
- Artificial sweeteners and sugar alcohols are alternatives to traditional sugars and carry their own risks and benefits.

Editor's note: Please consult with your physician or nutritionist regarding sugar intake and what kind of diet is best for you.

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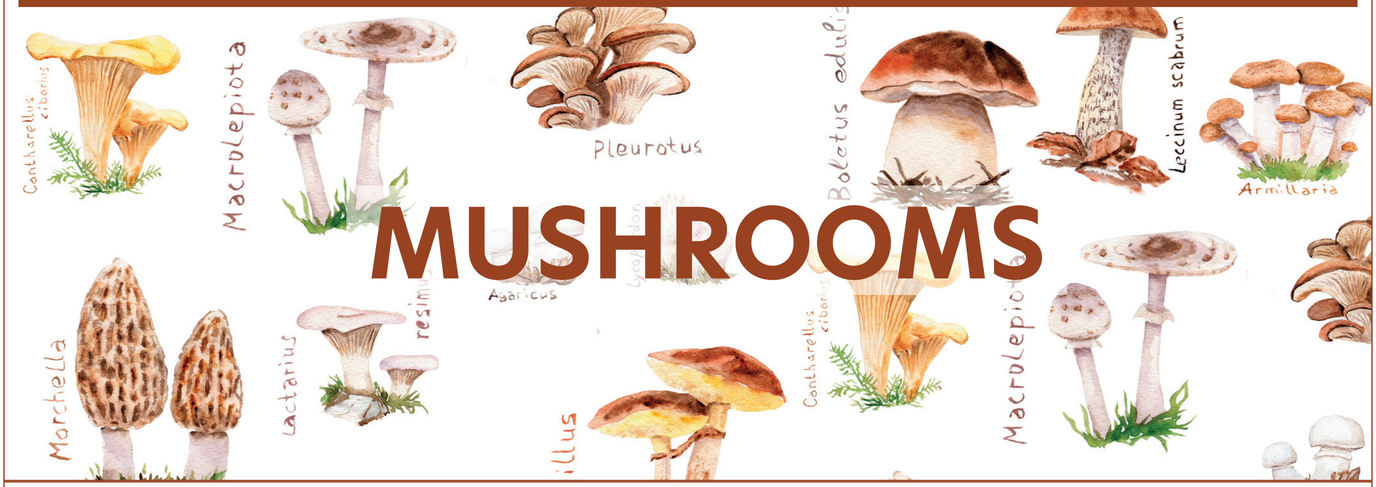
About the Author

Ms. Becker is the managing editor of *The Journal of Innovations in Cardiac Rhythm Management*. She also works as a freelance editor and as a teaching assistant for the George Washington University's Master of Professional Studies in Publishing program.

Superfood Spotlight



MUSHROOMS

A mushroom is a spore-bearing fruiting body of a fungus—a simple definition for a rather complex group of living organisms. Indeed, mushrooms and other fungi are considered neither plant nor animal—they comprise their very own self-named kingdom within the Eurkarya domain of the taxonomy of living things.[1] In fact, recent studies indicate that fungi are actually more closely related to animals than to plants and play an essential role across the various ecosystems of the world.[2] Unfortunately, describing what makes the over six million species of fungi worldwide different from plants and similar to animals, as well as how they impact nature as a whole, is well-beyond the scope of this article. So, you'll just have to settle for this review article in which we focus on edible species of mushrooms and the roles they play in human diet and health.

HISTORY OF MUSHROOM CULTIVATION

Cultivation of mushrooms likely began with the Chinese—Tao Hongjing (456–536 CE) included a commentary on cultivating the mushroom *Wolfiporia cocos* in *Bencao Jing Jinzhu*, an extension of an extension of the *Shennong Bencao Jing,* the oldest surviving Chinese materia medica, which categorized medicinal uses of 365 herbs.[3] In contrast, early cultivation of mushrooms in Europe was documented much later, during the mid-1600s, beginning in abandoned quarries and caves near Paris.[4] Both Asian and European mushroom cultivation practices were subsequently introduced in the United States in the 1870s.[5] Today, of about 2,000 species of mushrooms considered safe for consumption, 25 to 35 are widely eaten, and fewer than that are commercially cultivated.[6,7]

MUSHROOM NUTRIENT COMPOSITION

While the primary mass of most mushroom fruitbodies is water, depending on the species—and even within the same genus—mushrooms contain varying percentages of carbohydrates (3–42% dry matter [DM]), protein (4–44%; maximum, 57.3% DM), and lipids (2–6% DM).[8] Mushrooms are low in calories yet contain a variety of vitamins, polyphenols, carotenoids, macroelements, and other bioactive components.[8,9] In an analysis, the addition of an 84g serving of commonly consumed raw mushrooms (e.g., the white, brown/cremini, and portabella states of *Agaricus bisporus*) to United States (US) Department of Agriculture Food Patterns resulted in a 2- to 3-percent increase in fiber, an 8- to 12-percent increase in potassium, a 12- to 18-percent increase in riboflavin, an 11- to 26-percent increase in niacin, an 11- to 23-percent increase in selenium, and a 16- to 26-percent increase in copper depending upon the pattern type and calorie level but only one-percent or less increase in sodium, a one-percent increase in calories, and no effect on saturated fat or cholesterol.[10] Adding a serving of raw specialty mushrooms (*Pleurotus ostreatus*) also increased dietary vitamin D by 8 to 11 percent and dietary choline by 10 to 16 percent.[10]

The nutrient profiles of mushrooms can also vary depending on the environment in which they grow; for example, a comparison of wild and commercial species of mushrooms revealed that the latter generally contained more fat, less protein, and more sugar. When considering types of vitamin E, higher levels of α-tocopherol but undetectable levels of γ-tocopherol were found in the wild species, and the wild species also contained lower concentrations of monounsaturated fatty acids but higher concentrations of polyunsaturated fatty acids as well as higher concentrations of phenols but a lower concentration of ascorbic acid compared to commercial mushrooms.[11] A separate study confirmed the greater phenol content and antioxidant capacity of wild mushrooms compared to commercial mushrooms.[12]

MUSHROOMS AS MEDICINE

Views on the consumption of mushrooms varied across the ancient world; while leading Roman medical practitioners were wary of mushroom consumption due to numerous cases of accidental poisoning and excessive consumption of edible mushrooms leading to indigestion by the populace,[13] Eastern populations, such as the Chinese, Japanese, and Indians, have long viewed mushrooms as medicinal aids.[14,15] Today, the health benefits of various mushrooms are known to include antioxidant, prebiotic, antihypertensive, anti-inflammatory, antiviral/antimicrobial, neuroprotective, hepatoprotective, and antitumor/anticancer effects, among others.[16–18]

Cardiovascular and metabolic health. Research suggests that edible mushroom consumption may favorably alter metabolic markers (e.g. cholesterol, triglycerides) and reduce blood pressure,[19–21] although the effects can differ depending on the mushroom. For example, among spontaneously hypertensive rats (a common animal model of hypertension and cardiovascular disease) in one study, those fed maitake mushrooms (*Grifola frondose*) experienced a decrease in their total cholesterol level compared to the control group, while those fed shiitake mushrooms (*Lentinus edodes*) experienced a reduction in their free cholesterol level.[20] There was no difference in the plasma triglyceride or phospholipid levels between the experimental groups; however, shiitake consumption resulted in a decrease in both very-low-density lipoprotein ("bad") cholesterol and high-density lipoprotein ("good") cholesterol compared to the control group, while maitake consumption elicited a decrease in very-low-density lipoprotein ("bad") cholesterol only.[20] Some of the same investigators reported in another study that the blood pressure of spontaneously hypertensive rats was significantly reduced following eight weeks of maitake mushroom consumption, but this effect was not true with shitake consumption. Moreover, although the investigators affirmed the reduction in plasma-free cholesterol levels and reported reductions in triglyceride and phospholipid levels with shiitake intake, they did not observe reductions in either total or free cholesterol levels or triglyceride and phospholipid levels with the consumption of maitake mushrooms.[21] Keeping in mind all these findings and that free cholesterol has cytotoxic effects (which may be mitigated by high-density lipoprotein cholesterol),[22] the intake of both mushrooms (ensuring variety) rather than either alone, in combination with other healthy foods (i.e., those that increase high-density lipoprotein cholesterol and phospholipid concentrations on their own), may lead to the best outcome.

Collectively, edible mushrooms appear to support glucose control by a variety of mechanisms, including inhibiting glucose absorption, protecting β-cells (which produce and release insulin in the pancreas) from damage, increasing insulin release, and regulating different relevant pathways in the body.[23] In Type 2 diabetic C57BL/6 mice (which carry a genetic predisposition to develop Type 2 diabetes), oral administration of 250 or 500mg/kg of chaga mushroom (*Inonotus obliquus*) extract significantly alleviated insulin resistance, with a dose–effect relationship noted within a certain range; indeed, the authors reported that the 500mg/kg dose of extract achieved an effect similar to that of the diabetes drug metformin.[24] Along these lines, oral administration of 900mg/kg of chaga mushroom in another study led to reductions in fasting blood glucose levels, an improved glucose-tolerance ability, an increased hepatic glycogen level (to better prevent high blood glucose levels), and ameliorated insulin resistance in a Type 2 diabetic mouse model induced by a high-fat diet and streptozotocin (a compound with preferential toxicity toward pancreatic β-cells) compared to diabetic control mice.[25]

Immune function. Research has attributed the beneficial effects of edible mushrooms on the immune system to their ability to modulate different cytokine responses. In cancer, maitake, *Ganoderma lucidum* (reishi), *Cordyceps sinensis*, and *Trametes versicolor* (turkey tail) may increase the production of T helper (Th)1 cytokines, such as interferon-γ, which activate death receptors on the surfaces of tumor cells to help Th1 cells locate and kill them.[26] Edible Agaricus, maitake, reishi, Cordyceps, and turkey tail mushrooms may also downregulate Th2 cytokines, which reduce Th1 cytokine concentrations, thus showing an additional benefit in treating cancer by maintaining higher concentrations of tumor-destroying Th1 cells.[26]

Edible mushrooms may also increase the therapeutic efficacy of mainstay treatments for cancer.[26] During chemotherapy, chemotherapeutic agents penetrate and accumulate in tumor cells to induce cell cycle arrest and apoptosis; as such, some edible mushrooms, such as Agaricus spp., may help drugs such as doxorubicin to accumulate intracellularly at greater doses, increasing their therapeutic efficacy.[27] Other edible mushrooms, when combined with such drugs, may help to inhibit tumor growth; one study concluded that administering an extract of *Cordyceps sinensis* in combination with cisplatin could inhibit tumor growth,[28] and another determined that the combination of polysaccharide K (a derivative of turkey tail mushrooms) and trastuzumab reduced cell growth in colorectal tumors by 96 percent.[29] Mushrooms may also minimize associated undesirable side effects of chemotherapy and radiation therapy, such as nausea, bone marrow suppression, anemia, and insomnia.[30]

Other research has examined mushroom intake for managing inflammatory conditions. According to a literature search, the various bioactive molecules found in mushrooms, including peptides, polysaccharides, terpenes, sterols, fatty acids, and phenols, may inhibit major proinflammatory biomarkers

Mushrooms and Beta-Glucans

Beta-glucans, a type of polysaccharide found in bacteria, yeasts, fungi, and plants, help to regulate inflammation (e.g., by decreasing levels of pro-inflammatory cytokines[1]) and activate or enhance the functional activity of various innate and adaptive immune cell populations, including macrophages, dendritic cells, and lymphocytes.[2] In cancer, β-glucans may increase counts of M1-phenotype tumor-associated (antitumor) macrophages and decrease counts of M2-phenotype tumor-associated (protumor) macrophages.[3] Lentinan, a fungal β-glucan constituent, has shown the ability to prolong cancer patient survival when combined with chemotherapy, compared to chemotherapy alone,[4,5] and it has also been linked to reductions of systemic inflammatory markers, such as serum C-reactive protein and macrophage inflammatory protein-1α/chemokine C-C ligand 3, and increases in the anti-inflammatory response markers interleukin-4 and interleukin-10.[6] Lentinan may also be useful for reversing hyperglycemia in the early and late stages of Type 1 diabetes.[7]

Pleuran, the β-glucan isolated from *Pleurotus ostreatus*, was found to reduce peripheral blood eosinophilia and stabilized serum levels of total immunoglobulin E in children with recurrent respiratory tract infections, which the study investigators suggest is due to its potential antiallergic effect.[8] According to other research, supplementation with a β-glucan derived from *Aureobasidium pullulans* was effective for the prevention of influenza in mice,[9] and β-glucan supplementation also led to reduced mortality in a mouse model of influenza.[10] Finally, a comparative study of β-glucans from different sources determined that treating keratinocytes with a β-glucan derived from *Schizophyllum commune* promoted *in-vivo* wound closure.[11]

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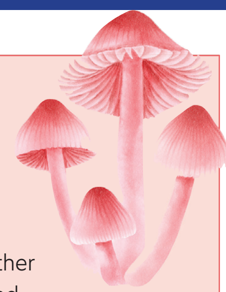
and associated pathways, thus exerting anti-inflammatory effects.[31] Mushrooms such as chaga,[34] maitake,[35] and reishi[36] also seem to have antiallergic effects by inhibiting the process of mast cell degranulation (during which mast cells release mediators, such as histamine).

Certain edible mushrooms may also combat viral infection by preventing viral entry or replication and stimulating immune cell responses. Polysaccharides from *Agaricus blazei Murrill*, for example, were found to reduce the cytopathic effects of Western equine encephalitis virus, herpes simplex virus (HSV), and poliovirus in Vero cells (a lineage of cells derived from kidney epithelial cells extracted from an African green monkey).[37] A sulfated derivative of a polysaccharide from *Agaricus brasiliensis Fr*. suppressed HSV-1 and HSV-2 cell attachment, cell penetration, and intracellular spread *in vitro*.[38] Interestingly, the sulfated derivative in question also displayed a synergistic antiviral effect against HSV when combined with the antiviral drug acyclovir, suggesting the potential of combining edible mushrooms with antiviral medications to improve treatment effects.[38]

Neuroprotection and neuroregeneration. According to investigators, edible mushrooms could play a role in the prevention[39] and treatment[40,41] of dementia, with various mushroom species displaying the potential to reduce or inhibit the production of beta-amyloid and phosphorylated tau.[42] However, mushroom consumption may also help to limit or prevent more general cognitive decline: among 663 participants 60 years of age or older in the Diet and Healthy Aging study in Singapore, those who consumed greater than two portions (>300g) of mushrooms per week had reduced odds of having mild cognitive impairment independent of age, sex, education, cigarette smoking, alcohol consumption, hypertension, diabetes, heart disease, stroke, physical activities, and social activities.[43] Similarly, greater mushroom intake was associated with better scores on certain cognitive performance tests among adults 60 years of age or older from the 2011–2014 U.S. National Health and Nutrition Examination Survey.[44] Along these lines, a

Mushrooms and the Central Nervous System



Different edible mushrooms may play a role in the prevention[1] and treatment[2,3] of dementia by reducing or inhibiting the production of β-amyloid and phosphorylated tau.[4] One study in which patients with mild Alzheimer's disease were administered either erinacine A–enriched lion's mane capsules or placebo demonstrated a significant reduction in the Cognitive Abilities Screening Instrument scores in the placebo group, a significant improvement in the Mini-mental State Examination scores in the lion's mane group, and a significant difference in Instrumental Activities of Daily Living scores between the two group after 49 weeks of treatment.[2] In mice, tests performed to evaluate memory and learning function suggested that lion's mane supplementation prevented the impairments of spatial short-term and visual recognition memory induced by amyloid β25–35 peptide.[5]

Lion's mane consumption may also benefit patients with depression and anxiety: in a study of 30 women, those who consumed lion's mane cookies for four weeks had reduced scores on the Center for Epidemiologic Studies Depression Scale and Indefinite Complaints Index, compared to those who consumed placebo cookies.[6] Separately, treatment with psilocybin, a naturally occurring psychedelic substance present in Psilocybe mushrooms, combined with psychedelic psychotherapy, relieved major depressive disorder symptoms in adult patients for up to one year,[7] and a systematic review and meta-analysis determined that psilocybin was more effective than placebo in treating state (threat-specific) anxiety for up to two weeks and trait (general) anxiety up to six months after treatment.[8]

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Poisonous Mushrooms and Medicine

Research has shown that edible mushrooms from a range of genera exert various anticancer treatment effects.[1] In addition, further investigation of α-amanitin, a toxin found in the poisonous *Amanita phalloides* mushroom, as a possible anticancer treatment has progressed with the development of antibody-drug conjugates, allowing for its safe delivery into the body,[2] and mouse studies have suggested its efficacy in treating colorectal cancer[3] and pancreatic cancer,[4] among others. *In vitro*, the administration of α-amanitin was also shown to inhibit subpopulations of cancer cells that survive in the presence of drugs (i.e., "drug-tolerant colonies"), suggesting its potential to prevent post-treatment cancer relapse.[5] Separately, illudins, which are terpene compounds derived from the poisonous mushroom *Omphalotus illudens* and related basidiomycetes, are rapidly (<2 hours) cytotoxic to different hematopoietic leukemia and solid tumor cells at pico- to nanomolar concentrations, while normal bone marrow progenitors and fibroblasts require longer exposure times at micro- or millimolar concentrations to experience similar effects,[6] which may support their development as cancer therapeutics. Importantly, mushrooms should not be used to replace prescribed medications or therapies without prior discussion with a physician.

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study from western Norway that recruited elderly participants (70–74 years) from the general population confirmed a linear increase in the dose-response association between mushroom consumption and cognitive test performance.[45]

The neuroprotective effects of edible mushrooms may be attributable to the amino acid ergothioneine, which the human body cannot synthesize itself but can source from certain foods, including mushrooms. Notably, however, whole-blood concentrations of ergothioneine were found to decline significantly after 60 years of age,[46] and ergothioneine levels were lower in individuals with mild cognitive impairment (plasma)[46] or Parkinson's disease (serum)[47] compared to age-matched healthy individuals. Some edible mushrooms, such as *Hericium erinaceus* (lion's mane), contain compounds that may also boost hippocampal memory by encouraging nerve growth.[48] The antioxidants in mushrooms may also help to control oxidative stress levels and maintain antioxidant defenses to prevent age-related neurodegeneration.[53]

Antioxidation. Mushrooms contain both primary and secondary antioxidants as well as compounds with antioxidant properties that act as cell signals and/or inducers, leading to alterations in gene expression that activate enzymes to eliminate reactive oxygen species.[50] Certain mushrooms also inhibit lipid peroxidation, a process in which reactive oxygen species trigger the oxidative deterioration of lipids.[55] One study determined that mushrooms contain unusually high amounts of ergothioneine and another antioxidant, glutathione, although the levels vary between species: among 13 species tested, maitake (2.41mg/g of dry weight) and *Agrocybe aegerita* (1.92mg/g of dry weight) mushrooms contained the most glutathione, and *Boletus edulis* (7.27mg/g of dry weight) and *Pleurotus citrinopileatus* (3.94mg/g of dry weight) mushrooms contained the most ergothioneine.[52]

Mushrooms also contain different amounts of other antioxidants, including phenolics, flavonoids, glycosides, polysaccharides, tocopherols, carotenoids, vitamins, minerals, and ascorbic acid.[50] In a study from Ethiopia, testing of two cultivated (*Pleurotus ostreatus* and shitake) and five wild (*Laetiporus sulphureus, Agaricus campestris, Termitomyces clypeatus, Termitomyces microcarpus*, and *Tapura letestui*) mushroom species indicated that, among them, *Agaricus campestris* exhibited significant antioxidant potential due to having the highest levels of multiple phenolic compounds, including ferulic acid, gallic acid, and p-hydroxybenzoic acid.[53] In another study investigating hot water extracts of *Agaricus, Antrodia, Auricularia, Coprinus, Cordyceps, Hericium, Grifola, Ganoderma, Lentinus, Phellinus*, and *Trametes* mushrooms, researchers reported concentrations of polyphenolic compounds and polysaccharides to be responsible for their high antioxidant potential, with *Ganoderma* mushrooms exhibiting the greatest antioxidant potential.[54] In another study, among 16 of the most popular edible species of wild-growing mushrooms, *Boletus chrysenteron* and *Boletus edulis* had high polyphenol contents and antioxidant activity.[55]

SUPPLEMENTING WITH MUSHROOMS

As an alternative to consuming mushrooms during meals, mushroom supplements are available and often combine multiple mushrooms that are heat-treated and milled to disrupt the chitinous cell wall matrix and increase the surface area for digestion and absorption.[56] When choosing a mushroom supplement, however, one may need to consider whether the mushroom mycelium (a web of fibers found underground) or the fruiting body (the cap and stalk) provides better nutrition, as different supplement companies opt to include one, the other, or both.[56] Ultimately, to secure one's preferred nutrient profile, the choice between a mycelium or fruiting body supplement may depend on the mushroom: one study comparing the antioxidant properties of commonly cultivated mushrooms between *in-vivo* (fruiting body) and *in-vitro* (mycelium) samples determined that the mushroom species with the greatest antioxidant potential was the brown *Agaricus bispous*, while, among the mycelium samples, shiitake mushrooms showed the highest antioxidant activity.[57] Similarly, other studies reported that the mycelium of *Pleurotus ostreatus* had greater concentrations of ergosterol and phenolic compounds than the corresponding fruiting body,[58] while fruiting bodies of *Agaricus bisporus*, when compared to both farm (old mycelium) and *in-vitro* (young) mycelium, contained higher levels of different phenols and ergothioneine.[59] In other cases, both parts of the same mushroom may contain unique nutrients: take, for example, lion's mane, where hericenones were isolated from the fruiting body but erinacines were isolated from the mycelium.[60]

A NOTE OF CAUTION

Like other foods, edible mushrooms should be consumed after being properly prepared. Cutaneous reactions (e.g., shitake dermatitis[61,62]) have been documented following the ingestion of raw or undercooked mushrooms. Raw Agaricus mushrooms also contain agaritine,[63,64] a hydrazine-derivative mycotoxin with carcinogenic properties in which concentrations may be reduced—although not removed entirely—by exposing the mushrooms to heat.[63] Similarly, *Agaricus bisporus* and another edible mushroom, *Gyromitra esculenta*, contain hydrazine analogs, which were found in an animal study following administration in drinking water continuously for life to directly or indirectly (by way of their derivatives) to cause tumors in various tissues in Swiss mice and Syrian (golden) hamsters.[65] Of course, serious anaphylactic reactions can occur in susceptible individuals following the consumption of even the most commonly eaten edible mushrooms.[66] Finally, mushroom supplementation should be monitored in individuals with more complex health conditions; for example, authors of a case series report of three Japanese patients with cancer suggested a causal relationship between the patients' severe hepatic damage and their use of *Agaricus blazei* extract as alternative medicine.[67]

Editor's note. Please discuss the consumption of mushrooms or mushroom supplements with your primary care practitioner.

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Mushroom Quinoa Burger with Special Sauce

Serves 4

Ingredients

1 large portobello mushroom, gills removed, roughly chopped
1 cup canned black beans, rinsed
2 tbsp almond butter
3 tbsp mayonnaise, divided
1 tsp ground pepper
¾ tsp garlic powder, divided
½ tsp salt
½ cup cooked quinoa
¼ cup rolled oats
1 tbsp ketchup
1 tsp Dijon mustard
1 tbsp olive oil
4 whole-wheat hamburger buns

Directions

1. Place chopped mushroom, black beans, almond butter, 1 tablespoon mayonnaise, pepper, 1/2 teaspoon garlic powder, and salt in a food processor. Pulse, stopping once or twice to scrape down the sides, until a coarse mixture forms that holds together when pressed. Transfer to a bowl and add quinoa and oats; stir well to combine. Refrigerate for 1 hour.
2. While mushroom mixture chills, whisk ketchup, mustard, and the remaining 2 tbsp mayonnaise and 1/4 teaspoon garlic powder in a small bowl until smooth. Set aside.
3. Shape the chilled mushroom mixture into four patties.
4. Heat oil in a large grill pan or nonstick skillet over medium-high heat. Add the patties and cook until golden and beginning to crisp, 4 to 5 minutes. Carefully flip and cook until golden brown, 2 to 4 minutes more.
5. Serve the burgers on buns with the special sauce and add your favorite toppings, such as lettuce, spinach, pickles, tomatoes, jalapeños, and/or red or sweet onions.

Estimated Nutrition Information (one sandwich)

Calories: 494; Total Fat: 15.8g; Saturated Fat: 2.1g; Cholesterol: 3mg; Sodium: 559mg; Total Carbohydrate: 72.6g; Dietary Fiber: 13.3g; Total Sugars: 6.6g; Protein: 19.8g; Calcium: 121mg; Iron: 6mg; Potassium: 1117mg NHR

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Nutrition

Nutrients for DNA Damage and Repair: Spotlight on Telomere Health

By Aliza Becker, BA, MPS
Ms. Becker is the Managing Editor of *The Journal of Innovations in Cardiac Rhythm Management*. She also works as a freelance editor, a consultant for *Origin Editorial*, and a teaching assistant for the George Washington University's Master of Professional Studies in Publishing program.

Deoxyribonucleic acid (DNA) damage in the body is responsible for both normal aging and the emergence of different health conditions.[1] Certain lifestyle choices, such as unprotected exposure to ultraviolet radiation or consuming unhealthy foods, can increase the amount of DNA damage incurred daily.[2] Making lifestyle changes, such as improving one's diet, may therefore have the potential to slow down aging and minimize disease onset by limiting or reversing DNA damage.

In the body, double-stranded DNA molecules coil around histone proteins to form chromosomes, which carry genomic information between cells.[3] Individual chromosomes are capped at both ends by regions of repetitive DNA sequences known as telomeres, which protect the ends of chromosomes from fraying or becoming entangled with each other.[4] In young cells, the enzyme telomerase keeps telomeres from wearing down; as cells continue to divide, however, there is no longer enough telomerase to go around, and telomeres become increasingly shorter until the cell can no longer divide successfully, at which point it dies.[4] Shorter telomeres may predispose individuals to a variety of diseases, including cancer, and a greater risk of mortality.[5] Telomere shortening is a natural part of the aging process, and inflammation may exacerbate the rate of telomere attrition, which leads to telomere dysfunction-mediated cellular senescence to further accelerate the aging process;[6] it has also been postulated that telomere shortening may promote inflammation,[7] leading to a potential feedback loop between the two phenomena.

Research suggests that diet can influence telomere length, although different macro- and micronutrients may have variable effects depending in part on their pro- or anti-inflammatory potential. It has been reported that dietary fiber is protective against high levels of C-reactive protein (CRP), a marker of acute inflammation,[8] and more fiber appears to be good for telomere health.[9] Cereal fiber, relative to vegetable and fruit fiber, has shown a more consistent association with lower inflammation,[10] and other research has concluded that cereal dietary fiber intake in particular is positively linked to leukocyte telomere length.[11]

Meanwhile, different types of fat seem to impact telomere length in different ways. Saturated fat and telomere length are negatively correlated.[12,13] Monounsaturated fatty acids collectively seem to have either a negative[12] or no association[13] with lymphocyte telomere length. Meanwhile, the reported effects of polyunsaturated fatty acids, although potentially positive overall,[12] are more complex: while the intake of linoleic acid (found in vegetable oils, nuts, seeds, meats, and eggs) was inversely associated with leukocyte telomere length,[11] that of another polyunsaturated fatty acid, arachidonic acid, was positively correlated with leukocyte telomere length.[12] In another study, blood levels of marine omega-3 fatty acids, another kind of polyunsaturated fatty acid, were also found to be inversely associated with the rate of leukocyte telomere shortening over a period of five years—that is, higher levels of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EHA) helped to slow down leukocyte telomere shortening over time.[14] It is important to note, however, that this study was conducted in a population of 608 outpatients with stable coronary artery disease,[14] and other research has suggested that the relationship between telomere shortening and macronutrients can be complicated by disease. Using data from the United States (US) National Health and Nutrition Examination Survey (NHANES), investigators in one study found that telomere length was positively correlated with high-density lipoprotein (HDL) cholesterol levels in individuals without diabetes, hypertension, coronary atherosclerotic heart disease, or hyperuricemia, yet the same relationship could not be identified in individuals with these conditions, which the authors attributed to the presence of HDL cholesterol dysfunction in these diseases.[15]

Other conditions, such as persistent high cholesterol (dyslipidemia), may also correlate with accelerated shortening of telomere length over time;[16] indeed, it is suggested that high serum lipid concentrations may be associated with systemic inflammation and atherosclerosis, which could lead to oxidative stress, resulting in telomere shortening and dysfunction.[17,18] In this vein, some research has suggested that antioxidant intake may positively influence telomere length. One study of Spanish children and adolescents found a positive correlation between the general dietary total antioxidant capacity and telomere length after adjustment for age and energy intake.[19] Other studies have also linked specific antioxidants to longer telomeres, including minerals, such as zinc and selenium;[20,21] vitamins C and E;[22,23] and carotenoids, such as lutein, zeaxanthin, and alpha- and beta-carotene.[24,25] However, one study determined that gamma-tocopherol (a form of vitamin E), found in nuts, vegetable oils, and seeds, but not alpha-tocopherol (another form of vitamin E), negatively impacted telomere length, with adults in the 75th percentile of gamma-tocopherol showing 2.8 to 3.4 years of greater cellular aging than those at the 25th percentile, depending on the covariates in the model.[26] The choice of antioxidant may therefore matter with regard to telomeric effects.

Consumption of sugar-sweetened beverages (SSBs) like soda and sports drinks have also been linked to shortened telomeres,[27] while the intake of 100-percent fruit juice may help to ensure longer telomeres.[28] Although it was unclear what the SSBs in question were sweetened with, other research contends that fructose, found in fruit juice, may lead to lower blood glucose and insulin concentrations[29] than either glucose or sucrose. The consumption of 100-percent fruit juice may also impart beneficial effects of phytochemicals and micronutrients (e.g., antioxidant vitamins) to balance out the negative effect of its sugar content.[30] However, other research contends that greater intakes of both total and added fructose are significantly associated with shorter relative telomere length,[31] and the intake of 100-percent fruit juice in the aforementioned study[28] led to only a marginal association with longer telomeres. Telomere shortening has also been linked to elevated fasting glucose, hemoglobin A1c (HbA1c), and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) values,[32,33] which can be indicators of progression toward diabetes, and patients with diabetes have shorter telomeres compared to healthy individuals.[34] Insulin resistance itself, the hallmark of diabetes, induces inflammation,[35] which has been linked to telomere shortening. As such, minimizing the consumption of all sugars may help to prevent accelerated telomere shortening.

Research on the link between protein intake and telomere length is limited; however, greater protein intake supports a lower-calorie diet,[36] helping to minimize inflammation.[37] Importantly, though, the source of the protein might matter; for example, the consumption of red meat[27] and particularly processed meats[27,38,39] has been inversely linked to telomere shortening. Although the trend may be linked to greater concentrations of certain nutrients, such as saturated fat, processed meat also contains high concentrations of advanced glycation end-products and nitrosamines that may promote inflammation and oxidative stress.[38,40] Moreover, considering for a moment other types of DNA damage, an analysis of tumors from patients with colorectal cancer revealed a specific "alkylating" pattern of DNA damage attributed to the production of certain compounds in the body following the consumption of red and processed meat,[41] and the intake of heterocyclic amines, a kind of carcinogen formed when meat, poultry, or fish is cooked at high temperatures, has also been suggested to result in DNA alkylation through their bioactivation upon consumption into reactive species.[42,43] As such, it is recommended to limit intake of animal products, especially processed meats, to avoid DNA damage, including telomere shortening.

Ultra-processed food, which typically contains greater amounts of saturated and trans fats, sugar, and salt—all of which trigger inflammation[44]—has been linked to shorter telomeres. A population of elderly Spanish individuals with the greatest consumption of ultra-processed food demonstrated almost twice the odds of having short telomeres, compared to those with the lowest consumption.[45] Beneficial nutrients are also typically stripped away during the industrial processes used to produce ultra-processed foods, and research suggests that deficiencies in folate, niacin, iron, and zinc as well as vitamins B12, B6, C, and E can mimic the DNA-damaging effects of radiation by causing single- and double-strand breaks, oxidative lesions, or both.[46]

Conversely, the Mediterranean diet in particular might support longer leukocyte telomeres;[47,48] one study of individuals at high risk for cardiovascular disease observed longer telomeres at baseline in participants with a more anti-inflammatory diet (lowest Dietary Inflammatory Index score) and, following a five-year intervention with the Mediterranean diet, longitudinal analyses suggested that a diet with greater anti-inflammatory potential could significantly slow down the rate of telomere shortening.[49] In other research comparing two major dietary patterns—"the prudent dietary pattern," which was characterized by a high intake of whole grains, fish and seafood, legumes, vegetables, and seaweed, and the "Western dietary

FOR A HEALTHY FRUIT SNACK, WHAT WOULD YOU CHOOSE?

Dried fruit has the best nutrition profile of all commercially available fruit snacks, with the highest nutrient density and fiber content and lowest added sugar content, according to a study from the University of Massachusetts Amherst. Canned fruit with juice and fruit puree also met current recommendations for nutrient dense snacks. Fruit-flavored snacks (e.g., gummies) had the highest added sugar content and lowest nutrient density and fiber content. Dried flavored fruit and canned fruit packed in something other than juice also had low nutrient density and high added sugar content.

Source: ScienceDaily. For a healthy fruit snack, what would you choose? 5 Mar 2024. https://www.sciencedaily.com/releases/2024/03/240305165908.htm. Accessed 26 Mar 2024. NHR pattern," which was characterized by a high intake of refined grain, red meat or processed meat, and sweetened carbonated beverages—the "prudent dietary pattern" was found to be positively associated with leukocyte telomere length, while an inverse trend was observed for the association between the "Western dietary pattern" and leukocyte telomere length.[27]

Finally, one study contended that the very act of cooking foods—including vegetables—at high temperatures might result in DNA mutations, abasic sites, or double-strand breaks by way of metabolic salvage; its authors noted distinct differences in the level of damage according to time and type of cooking, with roasting (220°C) causing more damage to food than boiling (100°C).[43] However, the authors of this study stress that more research is necessary.

Editor's notes. Although telomeres exist in all cells, leukocyte telomere length is the measure most commonly used in telomere length research.

Please discuss any health concerns, including those regarding your diet, with your primary care physician.

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HOW EATING DISORDERS CAN DAMAGE THE HEART

Eating disorders can lead to cardiovascular complications, such as bradycardia, congestive heart failure, and sudden cardiac death. The way eating disorders affect heart health can vary depending on the specific disorder. For example, weight loss and malnutrition in anorexia—which is characterized by body image distortion and restricted food intake and may involve excessive exercise and binge eating—can cause heart muscles to atrophy, which can then lead to bradycardia. Bulimia—which is characterized by body image distortion, binge eating, and purging behaviors—can cause electrolyte imbalances due to excessive vomiting and laxative use, thereby increasing the risk of abnormal heart rhythms. Postural orthostatic tachycardia syndrome (POTS) might also occur in individuals with eating disorders. Symptoms of POTS include rapid heartbeat, heart palpitations, dizziness, and lightheadedness. Eating disorder-related cardiovascular symptoms can include lightheadedness, chest pain, lack of energy, shortness of breath, and frequent nose bleeds. Treating the underlying eating disorder can help resolve cardiovascular complications.

Source: Williamson L. How eating disorders can damage the heart. American Heart Association. 26 Feb 2024. https://www.heart.org/en/news/2024/02/26/how-eating-disorders-can-damage-the-heart. Accessed 29 Mar 2024.