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Viewpoint

Ethical Issues in Patient Data Ownership

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Abstract

Patient data have conventionally been thought to be well protected by the privacy laws outlined in the United States. The increasing interest of for-profit companies in acquiring the databases of large health care systems poses new challenges to the protection of patients' privacy. It also raises ethical concerns of sharing patient data with entities that may exploit it for commercial interests and even target vulnerable populations. Recognizing that every breach in the confidentiality of large databases exposes millions of patients to the potential of being exploited is important in framing new rules for governing the sharing of patient data. Similarly, the ethical aspects of data voluntarily and altruistically provided by patients for research, which may be exploited for commercial interests due to patient data sharing between health care entities and third-party companies, need to be addressed. The rise of technologies such as artificial intelligence and the availability of personal data gleaned by data vendor companies place American patients at risk of being exploited both intentionally and inadvertently because of the sharing of their data by their health care provider institutions and third-party entities.

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data; privacy; ownership

Introduction

The history of patient records dates back 4000 years, when patient case records were stored in written form [1]. Unlike the modern technologically driven age, in ancient times, caregivers relied heavily on paper-derived means to maintain patient records. For example, ancient Egyptian hieroglyphics from 1600 to 3000 BC indicated that patient reports were inscribed on papyri [2]. In America, the clinical record pioneered major teaching hospitals in the 19th century, whereas medical records for direct patient care later developed in the 20th century. At this time, health records were traditionally written on paper, tediously organized, and divided into folders with only one copy per note. In an increasingly technological era, beginning in the late 20th century and the beginning of the 21st century, problems with the way patient records were documented began to emerge. Illegible handwriting and the inability to easily share, permanently store, and retrieve necessary information were some challenges faced in the predigital era. Studies from the time before technological development stated that tests were often reordered because of missing, illegible, or inaccessible components in patient records. One report from the late 20th century noted that 11% of laboratory tests were duplicated in one hospital because of unavailable information for the physician [3]. These were some of the driving factors in the need for a better health care system.

The trend toward automation of patient data recording coincided with the appearance of multiple new forms of reporting. Computers were introduced into hospital settings and used for administrative and financial purposes in the 1960s, with the goal of reducing clerical error and improving clinical decision making. The introduction of the electronic health record (EHR), and its less comprehensive counterpart electronic medical record (EMR), in the United States in the 1970s revolutionized the way patients were documented and treated. Although frequently interchanged, EMR refers to a digital record of a patient's treatment at a specific institution, whereas electronic health record is a complete longitudinal record of a patient's medical history and treatment. The Institute of Medicine (which changed its name to National Academy of Medicine in 2015) reported

that information technology is essential for quality patient care. The dawn of a digital age provided medical professionals an opportunity not only to obtain a greater depth of medical knowledge but also to access patient information almost effortlessly. With such technological features, physicians can now easily acquire a patient's list of allergies, medications and dosages, and past medical and surgical histories. EMR changed how the medical world maintains patient records by establishing an ease and convenience in how health reports are read and accessed today. However, there is debate in the United States on whether EMR is beneficial for patients [4]. In particular, there are arguments that digitalization may come at the price of patient privacy. A balance between upholding patient privacy, autonomy, and furthering medical knowledge through research and providing efficient, beneficial patient care, as outlined in the principle of beneficence, has become an increasingly important topic because of the rise of advanced technology integration into medical practice.

Legal Considerations for Patient Data in the United States

What distinguishes patient data, in particular, from browsing data and metadata is the legal binding of patient-physician confidentiality because of the provisions in the 1957 Code of Medical Ethics of the American Medical Association, section 4. In 1996, the Health Insurance Portability and Accountability Act (HIPAA) was established. The HIPAA Privacy Rule protects all "individually identifiable health information" and "protected health information" (PHI) held or transmitted by a covered entity or its business associate, in any form or media, whether electronic, paper, or oral. The Privacy Rule provides national standards and safeguards to protect individuals' personal health information and medical records. It sets the limits and conditions that govern the appropriate disclosure of such information with and without patient authorization. In addition, although HIPAA does not regulate the retention of information, there are legal requirements in place under the Code of Federal Regulations (CFR), namely 45 CFR §164.316(b)(1), for holding specific patient data in technology for a certain period. Thus, there exists a certain life cycle for patient records that consists of creation, utilization, maintenance, and ultimately destruction. This step-by-step management protocol is implemented through health record retention plans to make health information retrieval efficient and rapid. Plans address what data should be available that meet the required functions, such as continued patient care and legal purposes, time frames for data maintenance and destruction, and data destruction policies and procedures. Retention plans, such as the template of the Higher Education Act of 1965, must meet federal record retention requirements, state record retention requirements, and many disclosure requirements [5]. Legal requirements for holding patient data depend on federal and state requirements, which are specific to the type of documentation. For example, although records of patients with end-stage renal disease services must be maintained for 6 years, data on hospital radiologic services such as films and scans are maintained for 5 years [5]. Once a document has met its full retention period, an organization must ensure that paper and electronic records are destroyed in accordance with federal and state laws. Some methods of destruction include shredding and burning of paper records, pulverizing microfilm and laser disks, and magnetic degaussing of computerized data. However, anonymization is not currently considered a form of destruction.

The government also regulates the process of sharing patient information. Essentially, the Privacy Rule controls who can view and receive a patient's health information, including electronic, written, and oral forms. However, this rule presents additional problems with regard to confidentiality concerns. For example, there is an underlying challenge of protecting patients' privacy while communication occurs among health care providers, insurers, policyholders, and patients. Sharing confidential and sensitive patient information could affect patient coverage, billing, and claims processes. There is a possibility that disclosure results in denied justice, equity, or fairness based on shared sensitive patient data such as on sexual and reproductive health, mental health services, and substance abuse treatment. Although health care providers normally seek patients' consent when disclosing patient data for health insurance claims, the HIPAA Privacy Rule allows disclosure of PHI without patient authorization with organizations subject to the Privacy Rule, termed *covered entities*, for operations of treatment, payment, public safety, or requirement by law [6]. It should be noted that under 45 CFR §164.514, patient data in a HIPAA-limited data set can be shared without consent, and covered entities under the Privacy Rule include physician offices, clinics, psychologists, insurance companies, nursing homes, health care clearinghouses, and government agencies that contribute to health care. In all other cases, patient consent is required for the disclosure of information. An example of the exception under HIPAA for patient authorization is the requirement of insurers to send policyholders' explanation of benefits, which details service billing. As a result, the required disclosure of patient-sensitive information may have an effect of deterring or denying health care coverage. In addition, sharing sensitive patient information outside of the scope of the provider and patient runs the risk of stigmatization and discrimination in vulnerable populations and law enforcement involvement, such as in cases of immigration status. Physicians in cases such as these must balance the professional and ethical responsibilities of justice to provide quality care to all people regardless of their background [7].

Examples of Current Data Utility: Sharing and Distribution of Patient Data

Collecting patient data is fundamental in health care to provide the best and most appropriate care. It must also be conducted appropriately in a HIPAA-compliant manner. There are several software tools and research networks in the United States, such as Research Electronic Data Capture (REDCap), Research Action for Health Networks (REACHnet), and Agency for Healthcare Research and Quality (AHRQ), which demonstrate how patient data may be shared responsibly. Pooled patient data can help providers and researchers better recognize health issues, identify symptom similarities, advance treatment options, conduct studies, report trends, and stay updated with the current

literature, with the hope of improving patient outcomes. This is the basis for software programs such as REDCap. REDCap is a secure and intuitive web app created by Vanderbilt University for capturing data for clinical research and building and managing web-based surveys, databases, and projects. Most importantly, it is a highly secure data collection tool that complies with HIPAA and supports single- and multiple-site research studies. REDCap allows all project data to be stored at a local institution, while no data are transmitted from that institution to third-party institutions or organizations. Thus, it is limited to intrainstitutional study. In addition, patient information in REDCap can be marked as identifiable but can be easily deidentified by the user during export, providing safe intrainstitutional privacy and security [8]. Unlike the intrainstitutional limitation of REDCap, REACHnet is an interinstitutional data network consisting of multiple health systems, academic centers, and health organizations. Similar to REDCap, REACHnet's function is to conduct efficient yet multisite research to implement more effective health care decision making and improve population health.

Furthermore, the AHRQ has a mission to improve health care quality and make care more accessible, affordable, and equitable. The agency invests in health systems research and analyzes data to aid health care decision making and creates strategies to improve medical practice. The Healthcare Cost and Utilization Project (HCUP) is a collection of databases sponsored by the AHRQ. The HCUP network contains both clinical and nonclinical patient details, including patient demographics, diagnoses, procedures, charges, and insurance information. Thus, the HCUP enables research that focuses on many current health care policy issues such as access, cost, and quality of care [9]. An example is a statistical brief published in 2017 by the HCUP, which discusses the costs of emergency department (ED) visits for those with mental and substance use disorders. It reports that the rate of ED visits for mental health and substance abuse diagnoses increased by 44.1% from 2006 to 2014, translating to 20.3 visits per 1000 individuals [10]. Such studies by the AHRQ and its partner, the US Department of Health and Human Services, are focused on health policy concerns to improve, for example, ED service delivery costs for patients. In light of its beneficial nature in aiding policy decisions, patient data must be collected from the AHRQ databases. However, this can result in high costs. Depending on the scope of the reports, the cost of obtaining simple or comprehensive reports can vary, ranging from thousands to hundreds of thousands of dollars [11]. AHRQ, in addition to REDCap and REACHnet, presents a compelling argument on the benefit of patient data utility for health care improvement as well as examples of appropriate HIPPA-compliant use of patient information. These examples are in contrast with patient privacy problems found within the overlap of big tech companies and health care.

The Intersection of Big Tech and Health Care: Implications and Complications

The topic of patient privacy in technologically available patient data has gained traction in recent years, given the recent advances in big tech industries in health care [12]. The sale of patient data to commercial companies, such as Amazon, by hospitals and hospital networks has many disadvantageous implications. First, patient data may be exploited with unauthorized access by third parties (hackers). Second, individuals may lose control over their data when data collection companies are purchased by other companies. In these cases, the purchasing company gains access to the patient data and can use these data without the consent of the individuals in question. Third, there is a possibility that data that were anonymized and deidentified by these companies are reidentified. Data breaches in patient data may also result in the targeting of vulnerable populations and discrimination.

Big tech companies such as Amazon claim to enter the health care field for the benefit of the medical system, which is currently unable to synthesize the enormous patient database that is available. Another benefit of the technology industry is the ability to use medical data to develop new drugs, devices, and algorithms to help diagnose disease and help future patients. In particular, *Amazon Comprehend Medical* is Amazon Web Service developed to assist the medical system overwhelmed by patient information. The goal of Amazon Comprehend Medical is essentially to organize patient information into customized databases specific for pharmaceutical companies, hospitals, and researchers. Amazon's cloud service with advanced machine learning can theoretically *read* uploaded patient documents, identify the type of data, and categorize it into a database. This advanced program can pull key data points from unstructured health care data and published research. Comprehend Medical also helps the customer or, in this case, the patient. The service provides a platform for patients to easily gather information on their medical condition and appropriate medication and dosages from Amazon's database of doctor notes, clinical trial reports, and health records.

With Amazon's global reach and widespread user network, it is concerning how the company may not be doing enough to protect patient privacy and may misuse information for advertising purposes. Amazon claims that Comprehend Medical is HIPAA-eligible and can easily identify PHI before patient information is stored. As stated in HIPAA, PHI is based on a list of 18 identifiers (ie, name, age, and relevant dates) that can be used to recognize the identity of a patient and must be treated with special attention. Although Amazon reports that these identifiers can be detected, entities may not always map accurately to the list specified by Amazon's DetectPHI operation. In other words, Amazon Comprehend Medical contains all the relevant identifiers, but not all identifiers may be recognized and removed [13]. Furthermore, to protect patient privacy, federal restrictions are in place to prevent the use of medical data for marketing or any commercial purpose beyond patient care. Amazon reports that the cloud over which patient data are transferred does not collect or store any data processed by Comprehend Medical. However, it may be difficult to believe that PHI would not be used for product or service marketing given Amazon's heavy presence in the commercial world. One's apprehension toward Amazon Comprehend Medical may be furthered by the fact that it is *HIPAA-eligible* rather than HIPAA-compliant. HIPAA-eligible means that it is the

responsibility of the customer, medical institution, or health care organization that sells data to Amazon to ensure that it complies with patient privacy regulations [14]. Amazon may not be able to fully deidentify protected patient information; therefore, it is essentially on the patient and the providers to ensure compliance and uphold patient privacy.

As technology companies are increasingly merging with the health care field, concerns over patient privacy have become increasingly valid. First, patient information may be misused once personal data are shared in corporate mergers. In addition, patient data may be misused because of fraud and unauthorized access. For example, Amazon purchased the web-based pharmacy company PillPack in 2018 for approximately US $750 million, thereby inserting Amazon's dominance into supply chain management and delivery services. As a result of the acquisition, patient data and insurance information went to Amazon rather than a pharmaceutical company. PillPack functioned in combination with the third-party intermediary ReMyHealth and SureScripts, a company that gathered patient medical documentation and web-based prescriptions. PillPack used ReMyHealth to obtain patient data collected by SureScripts until 2019, when it was discovered that ReMyHealth had been involved in fraudulent activities. SureScripts alleged that ReMyHealth had provided unauthorized access to patient health information and exploited prescription information for marketing purposes. An investigation into ReMyHealth revealed that the company's fraud had manifested as several thousand requests for patient health insurance information and prescription drug price information, which was provided by ReMyHealth to other parties for marketing specific medications to consumers. Consequently, SureScripts terminated its contract with ReMyHealth. As ReMyHealth was the third-party company responsible for PillPack's information about patient prescriptions, SureScripts' termination with the company resulted in a blow to Amazon's PillPack, as it no longer had a clear or efficient way to access data [15].

Another intriguing example of a company accused of sharing and selling patient information, fraudulently or through deals with pharmaceutical companies, is 23andMe, a popular personal genomics and biotechnology company [16,17]. Companies such as 23andMe have made the discovery of an individual's ancestry as easy as swabbing one's cheek or spitting in a cup. However, similar to PillPack, ancestry discovery sites are not immune to fraud and confidentiality breaches. In fact, there was a privacy breach in 2017, in which more than 92 million accounts from the DNA testing service MyHeritage were found on a private server [18].

In addition to aiding in personal discovery, the company provides consumers the choice to opt for research conducted on behalf of academic and nonprofit organizations. It is no secret that DNA testing companies such as 23andMe and Ancestry share anonymized consumer genetic information with pharmaceutical giants such as GlaxoSmithKline, companies such as P&G Beauty, and university and research institutions as part of million-dollar deals, resulting in a further reduction in patient awareness and control of their own data utilization [19]. A main reason why consumers may choose to participate in research opportunities and discovery is simply consumer altruism toward improving health care and scientific knowledge. One may believe that if their DNA could help find the cause of, or a cure for, a disease, it would be worthwhile to contribute their genetic information. However, when a drug company actually brings a drug to market based, in part, on one's DNA, the general population will not be afforded a cheaper medication despite their altruistic efforts. Thus, in addition to the possibility of inappropriate distribution and commercial use of secure patient data, the fact that patients receive no financial compensation for the use of their own data provides a depth of complexity to the sharing and utilization of electronic health information. Simply put, patient privacy concerns may conflict with the advancement of knowledge through data sharing.

To further complicate matters on confidentiality, HIPAA's provisions for data protection do not necessarily mean that data are anonymous. For instance, deidentified patient data on Amazon Comprehend Medical may not remain anonymous. HIPAA-eligible Comprehend Medical can identify and redact certain PHIs to make web-based patient data anonymous. However, it is possible to reidentify patients from deidentified data [20-22]. A 2000 study from Carnegie Mellon University showed how anonymized US census data could identify some individuals simply by combining a few demographic details, such as city of birth and zip code [21]. Researchers in Europe have also claimed that they were able to correctly identify 99.98% of Americans in deidentified data sets using 15 demographic attributes [22].

Commercial Targeting of Vulnerable Populations: A Risky Possibility

Sharing sensitive patient information with other agencies and organizations could put vulnerable populations at risk. For example, agencies could potentially monitor sensitive demographic information such as transgender status and immigration for nonhealth purposes. The possibility of pharmaceutical companies using patient information to target vulnerable populations is also a relevant concern. In particular, in vulnerable populations, sensitive and confidential patient data may be used to deny justice, equality, or fairness. However, what is a vulnerable population? The term implies a disadvantaged subpopulation that requires more care, consideration, and protection in health care because of the risks of poorer health status, health care access, and life expectancy [23]. Older people, pregnant women, children, prisoners, minorities and refugees, and those with chronic illnesses are some examples of vulnerable populations. Sensitive information that vulnerable patients may fear of being monitored or exploited include history of domestic violence or substance use, genetic information, mental health information, sexual orientation, and immigration status. In addition to facing inequalities and provider bias, vulnerable populations might also have concerns regarding the use of patient data for profit utilization.

A contemporary example of health care systems targeting a vulnerable population for commercial purposes is that of recovering alcoholics and those with a history of substance use disorder. Alcohol or cigarette companies can exploit this addiction after disclosing individuals' past medical history by

providing triggering advertisements and marketing their products. If patient health care information is integrated into a technological world driven by business, it may not be difficult for pharmaceuticals to exploit sensitive information, such as sexuality, transgender status, immigration status, and history of substance use, and nonsensitive patient information, such as age and gender. One real case illustrating this possibility is that of Avanir Pharmaceuticals. In 2019, the company was charged with paying physicians kickbacks to promote prescriptions of its drug Nuedexta, primarily targeting long-term care facilities with older patients who may have presented with signs of dementia. However, the drug had no proven use in dementia treatment, and its purpose was clouded by the company's false and misleading information [24]. The purpose of these kickbacks was to raise Avanir Pharmaceutical's sales at the expense of the vulnerable older people and nursing care population. Furthermore, the state of Pennsylvania sued the pharmaceutical company Purdue Pharma in 2019 over claims that the company mass produces the drug OxyContin, thereby fueling the state's deadly opioid epidemic. Purdue allegedly targeted physicians and focused on the geriatric and veteran populations, assuring them that the drug was not addictive and downplaying any risk [25]. These are a few examples that indicate the risk associated with the commercial sharing of patient information that may be exploited by third-party organizations such as pharmaceuticals for commercial purposes. Vulnerable populations, such as older people, are more at risk than the average individual of being harmed by unethical marketing through manipulation or deception. Despite guidelines and legal requirements in place to protect vulnerable populations in fields such as labor and research (ie, Genetic Information Nondiscrimination Act, Americans with Disabilities Act, and Patient Protection and Affordable Care Act), vulnerable populations' health data are not protected on the web under these provisions.

It is important to note that pharmaceutical companies profiting from patient information do not necessarily need a comprehensive medical history or access to sensitive patient information to commercially target populations. Rather, drug companies can use browsing history, age, gender, and locations to piece together an individual's health issues and market appropriately. The power of advertising on pharmaceutical wealth has also been studied. For instance, a study by the Wharton school and the University of Southern California estimated that for every 10% increase in advertisement exposure, there was a corresponding 5% increase in the number of prescriptions purchased [26]. What lies behind what one sees on their computer screen is around a billion dollars spent by pharmaceutical companies and health care brands every year to market their goods on Facebook [27]. Although the pharmaceutical industry spent US $59 million on direct-to-consumer advertising on the internet in 2003, this number has risen to US $1 billion in recent years [28]. It is possible that direct-to-consumer drug advertising efforts on the internet have expanded, as searching for health-related information may become an increasingly common activity for web-based users. This presents an ethical *gray area* in terms of patient data and privacy, as even HIPAA does not address the crossing of drug companies and social media outlets. In addition, Amazon and companies such as Google and Microsoft have also purchased access to patient data. Just as social media platforms and pharmaceutical companies can exploit patient browsing history, tech companies such as these may pose similar privacy risks through the sharing of patient health information.

Potential for Improvement of Health Care Quality

Despite concerns about patient privacy, the integration of technology and medicine could improve the quality of health care. EMR and the benefit of Amazon Comprehend Medical in restructuring its data on both the patient and provider ends could empower a consumer to take charge of their own well-being and be more proactive in maintaining their health. Although it comes at a price of privacy, sharing patient information could equip consumer patients and partner organizations with more information about their health with the help of artificial intelligence (AI). Even nonhealth care–related data, such as patient habits and search history, could provide useful information. For instance, health care organizations could market cold and flu medicine to someone who frequently books appointments at the beginning of the flu season or recommend obstetricians to someone who recently bought prenatal supplements and pregnancy tests [29]. This type of predictive technology through AI can be used to help prevent hospital readmissions and identify at-risk patients. AI technology in health care could also enable the discovery of new patterns of disease, pathogenesis, and treatment. Some key categories of AI applications involve diagnosis and treatment recommendations, patient engagement and adherence, and administrative activities [30]. One of the most popular and increasingly relevant forms of AI in health care is machine learning and its application in precision medicine. Precision medicine in health care allows for the prediction of treatment protocol success based on patient traits and the context of the treatment. IBM Watson has gained much attention in the media because of its capability of precision medicine for cancer diagnosis and treatment. Google is also deriving an AI algorithm to create a prediction model that can alert physicians of high-risk conditions such as sepsis and heart failure [30]. Despite such immense achievements, full integration into health care processes and systems remains a challenge. Furthermore, although AI may have a future role in enabling the discovery of new disease patterns, pathogenesis, and treatment regimens, privacy and confidentiality risks remain ethical concerns in the field of AI in health care.

Privacy Solutions

The topic of patient privacy, in conjunction with the rising use of electronic records and the increasing realm of big tech companies, highlights a relevant point of study on whether sharing health care information does more harm than good. Patients generally want to share data to improve health care but want more control over sharing their personal health information. Thus, sharing clinical data should involve a degree of transparency in patient compliance. One study reported how respondents felt comfortable participating in research if they provided information about what aspects of their data were

being shared and with whom. The respondents were healthy volunteers who had responded to posted advertisements around the University of California San Diego within 4 months. A total of 83% showed a strong preference for the control of specific data, whereas 68% were concerned about the possibility of their information being used for commercial purposes [31]. Another study reports how patients prefer sharing their information with *granular* privacy control over which data would be shared and with whom. In addition, individuals have differences in preferences for which type of EMR data is shared. Regardless of whether individuals had sensitive information on record, they were less likely to want to share sensitive information when compared with nonsensitive information [32]. A study by Whiddett et al [33] supports this finding with a 2016 study of 4209 adults in New Zealand. This survey revealed that individuals are significantly more likely to share their data with nurses, doctors, and paramedics than with government agencies. In addition, individuals with sensitive information on records were significantly less likely to consent to sharing their records [33]. A large proportion of the population, especially vulnerable populations, is reluctant to share their records beyond health care professionals. Widespread distribution of patient information across platforms such as billing and insurance purposes, pharmaceutical involvement, and big tech companies may thus have adverse effects on the levels of patient trust in health care as well as the equal and fair treatment of patients in other facets.

It would be in patients' best interests to be actively involved in the development of policies on data sharing. Improving patient awareness about the type of data and nature of information contained in their records would be an appropriate measure, in addition to information regarding to whom their records are sent. Researchers should ensure that patients are given adequate informed consent regarding which aspects of their information are being used when seeking consent for data extraction. Maintenance of transparency among patients, providers, and research institutions is important. Patients should not only be notified when their data are used in research but also informed of the outcomes and future implications of this research. This, by definition, encompasses the solution of *dynamic* consent or the approach to informed consent that enables streamlined, continuous involvement and communication between individuals and the users of their data [34,35].

However, the transparency of dynamic consent is complicated by several factors such as the biases that individuals hold in sharing information; the question of what qualifies as *adequate* informed consent, including addressing various educational competencies; and differing expectations that individuals may have toward providing consent, which may involve varying expectations of their freedom to change the levels of consent or engagement [36,37]. Furthermore, big tech companies may attempt to share the least amount of information possible with individuals who still comply with consent requirements. First, the results of surveys that reveal how individuals are more likely to share their data with health care professionals may undermine or call into question the reliability and effectiveness of the obtained consent. Second, it is difficult to quantify or measure the extent of *adequate* consent. For instance, users of Amazon Comprehend Medical may not be aware of or understand the difference between HIPAA-compliant and HIPAA-eligible before providing the big tech company their sensitive health information. In this case, it is the company's duty and responsibility to inform all users of the risks in sharing patient information with the company and define their terms of HIPAA eligibility. Finally, individuals may have varying expectations on what is to be informed of them regarding the utilization and distribution of patient data. Although some may provide consent to many uses of their data with minimal disclosure, others may adopt a more limited approach to consent, with expectations of full transparency on use and anticipation of potential financial compensation before consenting. These differences in consent within a population make reevaluation of consent requirements more challenging. Thus, informed consent is difficult to generalize to a population. A solution to this dilemma is the model of *meta consent* as part of a smartphone app. The idea behind meta consent is that individuals should be asked how and when they would like to provide consent. It allows the patient to choose from a list of types of consent (specific consent, broad consent, blanket consent, and blanket refusal in the context) in the context of electronic patient records, data from samples, and commercial research. The meta consent app, a model successfully tested in an adult Danish population, is sensitive to individual consent preferences and caters to a wide variety of expectations regarding consent. Meta consent also allows greater transparency between individuals and data holders and places more control in the hands of individuals in choosing the terms of data use [38]. In addition to the meta consent model, individuals should be given the right to access, amend, and delete individually identifiable data held by data custodian or third-party processors. As such, this model should be used to collect consent preferences in the US population.

Given that HIPAA has not effectively protected patient information in several aspects such as vulnerable populations and in the realm of big tech, social media, and pharmaceutical involvement in health care, HIPAA laws should be amended to reflect current times. First, the definition of personal health information should be expanded to include broader protection for individuals. In this model, HIPAA would be revised to more closely resemble the 2018 California Consumer Privacy Act or the European Union's General Data Protection Regulation of *data concerning health* rather than the traditional American protection of data limited to health care [39,40]. This means that the 1996 law should add provisions detailing protection from the intersection of health-related Google searches and personal spending and commercial targeting. Essentially, web searches on a rare disorder and insurance coverage or buying a box of pregnancy tests should not result in increased web-based advertising of baby products or pharmaceutical endorsements. In addition, owing to the elevated concerns and apprehension of individuals toward sharing data with highly sensitive information, HIPAA should do more to protect vulnerable populations. Extra provisions should protect sensitive information from solicited distribution, such as between covered entities outlined in the Privacy Rule, and unsolicited distribution, such as data breaches and unauthorized sharing, of patient information that could result in altered insurance costs or any other form of inequality or unjust treatment.

Conclusions

This paper revealed the underlying conflict between what is overwhelmingly considered ethical in health care: patient autonomy and right to privacy, or beneficence, the ethical responsibility to do more good than harm. The integration of big tech companies such as Amazon into the realm of health care has many implications on confidentiality but could also have potential for advantageous discovery. We believe that collaboration on patient information on different fronts, such as the technological industry and medical centers, can provide valuable information that can enhance knowledge through research and improve patient-based care. However, digitalization and sharing of patient information have privacy implications that need to be addressed and fixed with modified provisions under HIPAA as well as enforcement of informed consent with flexibility in patient preferences. There are many factors that need to be considered legally and socially in terms of patient relationships when health information is shared with third parties, whether big tech, pharmaceuticals, or insurance companies. The rise of advanced technology in the 21st century presents this discussion as more relevant than ever.

Conflicts of Interest

None declared.

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Abbreviations

AHRQ: Agency for Healthcare Research and Quality
AI: artificial intelligence
CFR: Code of Federal Regulations
ED: emergency department

EMR: electronic medical record
HCUP: Healthcare Cost and Utilization Project
HIPAA: Health Insurance Portability and Accountability Act
PHI: protected health information
REACHnet: Research Action for Health Networks
REDCap: Research Electronic Data Capture

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Viewpoint

Cyberspace and Libel: A Dangerous Balance for Physicians

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Abstract

Freedom of speech and expression is one of the core tenets of modern societies. It was deemed to be so fundamentally essential to early American life that it was inscribed as the First Amendment of the United States Constitution. Over the past century, the rise of modern life also marked the rise of the digital era and age of social media. Freedom of speech thus transitioned from print to electronic media. Access to such content is almost instantaneous and available to a vast audience. From social media to online rating websites, online defamation may cause irreparable damage to a physician's reputation and practice. It is especially relevant in these times of political turbulence where the battle to separate facts from misinformation has started a debate about the responsibility of social media. The historical context of libel and its applicability in the age of increasing online presence is important for physicians since they are also bound by duty to protect the privacy of their patients. The use of public rating sites and social media will continue to be important for physicians, as online presence and incidents of defamation impact the practice of medicine.

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libel; reputation; physician; law; legal; defamation

Introduction

After many wars fought and won for freedom, Americans became free people living in a country under a democratically elected government. Although the government has control over civil conduct, its legitimate state power is seemingly unable to touch one monumental aspect of American lives—freedom of speech and expression. By definition, libel is a form of defamation conveyed by written text, pictures, signs or other physical forms of communication. It is detrimental to a person's reputation, personal or professional, and exposes them to public contempt or ridicule [1]. However, protection offered from the First Amendment has given the public a legal platform that facilitates discourse on current topics, on which ideas and opinions can be exchanged, and that offers protection against defamation in certain circumstances. The First Amendment states

> *Congress shall make no law respecting an establishment of religion, or prohibiting the free exercise thereof; or abridging the freedom of speech, or of the press; or the right of the people peaceably to assemble, and to petition the Government for a redress of grievances.* [2]

While the text explicitly states limitations applicable to Congress, the First Amendment has also been interpreted to encompass all branches of government, including federal, state, and local. This is the textual basis for the state action requirement that a plaintiff must demonstrate that local, state, or federal government sectors were responsible for a violation [3]. The United States Supreme Court ruling from the 1964 court case New York Times Co. v. Sullivan [4] added that it was prohibited that a public official receive financial recovery from a defamatory falsehood, unless it was proven that the statements were made with malice or reckless disregard [4,5]. This was a landmark case pertaining to freedom of press protection by the First Amendment which was later adopted in nonmedia defendant cases. It is also important to distinguish defamation from satire. Satire is a literary form of criticism that mocks and ridicules, commonly seen in political commentary

shows and used by political cartoonists or comedians to criticize public figures. Satire is implicitly protected by the First Amendment, under the free expression clause. Unlike libel, satire is not to be understood in a literal sense. However, like libel, satire can frequently be the topic of legal discussion.

Libel: A Historical Perspective

Libel has been a part of written communication for centuries. History provides plenty of antiquated, yet relevant, case examples of libel that sparked future discussions on the ethics of professional medical libel. During the 1793 yellow fever epidemic in Philadelphia, William Cobbett, a British journalist, published his concern over an American doctor's techniques to treat yellow fever in many papers. Dr. Benjamin Rush combatted the epidemic through mercury-based purgative and aggressive bloodletting—an approach largely discredited as a means of treatment later on in the 19th century. Although Cobbett was not a medical professional, he was a frontrunner in the application of medical epidemiology and biostatistics. Heralding evidence-based medicine, Cobbett used municipal records to prove that the perceived ghastly interventions performed by Rush did not in fact decrease the death rate from yellow fever. He presented data on mortalities during the epidemic, reporting that in the month following Rush's implemented treatment regimens, there was an average of 67 deaths per day [6]. While the use of data was revolutionary and his numbers did speak for themselves, Cobbett was a journalist and used his most powerful arsenal against Rush: the written word. Repeated published attacks against the doctor and his medical practice were publicly viewed and responded to, eventually leading to a medical libel lawsuit filed by Rush. In one text, Cobbett wrote,

> *...a mosquito, a horse-leach, a weasel – all are bleeders and understand their business full as well as Rush does his.* [7]

Rush openly said that such inflammatory texts had compromised his business and diminished his patient's confidence in his medical profession. After years of back-and-forth slander and trial hearings, Rush succeeded in his suit.

Through a contemporary lens, this result would be improbable given the added requisites in the United State Constitution for a case of libel. In the famous 1964 case New York Times Co. v. Sullivan [4], proof of actual malice was made a requirement to award of damages in a libel suit involving public figures. Justice William Brennan famously wrote that America has a

> *...profound national commitment to the principle that debate on public issues should be uninhibited, robust, and wide-open, [although] it may well include vehement, caustic, and sometimes unpleasantly sharp attacks on government and public officials.* [4]

The Court reasoned that open debate on public official conduct was more important than the potential damage to officials' reputations. A *public figure* is legally defined an individual of great public interest or fame such as politicians, celebrities, and well-known athletes. The term is commonly used in libel and defamation cases in which the standard for evidence is relatively higher, as proof that the remarks were published with *actual malice* is necessary. Proof of actual malice means that the publisher either knew that the statement was false or acted with reckless disregard for whether it was true or not. For example, one individual well-known for his revolutionary dieting advice, Dr. Robert Atkins, was considered a public figure in the 1975 court case Atkins v. Friedman [8], for he had sold millions of copies of his book Dr. Atkins Revolutionary Diet. A public figure under the legal tenet of actual malice, Atkins could not be compensated

> *...in the absence of proof that the defendant published the item with knowledge of its falsity or in reckless disregard of the truth.* [8]

Several additions and modifications to the court standing on New York Times Co. v. Sullivan have taken place in the years following the initial ruling. The 1974 court case Gertz v. Robert Welch, Inc. [9] was an exception to the precedent set by New York Times Co. v. Sullivan, stating that actual malice was not necessary for a case of defamation of private person if negligence is present. The Court rationalization is that public, unlike private, figures assume the risk of being attacked due to voluntarily entering the public light and must be prepared to face some attack. Furthermore, public figures have means of self-help and media to combat reputational harm that private persons simply cannot take advantage of to the same extent [10]. The second category of public figure is called the *limited purpose* public figure. Cited in the case Gertz v. Robert Welch, Inc., these individuals are those who have

> *...thrust themselves to the forefront of particular public controversies in order to influence the resolution of the issues involved.* [9]

Limited purpose public figures not only include individuals who shape debate on particular public issues and utilize media for influence, but also those who have distinguished themselves in a particular field. Just as famous basketball players in the National Basketball Association are considered public figures of the field of basketball, physicians can be considered limited purpose public figures, as they are especially distinguished in the field of medicine. However, the actual malice standard applies to both public figures and limited purpose public figures if the subject matter or controversy in question is related to the field in which the individual is prominent [11].

Unlike the ease with which Rush had filed a medical libel lawsuit in the 1700s, a professional in the modern day has to meet higher legal standards to establish a defamation action. Now, Cobbett's published words would simply be labeled as an opinion rather than as libel to which a case of defamation is applicable. As outlined in New York Times Co. v. Sullivan ruling, a plaintiff must show falsity in the statement of fact made, that it was defamatory and published, that an injury resulted from the publication, and that the defendant acted with a degree of fault. While private persons need not show proof of actual malice, negligence must be demonstrated. Like public figures, limited purpose public figures such as physicians must demonstrate actual malice. In addition, many websites that enable internet defamation, such as physician rating sites, are insulated against litigious claims from doctors under Section 230 of the 1996 Communication Decency Act [12], which makes

it more challenging to sue a web-based platform for defamation. This law states:

> *No provider or user of an interactive computer service shall be treated as the publisher or speaker of any information provided by another information content provider* [12]

If the physician can identify the author, they could file a case against the author; however, the cloak of anonymity often falls over commenters and reviewers on the internet, adding additional obstacles for physicians. These tenets provide the public means to express free speech and protect the principle that debate on public issues should be uninhibited, despite the potential caustic repercussions on individuals. Therefore, given these exacting requirements, physicians may find it difficult and may be unsuccessful in pursuing litigation for libel.

Libel in the Age of Social Media

While the 18th century had its share of defamation through newspaper writings, the 21st century introduced libel in the vast world of social media. With the invention of the internet and social media, people around the world can write what they experience, witness, and believe in a completely public arena. But that raises the question whether a tweet or public post on social media directed toward a medical professional constitutes libel. Is it considered libel if one were to express criticism about certain physician practices? The reality is that most people use the internet as a means to obtain information on health care professionals. One study [13] from 2005 shows that 80% of patients reported using the internet to research health topics such as specific medical conditions and prescription drug. Furthermore, a 2007 survey found that approximately one-third of internet users in California employ it for the purposes of finding a physician in a health network as well as for finding ratings of physicians on websites [14]. Another study [15] similarly notes that 24% of 61% of adults in the US who look online for health information have also looked online for ratings or reviews of doctors or other providers. More recent studies [16,17] have found that medically related internet searches were most related to symptom exploration. Subsequent reading about certain medical, and possibly unrelated, conditions without input from trained medical professionals may be a cause of acquiring and spreading false medical information. Recent reports have discovered that the internet can improve physician-patient relationships and communication, depending on the quality of information discussed [18]. Utilization of the internet for such health-related research could affect patient decision making when it comes to choosing their providers. Popular physician rating sites such as Vitals, Yelp, Angie's List, Healthgrades, RateMDs, and Zagat have become increasingly integrated into our lives and essential to assess before choosing care under a medical professional. With approximately 90% of physicians' professional information accessible online, it is no surprise that individuals use these platforms to write reviews, albeit most are positive [19]. A 2010 study [20] on online evaluations of physicians reported that, based on 33 physician-rating websites, 88% of reviews were positive in nature, while only 6% were negative.

Given these results, web-based platforms for physician ratings tend to be more beneficial than harmful, providing resources for patients and mostly positive feedback for providers. Physician-rating platforms are windows for individuals to report their experiences of a medical professional. If one considers how most individuals use rating platforms and the seemingly positive nature of most reviews, the chance of discovering anonymous criticism that is considered libel is slim. Furthermore, it would be legally difficult for a physician to file a case of libel, given the many requisites for this claim. First Amendment protections are broad, so rigorous requirements needed to be imposed to prove libel and genuine defamation of individuals, including state action requirements. As previously stated, per New York Times Co. v. Sullivan [4], in order for comments to satisfy the legal definition of defamation, they would need to be false (ie, lacking justification), communicated to a third party, and damaging to the injured party's reputation [21].

However, this may not always be the circumstance for cases of defamation. Defamation *per se* need not require evidence of harm to an individual for proving online defamation. In contrast to defamation *per quod*, where false statements are not inherently defamatory, defamation *per se* applies to false statements that are considered so damaging that they are deemed defamatory. While damage and actual malice must be proven in defamation *per quod*, statements are presumed harmful for defamation *per se* if false allegations fall into one of 4 categories: indication of involvement in criminal activity; indication of contagious, transmittable, and infectious disease; indications of heinous acts or sexual misconduct; and indications of behavior incompatible with managing professions, business, or trade [1]. Nonetheless, proving defamation is not easy, as statements that are considered opinions are not defamatory in the eyes of the law. In fact, negative comments on physician-rating websites qualitatively address physician interpersonal relationships, bedside mannerisms, and staff behavior [22]. Rather than illuminating aspects of the professional's medical expertise, the majority of online reviews place heavy emphasis on nonclinical attributes, such as office waiting time, etc. On the contrary, defamatory statements include false comments like that a physician is not board certified or other allegations that fall into the 4 previously mentioned categories. Furthermore, false allegations made online may be anonymously posted. In this case, physicians can file "John Doe" lawsuits. After demonstrating a prima facie case for defamation, a subpoena can be filed to track the internet protocol address to determine the identity of the poster.

While it is difficult for physicians to start a defamation lawsuit, it is not impossible. This does, however, come at a cost both for the physician on trial and for the defendant, the creator of the libelous statement. An abundance of time and expensive legal fees are just a few hurdles that both parties face. If the individuals responsible for the defamation are found guilty, they may face tremendous fees and could lose their employment [1]. One such case is that of Dr. Pieter Cohen versus Hi-Tech Pharmaceuticals from 2017 [23]. Dr. Cohen, an assistant professor at Harvard Medical School, had published a peer-reviewed scientific article revealing the toxic components

of weight-loss supplements manufactured by Hi-Tech. The company consequently filed suit for libel against Cohen. After 6 months of trials, the court ultimately ruled in favor of Cohen. Although he had won the lawsuit, it had left him with over $7000 in legal fees and the lost, irreplaceable time spent battling the pharmaceutical company rather than conducting research [23]. Dr. Cohen was one of the more fortunate individuals fighting a defamation lawsuit, as he had the financial support and occupational backing of Harvard Medical School. Others who make controversial claims as part of nonprofit organizations and small private institutions may, however, bear the brunt of such burdens. Observing this case from the lens of patients can explain why many may hesitate to express their thoughts online out of fear of repercussion from their medical providers, who, like Dr. Cohen, may be associated with large hospitals.

This, however, does not stop all patients from commenting on their provider's performance. It certainly would not be surprising if, of all medical practitioners, plastic surgeons received the most piercing online reviews in an age of aesthetic modification. In fact, one study [24] reports that, from 2011 to 2016, the number of online reviews on Google, Yelp, and RealSelf for breast augmentation grew at an average of 42.6% per year, with 69.5% of reviews commenting on aesthetic outcomes. One prominent case from 2014 was Loftus v. Nazari. Dr. Jean Loftus was a plastic surgeon who had performed a breast augmentation, breast lift, arm lift, and tummy tuck on patient Catherin Nazari. Unhappy with the results of her operation, Nazari took her frustration online and posted several negative reviews of Dr. Loftus on 3 rating sites. She most notably wrote that she was "left with permanent nerve damage in both arms, severe abdominal pain, horrible scars, and disfigurement in both breasts" because of Dr. Loftus [25]. In response, Loftus filed a defamation lawsuit against Nazari. Unfortunately for the physician in this case, the courts claimed that Nazari's remarks on her physical condition and Dr. Loftus' negligence were her opinions, as the comments were published on opinion websites [25]. The case of Loftus v. Nazari is one of several examples of defamation lawsuits in which pejorative comments are viewed as protected opinions by law.

The Libelous Arena of Twitter

The topic of libel in web-based platforms is also gaining more media attention following several recent tweets by government officials in the US. Most notably, Twitter labeled some of US President Donald Trump's tweets as misleading and a violation of the company's rules about glorifying violence. Other tweets by Trump describing mail-in-voting as fraudulent resulted in the company's placement of a fact-checking label on 2 of Trump's tweets [26]. Although one may think that it is important to distinguish the specific platforms in which allegations are expressed, the Florida Bar Journal states that the nature of the medium, whether public or private, is not as important as the content and nature of the communication [27]. On the contrary, comparing libelous statements on both private company sites such as Twitter and public forums such as RateMDs is like comparing apples to oranges due to Twitter's inability and RateMDs' ability to moderate misinformation and libel and remove users as it sees fit. The following is the physician review site's policy on ratings:

> *Reviews flagged for removal are reviewed by RateMDs and taken down if deemed inappropriate (for instance, because they contain demonstrably inaccurate or out of date information (to the extent that information was out of date at the time of the review), are libelous, or include accusations of unlawful activity, profanities or vulgarity, privacy violations, spam, or details that are not relevant or related to a patient's visit).* [28]

This is in stark contrast to Twitter's policy on the matter, which fosters discourse as long as it does not involve or incite violence, sexual exploitation, abuse, sensitive media, illegal services, and so on:

> *Twitter is a social broadcast network that enables people and organizations to publicly share brief messages instantly around the world. This brings a variety of people with different voices, ideas, and perspectives. People are allowed to post content, including potentially inflammatory content, as long as they're not violating the Twitter Rules. It's important to know that Twitter does not screen content or remove potentially offensive content.* [29]

While both RateMDs and Twitter foster online discourse, Twitter's requirements and standard for removal of content are much more extreme in nature, as libelous claims made against physicians are not considered "offensive content" enough for the private company to delete.

But how is Twitter able to house potentially damaging or libelous allegations, whether written about a physician or by the president? Section 230 of the Provision of the Communication Decency Act of 1996 is responsible [30]. It does this by protecting big social media websites from being liable for user content. The section states that

> *...no provider or user of an interactive computer service shall be treated as the publisher or speaker of any information provided by another information content provider.* [31]

Essentially, the function of the Communication Decency Act is to shield internet service providers from third-party content on their platform. Altering or revoking the protection afforded by this law may have interesting consequences: Would web-based platforms ensure that posted content is factually correct or would they stipulate authors to declare that their submissions are opinions? Both scenarios have implications for the medical community since vetted content is likely to lack misinformation and enforcement of an opinion label on posts would likely decrease credibility.

Solutions for Physicians

Patients are increasingly using web-based platforms to convey their views on medical providers. The challenge for physicians to build an adequate case for libel, and win, raises another question: How can medical providers develop strategies to

counter claims? What is expected of them when they are faced with libel or simply negative comments online? While most commentary on physician review websites is not legally defined as libel, there are instances of online defamation. Some cases may even surge onto the news and widespread public platforms. Arguably, the most important aspect that a physician must keep in mind when defending their reputation is to maintain professionalism and patient-physician confidentiality. Due to patient privacy provisions in the 1966 Health Insurance Portability and Accountability Act (HIPAA) and patient-confidentiality laws, physicians generally cannot easily or legally repudiate caustic or false comments on public forums without violating a privacy regulation [21]. The HIPAA Privacy Rule protects all

> *...individually identifiable health information held or transmitted by a covered entity or its business associate, in any form or media, whether electronic, paper, or oral...* [32]

and is termed *protected health information* [33]. When faced with negative commentary online, it would be in the provider's best interest not to respond, as posting reveals physician-patient relationship and violates HIPAA [34]. Nevertheless, HIPAA violations are rather common. The US Department of Health and Human Services reports that between April 2003 and September 2017, a total of 165,175 privacy rule complaints were received [34]. If a physician discusses or transmits protected health information without patient consent, they could face a financial penalty of up to US $50,000, depending on the nature and extent of the breach in confidentiality [35]. It is thus imperative for medical professionals, who choose to respond online to public scrutiny, to remain in accordance with HIPAA policies.

The question remains, what is a practical solution for physicians when faced with libelous claims? In addition to maintaining a professional physician-patient relationship and following HIPAA protocol, there are steps that medical professionals may take in the event of encountering defamation. Being proactive rather than reactive by monitoring and contacting public online spaces to remove the defamatory comments would be an appropriate step to take. Medical professionals should regularly check web-based platforms and set alerts to notify them of comments on their practice. Due to the tremendous financial cost and economic burden a medical practice may face with a defamation case, resorting to litigation should be approached with caution [1]. Physicians have the additional option of paying for reputation management software. For instance, RateMDs' Promoted Plus and Promoted packages for $359/month and $179/month, respectively, allow physicians to hide up to 3 unfavorable comments on the site.

Some doctors even go to the extent of nondisclosure agreements (NDAs), asking patients to sign a legal document that waives their right to post unauthorized online reviews in order to prevent risk of physician defamation. Dr. Jeffrey Segal is the chief executive officer and founder of Medical Justice, an organization that supports the use of such waivers [36]. NDAs, commonly called confidentiality agreements, are binding contracts that govern the sharing of information between people and organizations and that set limits for information use. NDAs are widely used in the workspace as a means of creating confidential employer-employee relationships and have become the topic of discussion in the rise of the #MeToo movement, as NDAs may prohibit victims of sexual harassment or assault from publicly discussing settlements or their trauma [37,38]. Dr. Segal's document, which has been adopted by several thousand providers and patients each year, states that physicians will provide additional privacy protection measures to patients in exchange for their agreement to not post positive or negative comments without the doctor's assent. However, patients still have plenty of avenues to speak about their experiences with family, friends, and other individuals, and review committees. While this movement is in no way an effort to forbid negative reviews and is not an antilibel intention, it is an attempt to provoke discussion on self-policing websites [39].

Physician Rating Through a Different Lens

Despite the negative perception that physicians may have of rating sites, online reviews and rating patterns could potentially help doctors improve or better manage their professional reputations. Given that studies show most reviews are positive and express opinions on physician attributes and overall satisfaction with the in-office visit, it would be expected that this online transparency should benefit providers [40]. This is the fundamental basis for the University of Utah health care system's venture in 2012 to survey all patients and post all their comments online [41]. Harvard Business Review cites University of Utah as the first hospital system in the United States to post all online physician reviews and comments. This strategy allows providers to privately receive their patient-experience data, which has reportedly resulted in conversations on how to improve the organization's approach to health care [42]. A physician can also receive a report card on their improvements, which patients in the system can review online due to implementation of transparent measures.

Conclusion

The internet has become intertwined in the daily lives of individuals in all professions and of all ages. The increasing use of web-based discussion, commenting, and spreading of information regarding physicians, however, should be a topic of interest. With the increasing utilization of web-based platforms to comment on a physician's practice, awareness of libel in the medical profession may grow as well. While filing a defamation claim may be enticing for a physician in sight of an inflammatory comment online, physicians should be aware of the difficulty, costs, risks, and requirements by law in pursuing such cases. Physicians do have several options on how to handle libelous claims, while, first and foremost, taking into consideration patient-physician confidentiality as outlined by HIPAA. It is also important to consider the use of web-based platforms and social media as an opportunity for improvement to medicine, rather than as an attack on their practice. Listening to online commentary may be able to help physicians acknowledge previously unrecognized faults or deficiencies

and better understand patient perspectives. While the internet may hold offensive commentary or false allegations, it may also become the building block of strong physician–patient relationships. In conclusion, whether the internet poses an opportunity for one to discover more about a disease, research a particular doctor, or speak at length about an unpleasant experience, it is undoubtedly shaping the landscape of medicine.

Conflicts of Interest

None declared.

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Abbreviations

HIPAA: Health Insurance Portability and Accountability Act
NDA: nondisclosure agreement

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Review

Surgical Treatments for Legg-Calvé-Perthes Disease: Comprehensive Review

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Abstract

Background: Legg-Calvé-Perthes disease (LCPD) is a common public health problem that usually occurs between the ages of 4 and 8 years, but it can occur between the ages of 2 and 15 years. This condition occurs due to the interruption of blood supply to the femoral head. Up to now, different surgical and nonsurgical treatments, including femoral varus osteotomy, innominate osteotomy, pelvic osteotomies, triple osteotomy, Chiari osteotomy, and shelf acetabuloplasty, have been suggested for noncontainable LCPD hips.

Objective: The aim of this comprehensive review was to investigate the various surgical techniques used for LCPD.

Methods: An advanced electronic search of the English-language literature was performed from October 8 to 14, 2020. The electronic databases PubMed, MEDLINE, Web of Science, Embase, Ovid, and Google scholar were searched using appropriate search terms. A manual search of references also was performed. After retrieving the studies, duplicates were removed, and the remining studies were screened based on the title, abstract, and full text. The quality of the selected articles was assessed, and the required data were extracted from eligible articles.

Results: A total of 22 studies were included in the review. Based on the results of the reviewed studies, there are three main factors that influence the treatment outcomes in patients with Perthes disease. These factors are onset age, femoral head involvement severity, and treatment method. The disease has a poor prognosis in children over 8 years old, but this group of patients can also benefit from advanced surgical methods. In patients aged less than 6 years, the disease has a generally good prognosis, but in those aged between 6 and 8 years, its prognosis is variable. Thus, the need for surgical intervention requires close observation of signs. Once any head signs are observed, dynamic arthrography is beneficial before choosing the treatment approach.

Conclusions: This review provides clinicians with a brief guideline for the treatment of patients with LCPD.

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KEYWORDS

surgical treatment; Legg-Calvé-Perthes disease; pediatric; hip; treatment outcome

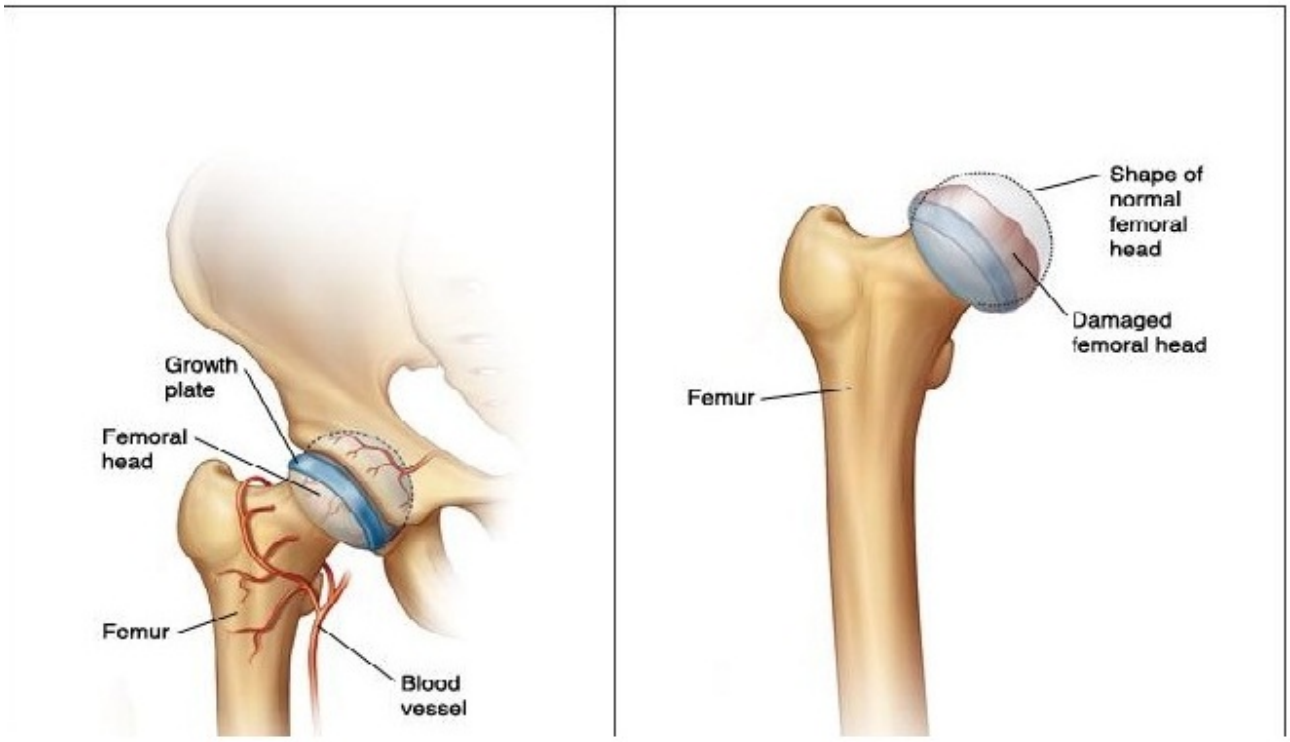
Introduction

Legg-Calvé-Perthes disease (LCPD) is a common childhood disease that commonly occurs between the ages of 4 and 8 years, but it can be found between the ages of 2 and 15 years. This condition occurs owing to the interruption of blood supply to the femoral head. The disease, which is described as aseptic necrosis of the juvenile femoral head, affects about 10 in 100,000 children worldwide [1-3]. Therefore, it is a common condition of the hip in childhood that was first recognized in 1910 by three physicians working independently, including Thornton Legg, Jacques Calvé, and Georg Perthes [4,5]. LCPD is characterized by idiopathic osteonecrosis of the femoral epiphysis that is attributed to arterial infarction [6]. Waldenström has indicated that the process of disease progression commences with aseptic necrosis, followed by a subchondral fracture and fragmentation, revascularization, and remodeling [7,8]. The prevalence of the disease is higher in boys than in girls [9,10]. Additionally, it is more prevalent between the ages of 4 and 8

years, and late onset of the disease in children above these ages has poorer results compared with onset at lower ages [11]. Current literature suggests that between 30% and 50% of children affected by LCPD will experience hip symptoms in adulthood [12,13]. Previous studies have documented some ethnic and geographical disparities in the incidence of LCPD [14].

The formation and progression of LCPD begins with the interruption of femoral head blood supply, which consequently results in changes in the femoral head, metaphysis, growth plate, and acetabulum (Figure 1). Subluxation and lateral displacement of the femoral head out of the acetabulum are among the first signs of the condition [15]. The femoral epiphysis is sensitive to deformation by loading. Lateral migration leads to deformation of the femoral head owing to presence on the edge of the acetabulum and uneven transfer of loading force [16]. Current LCPD treatment focuses on mechanical protection of the femoral head to prevent future hip deformity and degeneration [17], which maintains the plastic epiphysis in the acetabulum and can be done either by noninvasive or surgical techniques [18-20]. Clinicians use the concept of "at risk joint" as the conclusive criterion for the prognosis and treatment options of LCPD [21]. Additionally, imaging methods are used in patient assessment, which provide beneficial information and enable physicians to choose the best case-based strategy for disease management [22,23].

Figure 1. In the normal hip joint, the femoral head is smooth and round (left). In Perthes disease, the femoral head is damaged and loses its normal shape (right).



In general, LCPD, which is a childhood hip disorder and is related to interruption of blood supply, progresses over a rage of stages, including necrosis/initial, fragmentation, reossification/healing, and residual [7,24]. Follow-up studies indicate that up to 70% of patients will experience substantial hip pain and dysfunction caused by the disease until adulthood [25,26]. However, the majority of patients have a benign long-term prognosis and need minimal treatment [26]. Treatment of patients focuses primarily on maintaining the femoral head within the acetabulum during the remodeling period [27]. Many studies have been published regarding the treatment options for LCPD; however, the specific therapies are still controversial owing to a poor understanding of its etiology [28]. Treatment options vary from doing nothing to undergoing nonoperative or operative treatments, which have been reported to preserve containment. Nowadays, containment, which can be done with surgical and nonsurgical methods, is suggested as a means for directing the remodeling of the softened femoral head [29-31].

Current treatments for LCPD are largely focused on the early containment of the vulnerable femoral head in the acetabulum to keep the spherical femoral head and congruent joint during the repair period [32,33]. Nonoperative containment options, such as motion therapy, weight relief, and abduction splints, are more appropriate for younger patients, while surgical options are more suggested for older children with more severe LCPD [34]. In the past years, different surgical methods have been developed for treating LCPD, which were claimed to be more appropriate options than nonsurgical treatments for more severe cases of the disease and older patients [1,35,36]. Choosing the best treatment option for the management of LCPD depends on various factors, such as the physician's own preferences, the patient's age and disease stage, and the psychosocial status of

the patient and family [37-42]. Since various surgical techniques have been proposed for the hips in noncontainable LCPD, the aim of this study was to review the various surgical treatments in LCPD to provide a guide for clinical applications. Some reviews have been published on LCPD management, but each of them has a specific focus. For example, some studies categorized the treatment options as conservative and surgical treatments, with a brief description of each, but in this article, we aimed to review the surgical treatments for LCPD in detail, which differentiates this review from other published studies.

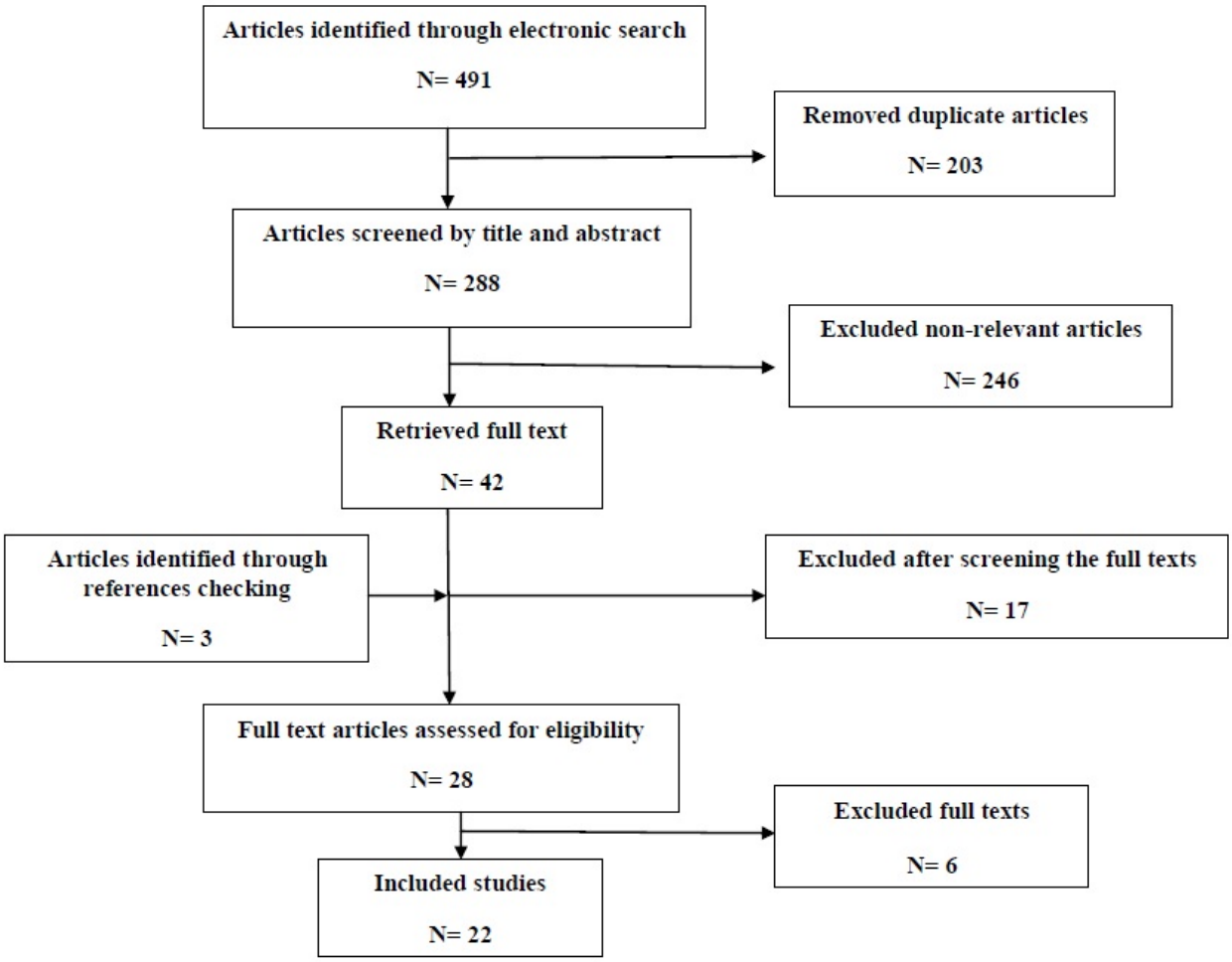
Methods

Databases and Search Strategy

We conducted an overview of the English-language literature involving various surgical treatments for LCPD. The electronic databases PubMed, MEDLINE, Web of Science, Embase, and Ovid were searched from October 8 to 14, 2020, for reports on the outcomes of surgical techniques in patients with LCPD. The search was updated on February 4 to 6, 2021. All published studies from January 01, 2000, to the search date were assessed for possible inclusion in this study.

Reference lists of published papers were then hand searched in an attempt to identify further studies (Figure 2). The following keywords were used: Legg-Calvé-Perthes disease, pediatric orthopedic diseases, Perthes disease treatment, avascular necrosis of the hip, osteonecrosis of the femoral head, surgical treatment, osteotomy, hip, and treatment outcome. The search terms were then entered into Google Scholar to ensure that articles were not missed.

Figure 2. Literature search and review flowchart for the selection of primary studies.



Inclusion Criteria

Studies written in English that reported various aspects of surgical treatments for LCPD and achieved enough quality scores were included in this study.

Exclusion Criteria

Papers were excluded if they were case reports or had a patient cohort; were not written in English; lacked documentation; and were nonhuman studies, narrative reviews, studies without clinical outcomes data, systematic reviews that did not pool data or perform a meta-analysis, or technique articles without outcomes. We obtained full manuscripts for those studies that met the inclusion criteria.

Study Selection

Full texts or abstracts of all studies identified during the advanced search were extracted. After excluding duplicates, we investigated the remaining articles by reviewing the titles, abstracts, and full texts. We also reviewed the findings of the

articles to prevent reprint bias. Two independent researchers (AM and MNB) selected studies based on the inclusion criteria. Screening was performed after restriction of the search strategy and exclusion of duplicates. Irrelevant studies were removed during the investigation of titles, abstracts, and full texts. The agreement between the selection results of the researchers was assessed based on kappa statistics suggested in the Landis & Koch guidelines [43]. The agreement was considered as slight (kappa 0-0.20), fair (kappa 0.21-0.40), moderate (kappa 0.41-0.60), substantial (kappa 0.61-0.80), and perfect (kappa >0.80). We also reviewed the findings of the articles to prevent reprint bias. Then, the quality of the selected articles was assessed using standard scales.

Quality Assessment

The quality of primary studies was assessed using appropriate standard checklists. We used the Newcastle-Ottawa Quality Assessment Scale and Jadad Scale for quality assessment of primary studies based on the type of study. Additionally, because the aim of this study was not to combine the results of primary studies using meta-analysis, the effect size was not estimated for the outcome. Therefore, evaluation of heterogeneity was not possible using statistical methods, and results were presented in a purely descriptive form based on the planned design for study.

Data Extraction and Analysis

All required data, such as authors, publication date, study location, sample size, and treatment technique, were extracted from the included studies using a researcher-made form. The review flowchart is presented in Figure 2.

Results

Overview

The characteristics of the included studies [1,9,10,32,44-61] are reported in Multimedia Appendix 1.

Etiology and Clinical Manifestations

One important predisposing factor for this disease is race, with the East Asian race being affected the least and the White race being affected the most. Additionally, latitude has an influence on susceptibility to Perthes disease [62]. Overall, the reported incidence rate is between 0.2 and 19.1 per 100,000 people [55]. Clinical onset tends to be between 4 and 8 years of age [63]. It has been reported that the incidence increases with the increase in latitude. On the other hand, genetics, repetitive trauma, abnormalities of the blood supply, and coagulation disorders are well-described causative factors [64]. The incidence is the lowest in equatorial regions and increases toward Northern Europe. The incidence is the highest in Whites and the lowest in African Americans [65]. It has been reported that a correlation might exist between acetabular retroversion and Perthes disease. However, the correlation of cause and effect is not known [66]. It has been demonstrated that circulating leptin is higher than normal in patients with LCPD [7]. Therefore, it can be concluded that obesity can play an important role in the initiation of Perthes disease [55].

The prevalence of Perthes disease in boys is five times more than in girls, and 10% to 15% of patients are affected bilaterally; however, bilateral cases are more common in girls [63]. Study findings are conflicting with respect to gender differences in prognosis. Physeal closure in girls occurs earlier, leaving less time for femoral head remodeling [67]. However, no difference between the genders has been detected in final radiographic results. The first presenting complaint is limping, and the second common complaint is pain, which occurs mostly in the anterior hip and medial thigh [55]. The general consensus is that Perthes disease results from the uncoupling of bone metabolism with increased resorption and delayed formation; however, the exact etiology remains unknown. Previous literature states that as patients with LCPD tend to have delayed bone age (on average, 2 years in girls and 1 year in boys), their femoral head ossific nuclei are smaller than those in children of similar age [34]. This makes the cartilaginous component of their epiphysis larger, and the traversing blood vessels are more vulnerable to mechanical compression [68].

Imaging

Simple radiographs remain the most useful imaging modality, which can be used for the initial diagnosis of LCPD and subsequent follow-up. The size and shape of the femoral head are of importance in this approach [55,63] Characteristic changes usually occur after a radiographically silent period in the first 3 to 6 months of the disease. A relatively thickened cartilage may widen the medial joint space. The involved hip has a smaller ossific nucleus, often with increased radiodensity. An increase in the joint space has been shown to be correlated with enlargement of the femoral head [69]. Prognostic radiographic signs rarely appear until Perthes disease is established, and this usually takes over 6 months after disease onset. Other techniques, such as magnetic resonance imaging and pneumoarthrography, can provide more comprehensive information regarding the stage of the disease [70].

Arthrography as an adjunct to standard radiography aids in the assessment of the range of motion and ability to contain the head in the acetabulum. After general anesthesia and strict sterile preparation, contrast is injected with fluoroscopic guidance to examine the features [71]. Sonography has been reported to detect hip effusion early in the disease when radiographs are undiagnostic [72]. Three-dimensional computed tomography can show early bone collapse, so it can be useful in visualizing complex head deformity, but the benefit of the information gained rarely justifies the radiation dose required [63]. Magnetic resonance imaging details the extent of bony infarction and the anatomy of the cartilaginous head and labrum, which can be useful early in the disease's course to differentiate it from other conditions that cause osteonecrosis [73,74]. In bone scanning, there is a strong correlation between the size of the uptake defect on the femoral head and prognosis. The indication is limited to patients who are suspected of being affected by LCPD, which further serves as a prognosticator as well [75]. A previous study showed that there is a significant correlation between hip deformity and labral and cartilage abnormalities of the hip on magnetic resonance imaging, and the main predisposing factors were loss of sphericity of the head and a decline in femoral head-neck offset [76].

Surgical Treatment Options

The treatment of Perthes disease depends on the age and stage of presentation. Simple observation is needed in children aged 2 to 3 years. The optimal treatment technique for LCPD and its prognosis are still not fully understood. In the past 20 years, some authors have tried to standardize the treatment principles for Perthes hip. Extent of femoral head involvement (lateral pillar classification or Catterall classification) and age at diagnosis are the most common classifications used to assess the outcomes following treatment [55]. In a large prospective review by Wiig et al [32], with medium-term follow-up, it was suggested that children aged 6 years or older, with more than 50% femoral head involvement (Catterall), had a better result if treated with surgery.

Arthrodiastasis

Arthrodiastasis is a relatively novel treatment method for LCPD, which uses an external fixator. Arthrodiastasis was initially used to describe a technique involving articulated distraction of the hip joint that was developed by surgeons in Verona, Italy, and has been used since 1979 [77]. It has been considered as an alternative treatment for LCPD beyond conventional surgical methods. This method was conceived as a conservative technique of restoring joint function, based on awareness that under certain conditions, regeneration and repair of damaged articular cartilage can occur, at least to some extent [78]. It is considered to be useful because it maintains the mobility of the hip joint and secures space for the femoral head in the joint while minimizing physical pressure and preserving synovial fluid circulation. Kim et al [79] reported that arthrodiastasis using an external fixator can be a relatively promising surgical procedure for the treatment of late-onset LCPD. Additionally, a systematic review by Ibrahim et al [80] investigated relevant literature to assess the efficacy of the use of arthrodiastasis in the management of Perthes disease and showed a significant increase in the postoperative range of motion compared with the preoperative range of motion. Final Stulberg classification was ascertained, and the majority of patients were in stages 2 and 3. Complications were also assessed, with the majority of them being superficial pin tract infections. They concluded that arthrodiastasis is a valid treatment option for Perthes disease; however, more studies need to be performed showing comparative data of arthrodiastasis versus other containment procedures. Arthrodiastasis of the hip joint with soft tissue release is considered as a surgical technique when other treatment options are contraindicated. This method also improves the range of motion, decreases superior and lateral subluxation, and provides better radiographic sphericity of the femoral head. Treatment with distraction may be performed even for stiff hips and hips with deformity [81]. Volpon [17] performed a prospective controlled trial to compare innominate osteotomy and arthrodistraction and concluded that despite similar final radiological outcomes, arthrodistraction was associated with higher morbidity; therefore, hip distraction is not recommended as the primary treatment in the early stages of LCPD.

Salter Osteotomy

Salter osteotomy, as a method for surgical containment in LCPD, was first introduced in 1962. This technique redirects the acetabulum as well as improves anterolateral femoral head coverage. Salter presented the concept of innominate osteotomy as a containment technique to avoid femoral osteotomy consequences [82]. Salter felt that acetabular rotation would also provide better containment than varus osteotomy of the femur; however, studies have shown little difference in the radiographic or functional results with either of these two techniques. The common indications for salter osteotomy are similar to other forms of containment [39]. Some of these indications include onset age over 6 years, more than 50% of the femoral head affected, and hip subluxation in the weight-bearing position. This operative method has been reported to produce better long-term outcomes than nonoperative techniques with regard to Stulberg classification [34]. Several studies [83,84] have compared Salter osteotomy and femoral varus osteotomy. Previous studies reported similar outcomes with respect to femoral head sphericity, but have shown increased femoral head coverage by the center-edge angle after Salter osteotomy [85]. Use of this technique can displace the acetabulum 1 cm medially and distally, thereby reducing the biomechanical stress over the hip joint and improving the generally associated leg length discrepancy [86]. It should be noted that radiographic assessment as well as cautious clinical examination is necessary before surgery. Some of the Salter osteotomy prerequisites include full range of hip motion preoperatively, especially abduction, and reasonable joint congruency [10].

The main benefit of Salter or innominate osteotomy is its effect on femoral head remodeling during remaining growth. This osteotomy alone is commonly indicated for younger children with recent clinical onset and no femoral head deformity or subluxation [39]. However, Salter osteotomy alone may not provide sufficient head coverage in all situations, especially in children older than 9 years. Thus, the combination of Salter and femoral varus osteotomies has been performed recently to manage a larger and deformed femoral head [40,87]. A previous study stated that the combined method of surgery may change the otherwise “poor” hip into a “fair” hip and improve the natural history in children with higher age [87]. The other advantages of the combined method include a reduction in the effect of increased intra-articular pressure from innominate osteotomy and compensation of the shortening from femoral osteotomy [10].

Femoral Varus Osteotomy

Femoral varus osteotomy has become one of the most popular surgical techniques for Perthes disease, since the first report by Axer in 1965 [38,88]. The aim of this method is to center the femoral head deeply within the acetabulum and allow correction of the flexion or rotational deformity simultaneously [10]. The prerequisites for this technique are good range of motion, hip congruency, and ability to contain the femoral head in abduction. This surgery is suggested in the early stage of fragmentation, when favorable biological and biomechanical effects may be anticipated. Many studies reported that femoral varus osteotomy

yields good long-term outcomes [37,38]. The reported number of hips treated operatively rose more sharply during the last decade in research from Europe and North America. With regard to the type of surgical treatment, femoral osteotomy was reported more frequently than pelvic osteotomy worldwide; however, pelvic osteotomy is comparably more common in North America, Australia, and South America, whereas femoral osteotomy is more frequently performed in Europe, Asia, and Africa [1].

The main goal of surgical methods is to contain the femoral head within the acetabulum in order to avoid femoral head deformation and subsequent premature hip osteoarthritis. This aim is achievable by the use of femoral varus osteotomy, innominate osteotomy, and other forms of pelvic osteotomies. Operative treatments can roughly be categorized as femoral, pelvic, and combined procedures. A comprehensive review by Braito et al [1] stated that femoral osteotomies were reportedly more frequent than pelvic osteotomies in the screened literature. They concluded that femoral osteotomies were tendentially preferred in Europe. Saran et al [24] showed that children older than 6 years benefit more from varus osteotomy compared with nonoperative treatments. Generally, femoral varus osteotomy allows realignment and identification of the best fit position of the hip, while restoring joint congruity and decreasing femoroacetabular impingement.

Combined Treatments

Any pelvic osteotomy can be combined with a proximal femoral osteotomy, especially if the femoral head cannot be contained by a pelvic or proximal femoral varus osteotomy alone [39]. The combined Salter and proximal femoral varus osteotomy for LCPD has been performed more recently [89,90]. These combined procedures are usually used for patients with an older age at clinical onset, those with deformed femoral heads, or those in whom osteotomy alone cannot provide adequate containment [39]. Javid and Wedge [87] used combined osteotomies in 20 older patients with LCPD and reported that outcomes improved with the combined osteotomies at skeletal maturity when compared to the natural history of untreated hips. Vukasinovic et al [90] investigated patients treated with combined Salter and proximal femoral shortening osteotomy. They showed a better center-edge angle in these patients. Their results were similar to those reported by other researchers [83,84].

Chiari Osteotomy

Chiari osteotomy is a popular salvage procedure for children with insufficient femoral head coverage [10]. One of the advantages of this method is the reduction of joint loading by medialization of the hip, which was considered an important factor for improving hip congruency and femoral head remodeling [91]. This technique has been recommended for severe cases of Perthes disease. Medial displacement or Chiari osteotomy is one of the categories of pelvic osteotomies. The most performed methods in Perthes disease are acetabular rotational osteotomies, especially Salter osteotomy. The Chiari medial displacement osteotomy procedure is usually used for salvage of a deformed femoral head [39].

Triple Innominate Osteotomy

Triple innominate osteotomy is another option for achieving containment in LCPD. Femoral varus osteotomy and Salter osteotomy are the most common techniques for surgical containment; however, the degree of femoral varus osteotomy required to contain the femoral head may further shorten the limb and cause prolonged limp, particularly in older children. On the other hand, use of Salter osteotomy may not provide enough acetabular rotation to cover the femoral head in severe cases, potentially leading to iatrogenic hinge abduction [92]. Because of certain practical limitations with these two procedures, advanced containment methods, such as triple innominate osteotomy, have been developed for more severe cases [40,93]. Some studies have reported that older age and extensive femoral head involvement were risk factors for unsatisfactory outcomes. A previous study showed that patients older than 10 years at onset had poor results regardless of surgical treatment [94]. Triple innominate osteotomy is anticipated to show better femoral head containment than can be achieved with Salter osteotomy alone and to avoid the leg length discrepancy associated with femoral varus osteotomy. Finally, this is one of the most efficient methods for femoral head containment in all conditions. However, over coverage can result in pincer impingement. For the prevention of pincer impingement, correction beyond 44 degrees of the enter-edge angle is not recommended [95].

Other Treatment Options

Lateral shelf acetabuloplasty is considered for severe Perthes disease when redirection osteotomy is thought to be insufficient to produce optimal coverage of the extruded femoral head. An intraoperative dynamic arthrograph is useful for further confirmation. In severe cases, a laterally displaced and enlarged femoral head will preclude normal motion of the hip. Previous reports have shown that shelf acetabuloplasty is a safe and effective method for managing cases with aspherical congruency or incongruency with hinge abduction [42,96]. When an arthrograph indicates femoral head deformity with unstable movement and hinge abduction, but stability in adduction and flexion, valgus and extension osteotomy can be an effective method for unloading the deformed epiphyseal segment and alleviating femoroacetabular impingement. The implication of femoral valgus extension osteotomy depends on redirection of the more congruent and round anteromedial part of the femoral head to the neutral position of weight bearing. This sagittal and rotational correction may improve gait and hip motion, decrease pain, and improve femoral head shape [97,98].

Transtrochanteric rotational osteotomy is considered a new technique for patients with onset of LCPD after 9 years of age. It is an effective method to treat late-onset Perthes disease in affected hips. In addition, the amount of head involvement and the lateral pillar influence surgical results [44]. Recent techniques are focused on reshaping the femoral head to match with the acetabulum and reduce impingement, as well as restoring the normal cartilage in the head weight-bearing zone [45]. Total hip arthroplasty is a salvage method for complications and subsequent osteoarthritis. Cementless total hip arthroplasty showed a 90% survival rate in an 8-year

follow-up. However, despite promising outcomes, nerve injury and intraoperative fracture are usual; therefore, care should be taken to avoid excessive limb lengthening [46].

Discussion

In this study, we reviewed the various surgical treatments for LCPD to provide a guide for clinical applications. Based on the results of the reviewed studies, there are three main factors that influence the treatment outcomes in patients with Perthes disease. These factors include onset age, femoral head involvement severity, and treatment method. For patients aged over 8 years, the prognosis is often poor, but advanced or salvage procedures still provide the benefit of improved femoral head coverage; therefore, they benefit from surgical intervention. For children aged less than 6 years, the prognosis is generally good. For children aged between 6 and 8 years, the prognosis is variable, and it is required to closely observe for the signs of "head at risk," which indicate the need for operation. Once any such signs are observed, dynamic arthrography under anesthesia is valuable before deciding the appropriate treatment approach.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The characteristics of the included studies.
[DOC File , 55 KB - ijmr_v10i2e27075_app1.doc]

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Abbreviations

LCPD: Legg-Calvé-Perthes disease

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Original Paper

Early Identification of COVID-19 Infection Using Remote Cardiorespiratory Monitoring: Three Case Reports

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Abstract

Background: The adoption of remote patient monitoring (RPM) in routine medical care requires increased understanding of the physiologic changes accompanying disease development and the proactive interventions that will improve outcomes.

Objective: The aim of this study is to present three case reports that highlight the capability of RPM to enable early identification of viral infection with COVID-19 in patients with chronic respiratory disease.

Methods: Patients at a large pulmonary practice who were enrolled in a respiratory RPM program and who had contracted COVID-19 were identified. The RPM system (Spire Health) contains three components: (1) Health Tags (Spire Health), undergarment waistband-adhered physiologic monitors that include a respiratory rate sensor; (2) an app on a smartphone; and (3) a web dashboard for use by respiratory therapists. The physiologic data of 9 patients with COVID out of 1000 patients who were enrolled for monitoring were retrospectively reviewed, and 3 instances were identified where the RPM system had notified clinicians of physiologic deviation due to the viral infection.

Results: Physiologic deviations from respective patient baselines occurred during infection onset and, although the infection manifested differently in each case, were identified by the RPM system. In the first case, the patient was symptomatic; in the second case, the patient was presymptomatic; and in the third case, the patient varied from asymptomatic to mildly symptomatic.

Conclusions: RPM systems intended for long-term use and that use patient-specific baselines can highlight physiologic changes early in the course of acute disease, such as COVID-19 infection. These cases demonstrate opportunities for earlier diagnosis, treatment, and isolation. This study supports the need for further research into how RPM can be effectively integrated into clinical practice.

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KEYWORDS

COVID-19; remote patient monitoring; wearable sensors; monitoring; case study; preidentification; lung; data collection; respiration; prediction

Introduction

Early identification of acute clinical deterioration can lead to proactive intervention and a reduction in morbidity in patients with or without chronic disease [1-3]. There are a number of reasons why patients may receive delayed medical care [4]. For example, patients may not recognize a change in their symptoms or may avoid contacting their provider so as not to burden themselves or the practice. The COVID-19 pandemic also appears to have exacerbated patient reluctance to seek care [5].

Early diagnosis of COVID-19, the disease resulting from SARS-CoV-2 infection, can lead to proactive management, such as increased monitoring [6] and daily prone positioning [7], as well as early patient isolation. For the novel monoclonal antibody therapies to be effective, it appears that they must be used before the patient develops severe illness [8].

Studies using data from consumer activity trackers have been reported to identify signs of COVID-19 infection before symptoms develop [9-11]. Despite the promise of medical-grade remote patient monitoring (RPM), physicians and health care organizations can be slow to adopt it. Valid reasons for this lag in acceptance include limited clinical data [12] and discomfort with unfamiliar technology [13]. Deployment of new technology can also be delayed due to a lack of technological infrastructure and integration into clinical workflow [14]. This report motivates study into how to effectively integrate RPM into clinical practice by describing three cases of patients with COVID-19 where physiologic changes were identified through RPM prior to their presentation to a medical practice.

Methods

The RPM system (Spire Health [15]) was studied, designed, and validated for long-term use with patients with chronic respiratory disease [16,17], and it contains three components: (1) Health Tags (Spire Health), undergarment waistband-adhered physiologic monitors that require minimal patient management and include a respiratory rate sensor; (2) an app on an in-home, stationary internet-connected device (a Nokia smartphone) configured to automatically collect and upload sensor data to the cloud; and (3) a web dashboard at the Spire Health website [15] that is monitored 7 days per week by respiratory therapists (RTs) who proactively engage patients by telephone in the event of significant changes in adherence, respiratory rate, pulse rate, or activity level. The dashboard notifies the RTs of significant patient-specific deviations in respiratory metrics, pulse rate, and activity. The notifications compare each patient's current metrics with their respective historical baseline. The system was designed to identify deviations associated with exacerbation of chronic respiratory disease.

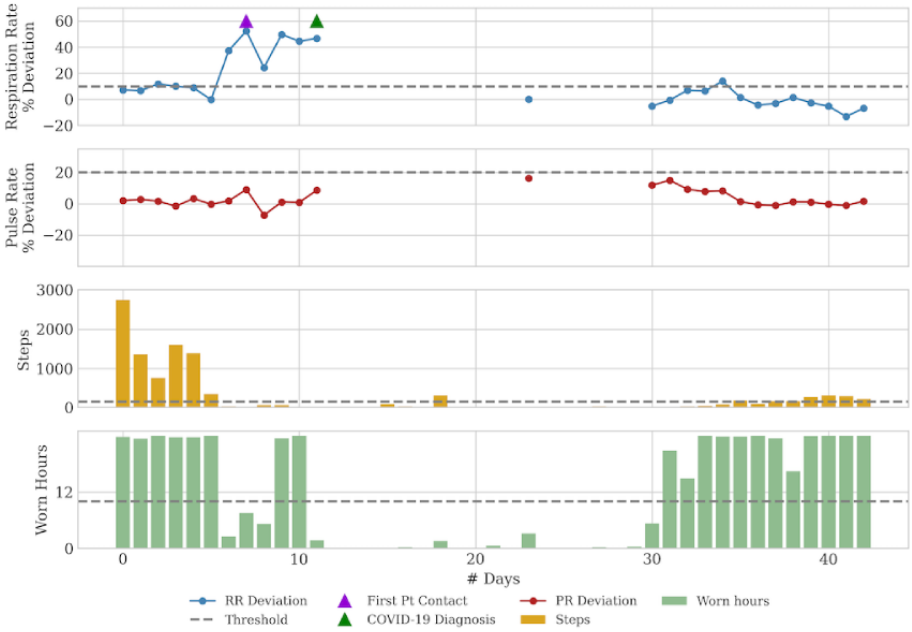
A US-based pulmonology practice offered RPM to chronic patients with respiratory disease and had not yet defined a clinical workflow for using RPM with patients with COVID-19. At the time of review, from approximately 1000 patients enrolled in the monitoring, 9 were confirmed to have contracted COVID-19. The RPM data of these 9 patients were retrospectively reviewed and evaluated based on whether the RPM had notified clinicians of physiologic deviation around infection onset. No evaluation of the predictive performance of the RPM was performed. Three case reports demonstrated differentiated clinical cases, and the patients gave consent to use of their data.

Results

Case 1: Symptomatic

Patient 1 is a 70-year-old woman with moderate chronic obstructive pulmonary disease (COPD) who had been receiving routine follow-up care. For the first 3 months of monitoring, she demonstrated stable parameters in her respiratory rate and heart rate as well as typical variations in her activity levels. Approximately 3 months prior to her next scheduled office visit, the patient was noted to have an acute increase in her respiratory rate accompanied by reduced step counts (see Figure 1). These physiologic changes triggered a notification in the monitoring system, leading to telephone contact of the patient. The patient reported feeling generally poor and attributed her symptoms to back pain. Further query by the RT call center staff did elicit increased shortness of breath and cough. Although the patient declined a pulmonary clinic visit, she was encouraged to monitor her symptoms and contact her physician or emergency department (ED) if her condition did not improve. The patient's respiratory rate remained elevated 5 days after the initial notification, and the she presented to the ED. She was diagnosed with COVID-19 and spent 17 days in the hospital before recovering to near baseline and returning home. Her respiratory physiologic parameters returned to baseline 20 days later. Her step counts were noted to return to baseline approximately 1 month after hospital discharge.

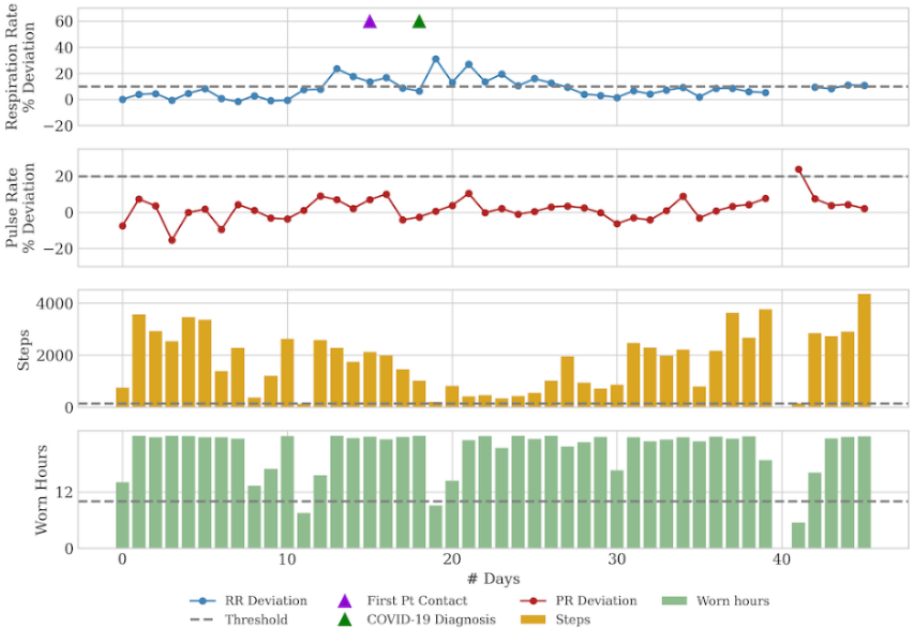
Figure 1. Daily physiology, activity, and adherence metrics for Case 1. The patient was hospitalized for COVID-19–related symptoms 5 days after she was contacted by the respiratory therapist call center. Physiology shows return to baseline after discharge 17 days later. Each point for RR and PR represents the percent difference between that day's median value and that patient's lifetime median baseline value. The thresholds are clinician-configurable points at which notifications are triggered. Default threshold values (for all three cases): worn hours <11 hours, RR % deviation: >10, PR % deviation: >20, and steps: <150. PR: pulse rate; Pt: patient; RR: respiratory rate.



Case 2: Presymptomatic

Patient 2 is a 72-year-old man with a history of idiopathic pulmonary fibrosis. After 6 months of stable physiologic parameters, the RPM triggered a notification of a respiratory rate increase 24% above baseline (see Figure 2). The patient was reached by telephone within 48 hours of the notification, and he reported no concerning symptoms. He declined further clinical evaluation at that time. Five days after the initial notification, the patient developed body aches and a general feeling of being unwell. That day, a COVID-19 test performed by the patient's primary care physician gave a positive result. The patient's physiology returned to baseline 15 days after infection onset.

Figure 2. Daily physiology, activity, and adherence metrics for Case 2. COVID-19 diagnosis was confirmed 3 days after the patient was contacted and 5 days after initial remote patient monitoring notification. PR: pulse rate; Pt: patient; RR: respiratory rate.

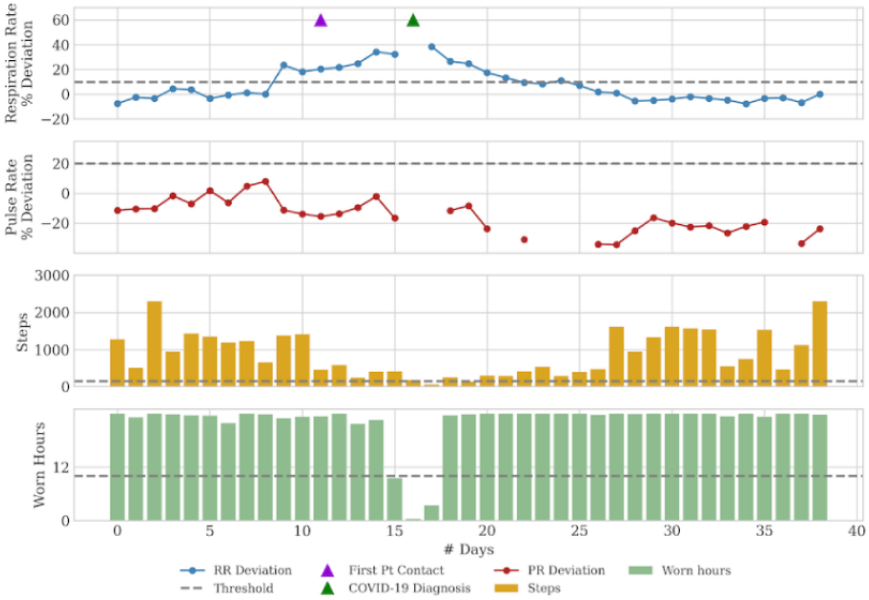


Case 3: Asymptomatic to Mildly Symptomatic

Case 3 is an 80-year-old man with moderate COPD who had started in the practice's remote monitoring program approximately 1 month prior to the first notification. The RPM reported a 24% increase in the patient's respiratory rate; the patient was reached by telephone the next day and reported mild allergy-type symptoms. He opted for over-the-counter symptomatic treatment and also declined a clinic visit, as he

had been seen in a clinic only 8 days prior. His respiratory symptoms remained mild 7 days after the initial notification; however, he was hospitalized for an unrelated reason. As part of hospital routine during the viral pandemic, he was tested and found to be positive for COVID-19 (see Figure 3). The patient's physiology returned to baseline 14 days after infection onset.

Figure 3. Daily physiology, activity, and adherence metrics for Case 3. Initial patient outreach based on RPM notification occurred 4 days before COVID-19 diagnosis. PR: pulse rate; Pt: patient; RR: respiratory rate.



Discussion

Case 1 demonstrates the capability to identify and engage patients earlier in the course of acute disease than would otherwise be possible without remote monitoring. Although the patient declined to see her provider at the time of the telephone call, she was notified of the physiologic changes and encouraged to seek early evaluation. Delayed care in COVID-19 leads to worse outcomes, and this is particularly relevant for patients with comorbid conditions [18,19].

Unlike case 1, the second patient denied having symptoms at the time of initial notification. For this reason, he declined further evaluation. It is known that physiologic changes can occur prior to patient-reported symptoms and recognition of COVID-19. Understanding the potential significance of physiologic changes, particularly during a viral pandemic, can lead to earlier diagnosis. Home-based and rapid COVID-19 testing should be deployed liberally during a pandemic to enable early identification and patient isolation [20]. As with case 1, this patient is over 65 years old and has comorbidities. These patients require increased monitoring when diagnosed with COVID-19, and current evidence supports the consideration of monoclonal antibody therapy prior to needing hospital-level care [8].

Case 3 demonstrates a patient with mild symptoms who was incidentally found to test positive for COVID-19. It is possible that he would have recovered without knowing he had been infected with COVID-19. Similar to the prior cases, significant time passed between physiologic identification and confirmed COVID-19 diagnosis. The exact burden of asymptomatic and presymptomatic spread of COVID-19 is uncertain but is felt to be significant [21]. Even if this patient makes a full recovery, the exposure to others prior to diagnosis has implications on pandemic control. During a viral pandemic, a high index of suspicion for infection must exist in patients who demonstrate signs of infection, even in the absence of significant symptoms or concerns.

In all three instances, COVID-19 was diagnosed 5 to 7 days after the initial notification. Optimally, the physiologic notifications and high suspicion of COVID-19 related to the RPM findings would prompt earlier diagnostic testing. However, patients' rationalization of symptoms and hesitancy to be evaluated factor into the delay [4]. Likewise, physicians may be less apt to intervene in cases where patient symptoms are minimal. Although these cases were selected by the authors, we suspect this delay in diagnosis is typical in most medical practices for the stated reasons.

One of the primary potential benefits of RPM is that deterioration can be treated earlier and more effectively. To increase RPM acceptance, data demonstrating improved patient outcomes is necessary. The success of RPM in providing these benefits is dependent on three requirements: the physiologic data is accurate, notifications are set at clinically significant levels, and medical interventions are effective and instituted in a timely manner. Continuous physiologic monitoring has shown itself to be accurate in patients with and without chronic disease [16,17]. There is emerging evidence regarding what physiologic changes from patient specific baselines on RPM are significant for various diseases, including COVID-19 [11].

The optimization and timing of medical interventions is less clear. With the expanded role of telemedicine, we propose a standardized short term clinical assessment after RPM notification, performed from the patient's home, with a low threshold to test for COVID-19. Further research is necessary to determine if this protocol alone would be sufficient to result in the desired clinical benefit.

Conclusion

This report suggests a blueprint in the approach to using RPM of patients with chronic respiratory disease during a viral pandemic. In these three cases, early physiologic changes secondary to COVID-19 infection detected using RPM were readily identified and patients were proactively engaged. Further research refining RPM use in clinical practice may lead to earlier diagnosis, isolation, and treatment.

Authors' Contributions

MP was the lead author and was responsible for the primary selection and description of the patients. NM was responsible for data extraction, figure generation, and supporting research activities.

Conflicts of Interest

MP is a paid consultant to Spire Health. NM is an employee of Spire Health.

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Abbreviations

COPD: chronic obstructive pulmonary disease
ED: emergency department
RPM: remote patient monitoring
RT: respiratory therapist

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Original Paper

Relevance of Anthropometric Measurements in a Multiethnic Obesity Cohort: Observational Study

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Abstract

Background: The prevalence of obesity is increasing worldwide, and the Middle East is not an exception to this increasing trend. Obesity increases the risk of multiple metabolic complications, such as diabetes mellitus. Measurement of obesity has primarily relied on the BMI to identify risk; however, both bedside and office-based anthropometric measures of obesity can provide more detailed information on risk.

Objective: This study aimed to investigate the prevalence of obesity-related diseases in a multidisciplinary weight management population and to determine its relationship with obesity anthropometric indices.

Methods: This cross-sectional study was conducted at Mediclinic Parkview Hospital (Dubai, the United Arab Emirates). In total, 308 patients have been evaluated from January to September 2019 as part of a multidisciplinary weight management program. Key demographics, anthropometrics, and clinical data were analyzed using SPSS (version 25, SPSS Inc).

Results: Our cohort of 308 patients included 103 (33%) males and 205 (67%) females of 38 nationalities. The mean age of the cohort was 41 (SD 9.6) years, with a median BMI of 34.5 (IQR 6.7) and 33.7 (IQR 7.8) for males and females, respectively. The mean waist circumference (WC) was 113.4 (SD 23.3) cm and 103.5 (SD 16.2) cm, fat percentage was 33.7% (SD 11.6%) and 45% (SD 6.8%), fat mass was 41 (SD 15.2) kg and 41.1 (SD 14.1) kg, and visceral fat mass was 6.5 (SD 3.2) kg and 3.1 (SD 1.8) kg for males and females, respectively. There was a strong correlation between BMI and WC (r=0.65 and r=0.69 in males and females, respectively; P=.01) and visceral fat (r=0.78 and r=0.90 in males and females, respectively). Furthermore, visceral fat was significantly associated with WC in both sexes (r=0.73 and r=0.68 in females and males respectively; P=.01). Furthermore, WC was significantly associated with a risk of diabetes, hypertension, and nonalcoholic fatty liver disease.

Conclusions: BMI and WC are the most representative measures of obesity in our population and correlate with abdominal adiposity– and obesity-related diseases. Further studies are required to assess the benefits of these measures during weight reduction interventions.

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KEYWORDS

anthropometrics; body mass index; cardiovascular health; comorbidities; liver disease; obesity; overweight; type 2 diabetes mellitus; visceral fat; waist circumference; weight loss; weight management

Introduction

The prevalence of overweight and obesity has increased worldwide, as defined by the BMI. In the United Arab Emirates, the obesity prevalence rate reported in 2016 was 29.9% [1,2]. There is a paralleled increase in the incidence of metabolic-related conditions, particularly type 2 diabetes, metabolic syndrome, and nonalcoholic fatty liver disease (NAFLD) [2]. Although BMI is the most used measure to classify at-risk individuals and to assign treatments, it does not

reflect abdominal obesity, which is a surrogate marker for visceral adiposity. Visceral adiposity is a strong predictor of cardiovascular [3] and metabolic risk [3].

Waist circumference (WC) is a simple anthropometric parameter to assess abdominal adiposity in clinical practice. WC is strongly associated with cardiovascular mortality [3,4]. Therefore, it has been recommended to determine the WC in conjunction with BMI to assess the metabolic risk in accordance with a 2008 expert consultation report of the World Health Organization [5].

The aim of our study was to validate the utility of anthropometric measures other than BMI in the assessment of obesity and their relationship with metabolic conditions including diabetes, hypertension, and NAFLD in a cross-sectional cohort of individuals with overweight and obesity.

Methods

Patients and Study Design

This cross-sectional observational study was conducted at Mediclinic Parkview Hospital (Dubai, the United Arab Emirates) between January and September 2019. A total of 308 patients enrolled in the hospital's multidisciplinary weight management program were included in this study. Patients in the program included those who were referred from outpatient Mediclinic cluster clinics, outpatient and inpatient consultations at Mediclinic Parkview Hospital, or those who self-referred to the program. Patients were then directed by the bariatric coordinator of the program to the dietician or physician as required. After initial assessments, the patients were provided individualized weight management plans including a dietetic plan, exercise, behavioral therapy, medication, or bariatric surgery as indicated. The weight management team included a dietician, an endocrinologist, a gastroenterologist, a bariatric surgeon, and a psychologist. Patients requiring bariatric surgery were discussed in multidisciplinary team meetings before surgery with close postsurgical follow-up.

Data were collected from electronic medical records of Bayanaty (InterSystems IRIS). The data were collected in four categories: demographic data, anthropometric measures, laboratory measurements, and clinical disease and risk factor status.

Demographic data included age, gender, and nationality. Anthropometric measures included height, weight, BMI, fat mass, body fat percentage, visceral fat mass, WC, hip circumference, and waist-hip ratio (WHR). Laboratory measurements included glycated hemoglobin (HbA_{1c}), renal function including creatinine and estimated glomerular filtration rate, liver function tests including aspartate transaminase and alanine transaminase activity, lipid profile including cholesterol, triglyceride, and low- and high-density lipoprotein (HDL) cholesterol. Clinical variables included the presence of diabetes, hypertension, polycystic ovarian syndrome, dyslipidemia, and NAFLD.

Obesity-Related Metabolic Risk Factors

Four metabolic syndrome components were included in the analysis: hypertension (systolic/diastolic blood pressure of ≥130/85 mmHg or taking drug treatment for hypertension), hyperglycemia (HbA_{1c}=6.5% or taking diabetes treatment), hypertriglyceridemia (≥150 mg/dL or 1.7 mmol/L or taking drug treatment for elevated triglycerides), and low HDL cholesterol (<40 mg/dL or 1.0 mmol/L in men and 50 mg/dL or <1.3 mmol/L in women or taking drug treatment).

Obesity Parameters and Anthropometric Variables

BMI was defined as the body weight divided by the square of the height in meters (kg/m^2). World Health Organization recommendations were used to categorize individuals by weight as follows: healthy weight (BMI=20.0-25.0), overweight (BMI=25.0-29.9), and obese (BMI≥30.0) [6].

WC was defined as the measurement midway between the lowest rib and the iliac crest by using a flexible tape measure. Hip circumference was measured at the level of the greater trochanters to the nearest millimeter by using a flexible tape measure. WHRs were obtained by dividing the WC by the hip circumference. Although many have recommended different ethnicity-based WC cut-offs, there is insufficient evidence to recommend different cut-offs for individuals of European rather than those of Middle Eastern or African ethnicities [7]. Therefore, for these ethnicities, "the cut-off WHRs were 94.0-101.9 cm and 80.0-87.9 cm for men and women with overweight and >102 cm and >88 cm for men and women with obesity, respectively. Although there is evidence that WC cut-offs for obesity in Asian populations vary from those of Europeans [8], this population constituted a small proportion of Asians; hence, separate cut-offs were not assigned. Men with a WHR of <0.90, 0.90-0.99, and ≥1.0 were classified as having a normal weight, overweight, or obesity, respectively, and women were classified in the same categories on the basis of a WHR of <0.80, 0.80-0.84, and ≥0.85, respectively.

Anthropometric data were collected using a body composition analyzer (Seca GmbH), which uses bioelectric impedance analysis to determine the body fat mass, body fat percentage (% fat and % fat mass), and the visceral fat ratio. The normal fat percentage for women is 21%-35% and that of men is 8%-24%. A normal visceral fat ratio is >1.2 and >2.1 for women and men, respectively [9].

Statistical Analysis

Data were entered in a computer, using SPSS for Windows (version 25.0, SPSS Inc). Frequency tables, the measure of percentage, and the measures of tendency and dispersion were analyzed as descriptive data. Categorical variables were cross-tabulated to examine the independency between variables; for such variables, the chi-square test or Fisher-exact test was used as appropriate. The Kolmogorov–Smirnov test was used to test the normality of continuous variables. The Mann–Whitney *U* test was used to compare the means between 2 groups if the normality was not confirmed, while the 2-tailed *t* test was used for normal data per groups. A *P* value less than .05 was considered significant.

Ethics Statement

Ethics approvals were obtained from the local Mediclinic Institutional Research Board and the Dubai Scientific Research Ethics Committee, Dubai Health Authority.

Results

A total of 308 patients who had participated in the weight management program were included in the study, and all had either overweight or obesity. A larger proportion of females participated in the weight management program (n=205, 67%) with a mean age of 41 years. The enrolled patients represented 38 different nationalities. The majority were of Middle Eastern and North-East African ethnicity (n=166, 54%), and the remaining were of European and Asian ethnicity (n=80, 26% and n=58, 19%, respectively).

Table 1 shows the prevalence of obesity-related metabolic conditions (Table 1). Diabetes was prevalent among almost half of the male patients with obesity (n=28, 49%) compared to only 8% among patients with overweight. Among females, dyslipidemia, NAFLD, and hypertension were significantly more prevalent among patients with obesity than among those with overweight.

Table 1. Comparison of complications between patients with overweight and those with obesity by gender (N=308).

Complications	Male patients (n=103)			Female patients (n=205)		
	Overweight, n (%)	Obesity, n (%)	*P* value	Overweight, n (%)	Obesity, n (%)	*P* value
Diabetes			.008			.28
No	11 (92)	29 (50)		37 (79)	63 (72)	
Yes	1 (8)	28 (49)		10 (21)	24 (28)	
Hypertension			.36			.006
No	7 (58)	28 (48)		40 (91)	60 (71)	
Yes	5 (42)	31 (53)		4 (9)	25 (29)	
Polycystic ovarian syndrome			N/A[a]			.24
No	11 (100)	42 (100)		34 (79)	62 (74)	
Yes	0	0		8 (19)	22 (26)	
Dyslipidemia			.11			.02
No	5 (42)	10 (18)		22 (60)	39 (53)	
Yes	7 (58)	47 (82)		15 (41)	35 (47)	
Nonalcoholic fatty liver disease			.25			.045
No	3 (60)	19 (46)		20 (95)	39 (72)	
Yes	2 (40)	23 (55)		1 (5)	15 (28)	

[a]N/A: not applicable.

Laboratory parameters that are used to define diabetes, NAFLD, dyslipidemia, and chronic kidney disease were compared between male and female patients with overweight and those with obesity (Table 2). HbA_{1c} values were not significantly different between the 2 groups (*P*=.30 for men and *P*=.20 for women). Mean alanine transaminase levels, a marker of NAFLD, were higher in patients with obesity than in those with overweight, but this difference was only significant in female patients (21.9 U/L vs 34.3 U/L, respectively, *P*=.05). In terms of lipid parameters, triglyceride levels were found to be significantly higher in patients with obesity than in those with overweight among men (2.4 mmol/L vs 1.2 mmol/L, respectively; *P*=.01). In women, HDL cholesterol levels were lower in patients with overweight than in those with obesity (1.5 mmol/L vs 1.2 mmol/L, respectively; *P*=.004).

Table 2. Laboratory parameters compared between male and female patients with overweight and those with obesity (N=308).

Parameter	Male patients (n=103)			Female patients (n=205)		
	Overweight, mean (SD)	Obesity, mean (SD)	*P* value	Overweight, mean (SD)	Obesity, mean (SD)	*P* value
HbA_{1c} levels			.30			.20
HbA_{1c}, %	5.6 (0.6)	6.2 (2.0)	N/A[a]	5.8 (0.7)	5.5 (1.0)	N/A
HbA_{1c}, mmol/mol	38 (0.6)	45 (2.0)	N/A	39 (0.7)	37 (1.0)	N/A
Creatinine, µmol/L	94.8 (21.0)	82.2 (20.0)	.20	62.3 (8.0)	65.1 (8.0)	.20
Estimated glomerular filtration rate, mL/min/1.73 m^2	86.3 (20.0)	93.7 (21.0)	.40	105.1 (12.0)	98.8 (18.0)	.10
Aspartate transaminase, U/L	35.8 (23.0)	31.7 (23.0)	.70	21.8 (7.0)	30.7 (29.0)	.70
Alanine transaminase, U/L	31.2 (11.0)	47 (39.0)	.40	21.9 (13.0)	34.3 (30.0)	.05
Cholesterol, mmol/L	5.9 (0.3)	9.4 (29.0)	.70	5.2 (2.0)	10.4 (33.0)	.50
Triglycerides, mmol/L	1.2 (0.3)	2.4 (1.0)	.01	1.1 (0.5)	1.6 (0.8)	.07
Low-density lipoprotein cholesterol, mmol/L	3.4 (2.0)	6.4 (21.0)	.70	3.6 (1.0)	3.6 (1.0)	.90
High-density lipoprotein cholesterol, mmol/L	2.3 (2.0)	1.9 (6.0)	.70	1.5 (0.4)	1.2 (0.3)	.004

[a]N/A: not applicable.

Table 3 shows the anthropometric measurements of all the patients. Males had significantly higher weight, height, WC, BMI, and visceral fat mass (6.5 kg vs 3.1 kg in males and females, respectively; *P*<.001), while females had a higher fat percentage than males, but this difference was not significant (45% vs 37%, respectively; *P*=.40).

Table 3. Gender-specific anthropometric characteristics of patients (N=308).

Characteristics	Males (n=103), mean (SD)	Females (n=205), mean (SD)	*P* value
Weight, kg	110.2 (24.0)	89.0 (20.0)	<.001
Height, cm	171.0 (36.0)	155.4 (34.0)	<.001
BMI, kg/m^2	34.5 (7.0)	33.7 (8.0)	.006
Waist circumference, cm	113.4 (23.0)	103.5 (16.0)	<.001
Hip circumference, cm	127.0 (12.0)	124.2 (15.0)	.39
Waist-hip ratio	0.9 (0.2)	0.8 (0.1)	.78
Fat mass, %	41 (15)	41 (14)	.86
% Fat	37.0 (6.6)	45.0 (6.8)	.43
Visceral fat, kg	6.5 (3.2)	3.1 (1.8)	<.001

In order to determine the relationship among anthropometric measures, multiple correlation analysis was conducted with the matrix of correlation shown in Table 4. This revealed a strong correlation between BMI and WC (females: *r*=0.65, males: *r*= 0.69; *P*<.001) and visceral fat (females: *r*=0.78, males: *r*=0.90). Furthermore, visceral fat mass was significantly associated with WC in both genders (females: *r*= 0.73, males: *r*=0.68; *P*<.001). Unsurprisingly BMI, weight, and height were strongly correlated with one another because they were interdependent variables.

Table 4. Matrix of correlation of the measurements of the anthropometric indicators[a] of obesity.

Indicators	BMI	Waist circumference	Visceral fat mass	% Fat	Hip circumference	Waist-hip ratio
BMI	—[b]	0.69[c]	0.90[c]	0.34[c]	0.89[c]	0.06
Waist circumference	*0.65* [c]	—	0.68[c]	0.43[c]	0.85[c]	0.42
Visceral fat mass	*0.78* [c]	*0.73* [c]	—	0.63[c]	0.75[c]	0.52[d]
% Fat	*0.18* [c]	*0.30* [c]	*0.48* [c]	—	0.48[d]	0.58[d]
Hip circumference	*0.53* [c]	*0.65* [c]	*0.72* [c]	*0.52* [c]	—	0.14
Waist-hip ratio	*0.38* [c]	*0.54* [c]	*–0.13*	*0.40* [c]	*–0.23*[d]	—

[a]Values of *r* for females are shown in italics.

[b]—: not applicable.

[c]*P*<.001.

[d]*P*<.05.

Discussion

Principal Findings

This observational study shows that anthropometric measurements in combination with BMI, particularly WC, can provide more detailed information on metabolic risk. Our findings have confirmed higher rates of obesity-related factors in individuals with obesity, which is consistent with all existing data [10]. Further, the study has clearly shown a strong relationship between waist circumference and estimated visceral fat mass through body composition analysis, thus emphasizing the routine inclusion of these measures in the assessment of such patients. Our results are similar to those of several other studies showing a strong association between metabolically active visceral fat and cardiovascular risk factors [4,11].

The prevalence of obesity in this study was much higher than that estimated nationwide in the United Arab Emirates (70% vs 34%, respectively) [12] as the weight management program would have enrolled more individuals with obesity. In unselected populations in the United Arab Emirates, the estimated prevalence of obesity was reported to be 34% in 2016 [13]. The multinational, multiethnic composition of the study population renders our findings more generalizable to other populations. Our study participants were of 38 different nationalities, as Dubai is a multicultural city with individuals of >200 nationalities [14].

The BMI definition of obesity does not account for different phenotypes of obesity, in terms of fat distributions and the difference between subcutaneous and visceral adiposity. Particularly, central visceral adiposity is more strongly predictive of metabolic risk factors. Accordingly, our data show that WC and visceral fat mass are significantly correlated with each other. Therefore, this simple and inexpensive measurement should supplement BMI in defining obesity and metabolic risk with potential implications on treatment allocations [15]. Kamadjeu et al [16] reported similar results in a cohort from Cameroon with respect to the burden of diabetes baseline data. It is notable that an increase in abdominal visceral adiposity is reflected by WC and is related to an increased cardio-metabolic risk [3]. WHR had a weak correlation with other anthropometric measures in our cohort.

Furthermore, there are gender differences in the rates of metabolic-related disorders. Our data show higher rates of NAFLD, dyslipidemia, and diabetes in females with obesity but could not be linked to anthropometric variables, particularly WC and the visceral fat ratio. This is likely owing to the small numbers of individuals in some of the groups.

The findings of our study have important implications in the assessment of obesity in clinical practice, as they reinforce the use of anthropometrics as indicators of obesity. The International Atherosclerosis Society and International Chair on Cardiometabolic Risk working group have also published a consensus statement on visceral obesity in March 2020. It is recommended to use the WC value as a critical target for reducing adverse health risks for both men and women [17]. Recent Canadian guidelines for obesity in adults also recommend the measurement of WC in addition to BMI to identify individuals with increased visceral adiposity and adiposity-related health risks [18].

Strengths and Limitations

The limitations of our study are its sample size and the cross-sectional assessment of anthropometric parameters. More studies are needed to analyze the implications of longitudinal anthropometrics on the occurrence of metabolic-related conditions and the effect of different weight management interventions in modifying this risk.

In summary, this study demonstrates a strong correlation between conventional obesity measures and anthropometric measures, particularly the WC. It highlights the importance of using anthropometrics such as WC as a measure of obesity, especially as it is an easy-to-use and inexpensive clinical tool.

Conclusions

In conclusion, our study shows that BMI and WC are the most representative measures of obesity in our population and correlate with visceral adiposity and obesity-related diseases. This study highlights the importance of incorporating anthropometrics in the clinical assessment of patients with

obesity to further determine their metabolic risk. Further studies are required to assess the benefits of these measures during weight reduction interventions.

Conflicts of Interest

None declared.

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Abbreviations

HbA_{1c}: glycated hemoglobin
HC: hip circumference

HDL: high-density lipoprotein
NAFLD: nonalcoholic fatty liver disease
WC: waist circumference
WHR: waist-hip ratio

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Original Paper

Knowledge of Sleep Disorders Among Physicians at a Tertiary Care Hospital in Qatar: Cross-sectional Study

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Abstract

Background: Sleep disorders constitute a major health problem because of their relatively high and rising prevalence. Several studies worldwide have analyzed health care providers' knowledge of sleep disorders.

Objective: In this study, we aimed to assess the knowledge of sleep disorders among physicians in Qatar.

Methods: A total of 250 physicians were surveyed regarding their knowledge of sleep medicine by using the validated 30-item Assessment of Sleep Knowledge in Medical Education (ASKME) Survey. The participants included residents, fellows, and consultants in medicine and allied subspecialties. A high score was defined as ≥60% of correctly answered questions, implying the respondent has adequate knowledge of sleep disorders.

Results: Responses were received from 158 of the 250 physicians, with a response rate of 63.2%. This included responses from 34 residents, 74 clinical fellows, and 50 consultants. The overall mean score was 15.53 (SD 4.42), with the highest possible score of 30. Only 57 of 158 (36.1%) respondents were able to answer ≥60% of the questions correctly. No statistically significant difference was found in the scores of participants with regard to their ranks (ie, residents, fellows, or consultants) or years of medical training.

Conclusions: This study demonstrates that health care providers in Qatar have decreased awareness and knowledge about sleep medicine, which may reflect reduced emphasis on sleep disorders during medical school and training. Increasing awareness regarding sleep medicine among nonspecialist physicians will allow early detection and treatment of sleep disorders, thereby reducing the morbidity associated with these disorders.

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KEYWORDS

sleep disordered breathing; obstructive sleep apnea; sleep; physician; physician knowledge; sleep disorder; survey method; attitudes; practice

Introduction

Sleep disorders are defined as a range of sleep problems, including conditions causing hypersomnia (such as sleep apnea and narcolepsy), parasomnia (restless leg syndrome and sleepwalking), insomnia, and sleep-wake cycle disturbances. All these sleep disorders share a common outcome—nonrestorative sleep [1]. Excessive daytime somnolence (EDS) is a consequence of sleep disorder, which can impact focus, concentration, and memory. Nonrestorative sleep and EDS are related to respiratory, cardiovascular, and neurological problems such as increased reaction time, which in turn can lead to motor vehicle and other serious accidents in

situations where alertness is required for safety and critical decision-making [2-4]. Hence, sleep disorders are a major risk to public health. Obstructive sleep apnea (OSA), central sleep apnea, and obesity hypoventilation syndrome are treatable sleep disorders that affect a significant proportion of the population worldwide, with OSA prevalent in 3%-5% of middle-aged men and 2%-5% of women [5]. A population-based regional survey evaluating OSA in Saudi Arabia found similar data, with OSA prevalence reported at 4% and 1.8% among men and women, respectively [6].

Given the impact that sleep disorders have on the health and well-being of a significant portion of society, physicians, regardless of their specialty, will inevitably encounter patients with sleep complaints; they should, therefore, have the knowledge and awareness to diagnose sleep disorders. Unfortunately, despite the common presentation and clinical significance of these conditions, sleep disorders remain underdiagnosed or misdiagnosed and, consequently, untreated [7]. In the 2005 National Sleep Foundation's *Sleep in America* poll, 70% of the respondents reported that their doctor had never asked about their sleep habits or patterns [8].

As a result, sleep disorders and associated modifiable risk factors such as obesity remain unaddressed and continue to progress, leading to the worsening of disordered sleep patterns and their ensuing complications [9].

Limited studies have addressed the knowledge of sleep disorders among practicing health care practitioners in the Middle East and, to the best of our knowledge, no similar studies have been conducted on health care practitioners in the State of Qatar. Therefore, we aimed to address this gap by conducting a survey to assess the knowledge of sleep disorders among physicians working at a tertiary care center in the State of Qatar.

Methods

Study Group

We conducted a survey-based study from August 2018 to December 2018. The target population comprised postgraduate medical trainees and health care practitioners. Our study sample included residents in the Internal Medicine program and fellows in allied medical subspecialties, undertraining programs at Hamad Medical Corporation accredited by the Accreditation Council for Graduate Medical Education–International (ACGME-I), and consultants in General Medicine and subspecialties at Hamad General and Heart Hospitals, Qatar.

Survey

We used the Assessment of Sleep Knowledge in Medical Education (ASKME) Survey, a validated 30-item questionnaire that has been designed as a standardized tool for the assessment of medical education in sleep [10]. The survey assesses five separate areas of sleep knowledge, including (1) basic sleep principles, (2) circadian sleep/wake control, (3) normal sleep architecture, (4) common sleep disorders, and (5) effects of drugs and alcohol on sleep. Possible responses to the survey items are “true,” “false,” and “I don’t know.” Participants were categorized into two groups: (1) a high score group comprising participants with correct scores ≥60% and (2) a low score group comprising participants with correct scores <60%, based on the cut-off pass threshold mark used in the majority of medical schools across the Gulf states.

Statistical Analysis

Continuous data are presented as means and SD, and categorical data are presented in the text and tables as absolute numbers (n) and percentages (%). One-way analysis of variance (ANOVA) was performed for comparison between more than two groups. A P value ≤.05 was significant. Statistical analysis was conducted using Stata Statistical Software (Release 16; StataCorp LLC).

Results

The survey was administered to 250 participants. Responses were received from 158 participants, with a response rate of 63.2%. These included data collected from 34 residents in internal medicine; 74 clinical fellows training in internal medicine, cardiology, endocrinology, neurology, rheumatology, and nephrology; and 50 consultants in general medicine (Table 1). The majority of respondents (121/158, 76.6%) were male and aged above 30 years (Table 1). The participants’ mean overall score was 15.53 (SD 4.42), with the highest possible score of 30. Only 57 of 158 (36.1%) participants scored ≥60%.

Table 1. Demographics of the survey participants (N=158).

Variable	Participants, n (%)
Age (years)	
25-30	37 (23.4)
>30	121 (76.6)
Gender	
Male	131 (82.9)
Female	27 (17.1)
Level of training	
Resident	34 (21.5)
Fellow	74 (46.8)
Consultant	50 (31.6)
Year of training	
First year	25 (15.8)
Second year	16 (10.1)
Third year	32 (20.3)
Fourth year	11 (7.0)
More than 4 years	74 (46.8)
Country of graduation	
Pakistan	25 (15.8)
Jordan	16 (10.1)
Libya	14 (8.9)
Syria	12 (7.6)
Sudan	12 (7.6)
India	10 (6.3)
Egypt	8 (5.1)
Qatar	7 (4.4)
United Kingdom	4 (2.5)
Palestine	4 (2.5)
Ireland	3 (1.9)
Yemen	3 (1.9)
United Arab Emirates	2 (1.3)
Unknown[a]	38 (24.1)

[a]38 respondents did not respond to the question about their country of graduation.

Further analysis showed that the high-score group (n=57) comprised 7 (12%) residents, 32 (56%) fellows, and 18 (32%) consultants, whereas the low-score group (n=101) comprised 27 (26.7%) residents, 42 (41.6%) fellows, and 32 (31.7%) consultants (Table 2). Figure 1 shows the percentage of high and low scores across gender and different groups of physicians.

No statistically significant difference was found between the scores of respondents in the 25- to 30-year age group and those aged above 30 years. Rank of the physician (ie, residents, fellows, or consultants), year of training among residents and fellows, and country of graduation also did not have a statistically significant effect on the total scores (Table 3).

Table 2. Comparison of age, gender, and designation of participants in the high-score group (n=57).

Variable	Participants who scored ≥60%, n (%)	*P* value
Age (years)		.62
25-30 (n=37)	12 (32)	
>30 (n=121)	45 (37)	
Gender		.59
Male (n=131)	46 (35)	
Female (n=27)	11 (41)	
Level of training		.23
Residents (n=34)	7 (21)	
Fellows (n=74)	32 (43)	
Consultants (n=50)	18 (36)	

Figure 1. Percentages of high and low scores across gender and different groups of physicians.

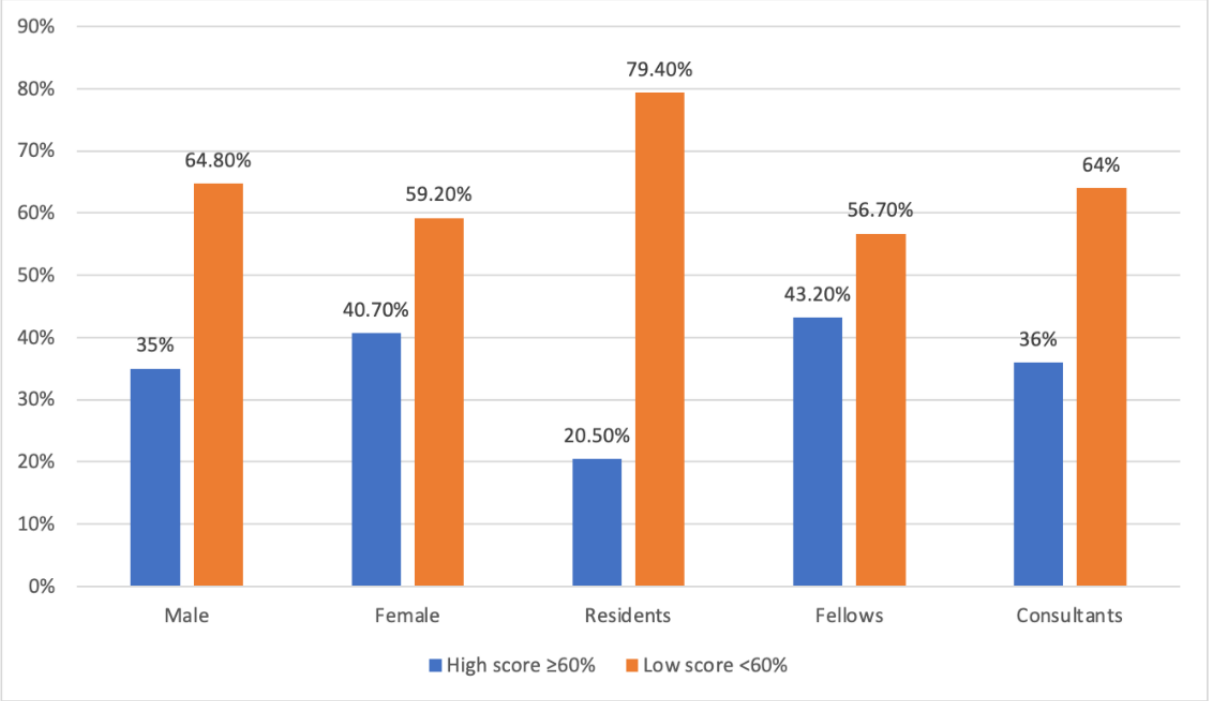


Table 3. Comparison of the years and level of training and country of graduation of participants in the high-score group (n=57).

Variable	Participants who scored ≥60%, n (%)	*P* value
Year of training		.84
Resident		
First year (n=10)	2 (20)	
Second year (n=4)	2 (50)	
Third year (n=16)	2 (13)	
Fourth year (n=4)	1 (25)	
Fellow		
First year (n=15)	7 (47)	
Second year (n=12)	6 (50)	
Third year (n=16)	8 (50)	
Fourth year (n=5)	1 (20)	
More than 4 years (n=26)	10 (38)	
Country of graduation		.63
Pakistan (n=25)	10 (40)	
Jordan (n=16)	4 (25)	
Libya (n=14)	3 (21)	
Syria (n=12)	5 (42)	
Sudan (n=12)	6 (50)	
India (n=10)	5 (50)	
Egypt (n=8)	5 (63)	
Qatar (n=7)	3 (43)	
United Kingdom (n=4)	1 (25)	
Palestine (n=4)	2 (50)	
Ireland (n=3)	1 (33)	
Yemen (n=3)	1 (33)	
United Arab Emirates (n=2)	1 (50)	
Other unknown countries[a] (n=38)	10 (26)	

[a]10 participants who scored ≥60% did not disclose their country of graduation.

Discussion

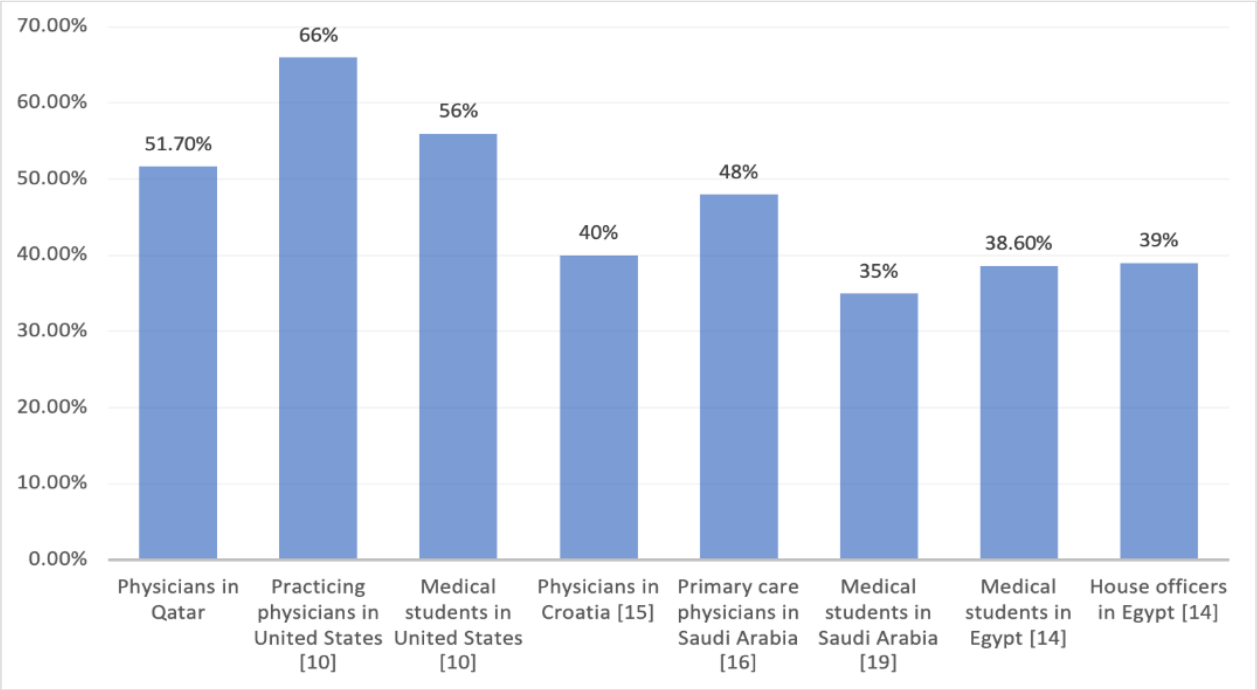
Our study shows that postgraduate medical residents, fellows, and consultants in internal medicine or subspecialties at the largest tertiary care government hospital in Qatar have average to below-average knowledge in sleep medicine. The prevalence of obesity in Qatar is quite high, with 35% of men and 45% of women having a BMI higher than 30 [11]. Prevalence of obesity and consequent sleep-related breathing disorders are constantly rising, which can be attributed to the sedentary lifestyle, decreased physical activity, and unfavorable weather conditions possibly hindering a more active lifestyle. Sleep disorders are common worldwide; however, epidemiological studies on its prevalence are lacking in the State of Qatar. Anecdotal evidence reveals that, on average, 10 new patients with sleep-related breathing disorders are diagnosed in pulmonary clinics every week. This points to a high prevalence of sleep-related breathing disorders in the country.

In our study, only 35.8% of participants correctly answered more than 60% of the questions. Our results did not differ much from the previous studies assessing sleep knowledge across different countries in the Middle East region. For instance, a study comprising 215 physicians in Turkey showed that 45.3% of them answered questions correctly on a questionnaire assessing knowledge about sleep medicine [12]. Another similar study comprising primary health care physicians, of whom 94% were board-certified and 76% were certified in more than one field, rated their knowledge of sleep medicine as *fair* or *poor* [13]. In Egypt, Zaki et al [14] assessed the knowledge of normal sleep and sleep disorders among final-year medical students and house-officers from seven different medical faculties, also using the ASKME questionnaire. They found that 91% of the

study participants had limited knowledge of sleep disorders, which is consistent with our results.

In our study, the mean score obtained by the participants was 15.53 (ie, 51.7%), which was significantly lower than the mean score obtained by practicing physicians (66%) and medical students (56%) in the United states [10]. However, physicians in our study fared better than practicing physicians in Egypt, Croatia, and Saudi Arabia [14-16]. Comparison of mean ASKME scores of participants of our study and those of studies carried out in other countries is presented in Figure 2. Similar results were reported when a different survey was used to assess sleep knowledge. For example, a cross-sectional survey of general practice physicians in Ecuador, Peru, and Venezuela, using the OSA Knowledge and Attitudes (OSAKA) questionnaire demonstrated that although 73.5% of the physicians felt confident in identifying patients at risk for OSA, only 35.4% felt confident in managing these patients [17]. Similarly, behavior, attitude, and knowledge of sleep medicine assessed using MED sleep survey among interns and medical residents in university hospitals of central India revealed that average scores were 12.6 (ie, less than 50%). Moreover, 52.6% of the residents and 31.15% of the interns participating in this study obtained a score of more than 50%, which could be attributed to the increased exposure of residents to the medical literature [18]. Our study findings showed that trainees in fellowship programs had more knowledge in sleep than did interns and consultants, likely from increased exposure to consultations and a strong knowledge base from attending board certification residency exams.

Figure 2. Comparison of the mean Assessment of Sleep Knowledge in Medical Education (ASKME) Survey scores obtained by physicians participating in this study and those obtained by physicians and students in studies in other countries using the same assessment tool [10,14,16,20].



It is worth mentioning an interesting study conducted in Hyderabad, India, wherein they found that only half of the practicing chest physicians could correctly answer 50% of the questions related to sleep-disordered breathing and only 10% of the respondents could answer 75% of the questions correctly [20]. These estimates demonstrate that even respiratory physicians exhibit a poor understanding of sleep disorders. Although our target population excluded chest physicians, our study shows similar results highlighting that after completion of graduate and/or postgraduate training, physicians are likely less exposed to updates or educational activities in sleep medicine, resulting in a decrement of knowledge of sleep disorders. Based on these findings, we can infer that health care providers worldwide exhibit a poor understanding of sleep disorders.

Most of the studies have not explored the obstacles related to poor knowledge of sleep disorders among health care providers. The lack of knowledge regarding sleep medicine could be the result of the limited time assigned for teaching sleep medicine at medical schools. A study from Saudi Arabia comprising undergraduate medical students using the ASKME Survey showed that the majority of the participants recorded their sleep knowledge as *below average*, with no difference in the scores observed among participants of different universities, gender, or academic level [19]. The main factor identified for this level of performance was the low priority for sleep medicine in the medical curriculum and the lack of time required to implement it. In 1998, a survey by the American Sleep Disorders Association and Sleep Research Society in the United States reported similar findings, with an average of 2.1 hours devoted to sleep medicine instruction at medical school. About 79% of respondents reported spending between 0.75 and 2.0 hours on the topic, 12% reported spending between 2.5 and 4 hours, and only 9% reported being provided 6-10 hours of sleep instruction. Respondents indicated that the greatest need was more instruction time—a tall order for an already crowded curriculum [21]. The absence of any significant difference in scores based

on the country of graduation, as found in our study, also echoes these findings, thus underlining the deficiency of focus on sleep medicine in medical curricula across countries.

In the postgraduate internal medicine residency training program at our hospital, the average number of hours focused on sleep medicine training is less than 1 hour (in the form of didactic lectures). Majority of the knowledge is gained from clinical experience and through taking various international certification exams. Although there are faculty-trained and board-certified physicians in sleep medicine who regularly conduct sleep clinics with the support of a sleep laboratory run by two certified sleep technologists, there is no structured sleep medicine training or fellowship program in Qatar yet. This could also account for the low scores obtained among the trainees in our study. A review of sleep physiology and didactic lectures on obstructive sleep apnea and other sleep disorders along with their management is provided only in the pulmonary fellowship training program. Trainees in the pulmonary fellowship have electives in a sleep laboratory to understand how sleep studies are conducted and interpreted. Furthermore, a 2007 review of medical specialty textbooks found that information on sleep and sleep disorders constituted only about 2% of the overall content [22]. This lack of emphasis has contributed to the medical culture in which few physicians, other than sleep specialists, ask questions about sleep when recording a patient's history [8]. Our survey findings highlight the need for improving training in sleep medicine among postgraduate trainees in internal medicine and subspecialties. Didactic lectures can be complemented with sleep medicine modules. Introduction of educational modules has shown that successful learning can be achieved from these modules as well, when compared to the traditional educational metric on time spent on clinical rotation [23]. Distance learning and e-learning with collaborative institutes could also serve as a platform to enhance the knowledge and attitudes in sleep medicine. It is important to develop the structural framework for clinical experience, sleep education, conduct, and interpretation of sleep studies in relevant subspecialties. This would ensure more fellows entering the field of sleep medicine.

The gap between what we know about sleep and the limited exposure to that knowledge an average trainee or consultant receives at both the undergraduate and postgraduate levels highlights the need for more instruction time devoted to this topic. At the undergraduate level, integrating information on sleep and sleep disorders into the existing medical school curriculum could help, whereas at the postgraduate level, introduction of sleep modules and structured sleep medicine training programs may enhance knowledge of screening, diagnosis, and treatment of sleep disorders.

Conclusions

Physicians working at Hamad Medical Corporation, Qatar, exhibit poor knowledge of sleep medicine, which could be attributed to the weak level of education in this field of medicine. Sleep disorders constitute a significant health problem and, if detected early, can generally be treated, improving the health and quality of life for these patients. Therefore, its necessary to emphasize on sleep medicine and sleep disorders during medical school education and residency training.

Acknowledgments

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Authors' Contributions

IUH and MAH conceptualized the study. IUH, KSS, and SA obtained the data. MA and AAA assisted with data collection and interpretation. Funds were collected by SA and AAA. MMT, MAH, and AMMO performed data analysis and created all tables. MMT, MAH, and IUH wrote the manuscript with input from all the authors.

Conflicts of Interest

None declared.

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Abbreviations

ACGME-I: The Accreditation Council for Graduate Medical Education–International
ASKME: Assessment of Sleep Knowledge in Medical Education
EDS: excessive daytime sleepiness
OSA: obstructive sleep apnea
OSAKA: Obstructive Sleep Apnea Knowledge and Attitudes

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Original Paper

A Handheld Metabolic Device (Lumen) to Measure Fuel Utilization in Healthy Young Adults: Device Validation Study

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Abstract

Background: Metabolic carts measure the carbon dioxide (CO_2) produced and oxygen consumed by an individual when breathing to assess metabolic fuel usage (carbohydrates versus fats). However, these systems are expensive, time-consuming, and only available in health care laboratory settings. A small handheld device capable of determining metabolic fuel usage via CO_2 from exhaled air has been developed.

Objective: The aim of this study is to evaluate the validity of a novel handheld device (Lumen) for measuring metabolic fuel utilization in healthy young adults.

Methods: Metabolic fuel usage was assessed in healthy participants (n=33; mean age 23.1 years, SD 3.9 years) via respiratory exchange ratio (RER) values obtained from a metabolic cart as well as % CO_2 from the Lumen device. Measurements were performed at rest in two conditions: fasting, and after consuming 150 grams of glucose, in order to determine changes in metabolic fuel usage. Reduced major axis regression and simple linear regression were performed to test for agreement between RER and Lumen % CO_2.

Results: Both RER and Lumen % CO_2 significantly increased after glucose intake (P<.001 for both) compared with fasting conditions, by 0.089 and 0.28, respectively. Regression analyses revealed an agreement between the two measurements ($F_{1,63}$=18.54; P<.001).

Conclusions: This study shows the validity of Lumen for detecting changes in metabolic fuel utilization in a comparable manner with a laboratory standard metabolic cart, providing the ability for real-time metabolic information for users under any circumstances.

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KEYWORDS

resting metabolic rate; Lumen; ParvoMedics TrueOne 2400; validation; respiratory exchange ratio; metabolism; fuel utilization; indirect calorimetry; breath; lung; respiratory; young adult; measurement; testing

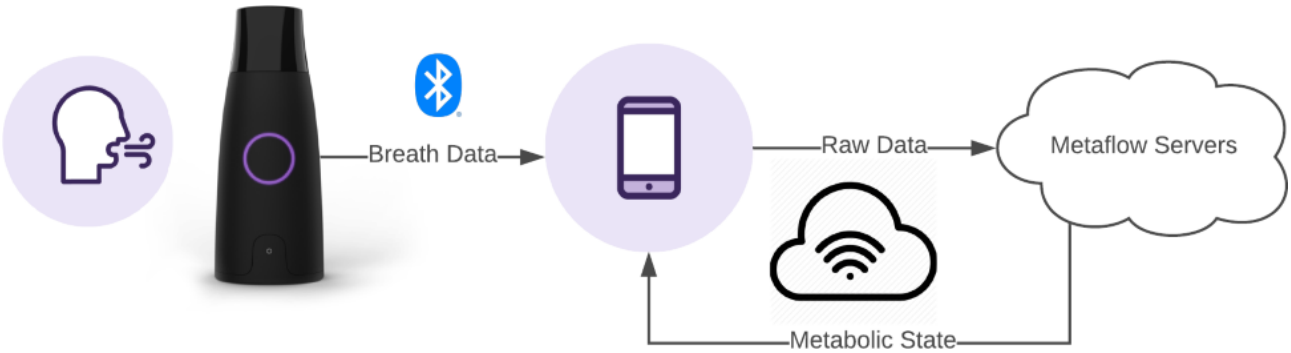
Introduction

Indirect calorimetry (metabolic cart), which is currently the preferred method for determining metabolic fuel utilization, measures the carbon dioxide produced (VCO_2) and oxygen consumed (VO_2) when breathing. The ratio between VCO_2 and VO_2 is the respiratory exchange ratio (RER), which provides insight into the relative contribution of carbohydrates and lipids to overall energy expenditure [1,2]. Though indirect calorimetry is not invasive, this method is time-consuming (up to 40

minutes), only available in test laboratory settings, and requires technical and physiological expertise for handling the metabolic cart and interpretation of the metabolic data obtained.

Metaflow Ltd developed Lumen, a novel metabolic fuel utilization breathalyzer, which is a personalized handheld device that provides an individual's metabolic state in real time by measuring CO_2 from exhaled breath (Figure 1). The device indirectly measures metabolic fuel usage via a CO_2 sensor and a flow sensor to determine the rate of CO_2 production from a single breath maneuver. The % CO_2 in the exhaled volume of air is determined from a specific breathing maneuver with a breath hold of 10 seconds. This concept is based on the fact that oxygen consumption is stable under resting conditions [3]; thus, a change in metabolic fuel use will generally be represented by changes in CO_2 production. For carbohydrate oxidation, more carbon dioxide is produced relative to the consumption of oxygen. For fat oxidation, less carbon dioxide is produced [4]. The use of a smartphone app enables the user to track metabolic status outside of physiologic test laboratories.

Figure 1. A schematic representation of the Lumen device and app.



Previous exploratory studies for algorithmic development of Lumen were performed to compare the Lumen measurement to the metabolic cart. In this study, we aim to evaluate agreement between the Lumen measurement and that of the metabolic cart in healthy participants before and after glucose ingestion under stable resting conditions.

Methods

Participants

A total of 54 healthy volunteers reported to the Exercise Physiology Laboratory in the Department of Kinesiology at San Francisco State University to participate in this study. Inclusion criteria were being aged between 18-45 years with a BMI less than 30 kg/m^2. Exclusion criteria were participation in high-intensity aerobic training or having a known cardiovascular, pulmonary, and/or metabolic disease. The study was approved by the university's Institutional Review Board for Human Subjects, and written informed consent was obtained from each participant before testing.

Study Design

Participants were recruited and their height and weight were measured using a stadiometer and Seca scale (Seca). If they met the BMI criteria, they were provided their own Lumen device, which was labeled with their unique identification number. The Lumen device was paired and synchronized to the participant's smartphone together with the Lumen app. Participants practiced the Lumen breathing technique while supervised and took the device home for a further familiarization period in order to show proficiency with the device and app. They were instructed to perform Lumen metabolic measurements for at least 30 sessions, with each session consisting of 3 breath maneuvers, and to complete 3 sessions at different time points each day. After the minimum amount of home breath sessions were collected, participants were scheduled for the study laboratory measurement day. All participants came to the test laboratory between 7 AM and 11 AM after a 12-hour fast and had abstained from any form of physical activity (other than walking).

On the laboratory testing day, blood glucose samples were taken by sterile finger prick blood sample and measured by a glucometer (OneTouch, LifeScan Inc). For the indirect calorimetry measurement, the participant had to lay down in supine position on a padded examination table, where a rigid clear plastic canopy with a comfortable, flexible seal was placed over the head and upper part of the torso. Once the metabolic cart measurement was completed, the participant was seated in a comfortable chair. After 5 minutes of rest, they were asked to perform two Lumen breath sessions (5-minute break between each session). The first Lumen session immediately after the metabolic cart measurement was used for data analysis. In case of an invalid first session (difference between breaths >0.2% CO_2), the second session was used for analysis.

Once finished, participants were asked to drink 150 grams of a glucose solution (3 servings of 50 grams with 20-minute intervals between each serving). Subsequently, 45 minutes after the intake of the first drink (corresponding to 5 minutes after finishing the last serving), their glucose levels were reassessed, and the same assessment procedures as during the fasted state before the glucose intake were repeated. Participants were removed from the analysis if they were unable to finish all glucose drinks.

Metabolic Cart

RER was analyzed using a calibrated TrueOne 2400 metabolic cart (ParvoMedics), which was previously determined to provide a valid measurement for RER with 5% coefficient of variation [5]. This system uses a paramagnetic oxygen analyzer and infrared carbon dioxide analyzer with a Hans Rudolph heated pneumotach. The ParvoMedics system was warmed up for at least 60 minutes each day before testing to ensure accurate and

stable readings. The gas analyzers and flow sensor were calibrated as per manufacturer's recommendations: calibration of the analyzers was performed using a high-precision gas mixture (O_2, CO_2, remainder N_2) and calibrated and accepted with a <0.1% error with the calibration gas. Flow and volume were calibrated using a calibrated 3 L syringe (Hans Rudolph, model 5530) to ≤1% error. In addition, verification of the calibration process was performed to ensure stability of the system. The ambient temperature was kept between 22 °C and 26 °C in the test laboratory. Relative humidity was maintained stable at roughly 60%. Once calibration was acceptable and complete, a ventilated hood with subject cover was placed over the participant's head and positioned around the upper torso area to ensure no air could escape from the hood. The participants were required to stay awake during the measurement procedure. The hood ventilation was measured during the recording, and CO_2 and O_2 concentrations were measured from it. VCO_2 and VO_2 parameters were calculated and taken as 30-second averages. For this study, we defined the subject steady-state metabolic measurement based on observed variations in the VO_2 and VCO_2 of less than ≤5% coefficient of variation for a period of at least five consecutive minutes, with a subsequent RER stability of 2.5% in a fasted state and 3.7% after glucose consumption, in a similar manner to previous studies [6]. Inability to meet these criteria resulted in removal of the data from the analysis.

Lumen

Lumen is a device designed to be calibration-free, with a warm-up time of less than 10 seconds and the CO_2 sensor taking into account the room CO_2 concentration during every measurement. During the measurement day, participants completed 2 sessions of 3 Lumen breaths each after the metabolic cart measurement. The Lumen breathing maneuver consists of three phases, starting from the end of a normal expiration (functional residual capacity). The participant takes a deep breath in through the Lumen device, followed by a 10-second breath hold. Afterward, the subject exhales through the Lumen device, with a steady exhalation flow to at least the starting level of the maneuver. In order to confirm repeatability, breaths are taken in triplicate for each session. The Lumen smartphone app guides the participant through each phase of the Lumen maneuver. Each Lumen session was repeated after a 5-minute pause interval. Validity of breath maneuvers was systematically evaluated by the Lumen app. Inability to perform valid Lumen breath measures resulted in removal of the data from the analysis.

Statistical Analyses

All variables were tested and visualized for normal distribution before the tests.

To evaluate the changes after glucose intake, two-tailed paired parametric *t* tests were performed for blood glucose levels, RER levels, and Lumen % CO_2 before and after glucose intake.

For agreement validation, major axis regression (Deming method) was performed to compare RER of the metabolic cart and % CO_2 from the Lumen device [7]. As RER and % CO_2 are in different units, the analysis is identical to ordinary least products regression (also known as reduced major axis regression), which is the most suitable analysis for comparison between two methods of measurement [8]. Moreover, a simple linear regression (ordinary least squares) was performed to determine the ability to predict Lumen values from the gold-standard value of RER.

Statistical analyses were performed using GraphPad Prism 8 (GraphPad Software Inc). The threshold for significance was set at $P<.05$.

Ethics Statement

This study was approved by San Francisco State University's Institutional Review Board for Human Subjects, and written informed consent was obtained from each participant before testing.

Results

From the original 54 participants recruited, 12 were excluded prior to laboratory testing and 9 had to be excluded during the testing day for failing to meet the inclusion criteria as detailed in the methods section: 1 participant was unable to consume all glucose drinks due to nausea, 3 participants did not achieve 5 minutes of stable metabolic cart measurement (coefficient of variation <5% in VO_2 and VCO_2), and 5 participants were unable to perform a valid Lumen measurement (Figure 2). Characteristics of the final 33 participants are presented in Table 1.

Figure 2. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. CV: coefficient of variation.

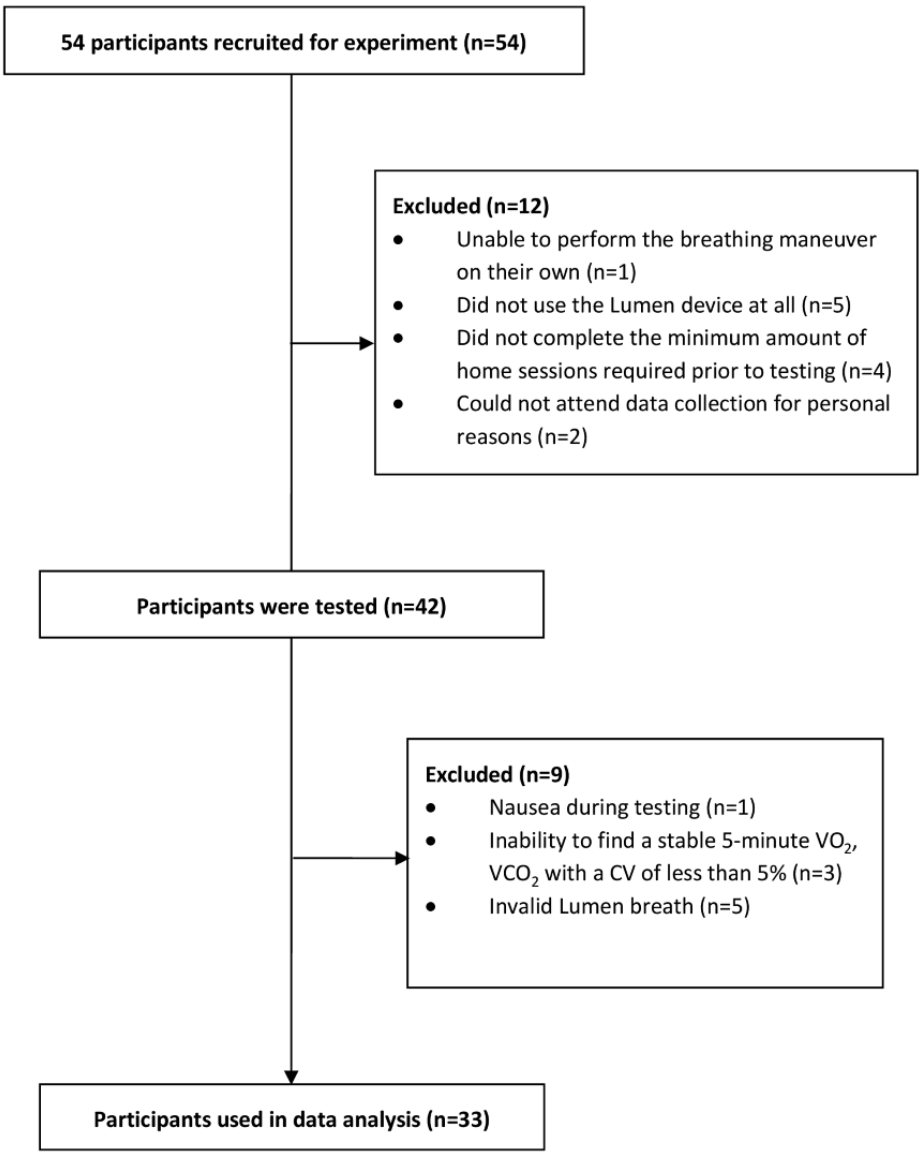
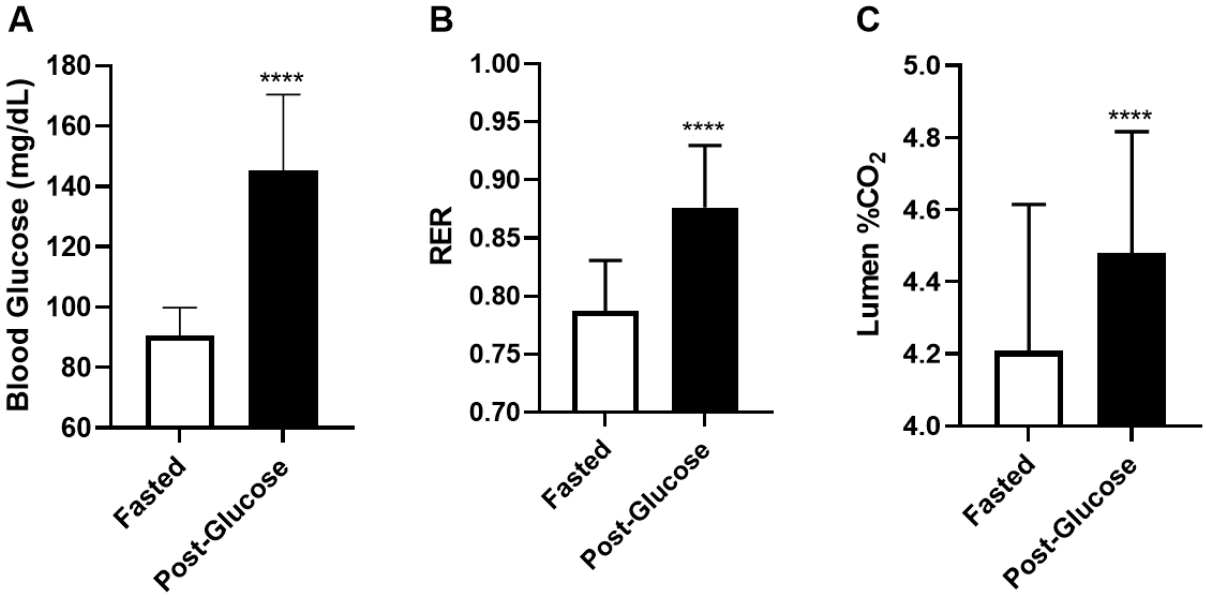


Table 1. Descriptive statistics of study participants.

Gender	Count	Age (years), mean (SD)	Weight (kg), mean (SD)	Height (cm), mean (SD)	BMI (kg/m^2), mean (SD)
Male	17	24.0 (3.0)	73.7 (10.2)	171.7 (7.8)	24.9 (2.5)
Female	16	22.3 (4.5)	59.1 (6.4)	160.9 (5.5)	22.9 (2.6)
Total	33	23.1 (3.9)	66.2 (11.1)	166.1 (8.6)	23.9 (2.7)

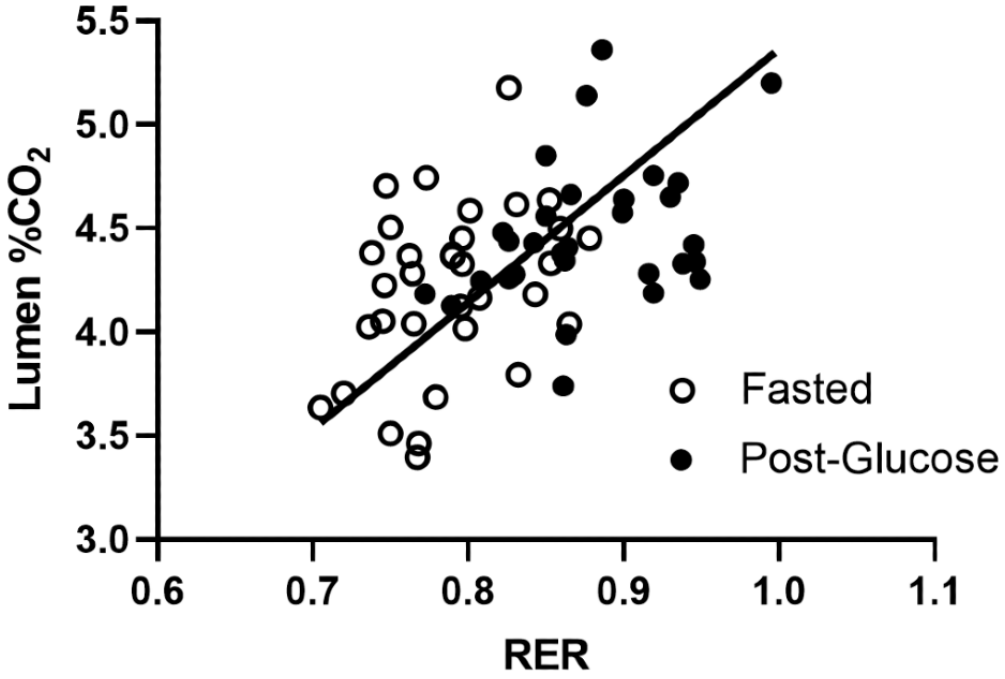
Blood glucose levels increased from 90.6 (SD 9.2) mg/dL to 145.2 (SD 25.3) mg/dL as a result of glucose intake (t_{32}=11.04, P<.001; Figure 3A). RER levels increased from 0.787 (SD 0.043) to 0.876 (SD 0.053) in response to glucose intake (t_{32}=10.84, P<.001; Figure 3B). Moreover, Lumen CO_2 concentrations significantly rose from 4.20 (SD 0.4) to 4.48 (SD 0.34; t_{32}=5.978, P<.001; Figure 3C). These analyses have confirmed the ability of both the metabolic cart and Lumen to detect changes in metabolic fuel utilization.

Figure 3. Changes in blood glucose as determined by (A) blood glucose test, (B) RER, and (C) Lumen % CO_2. Data are presented as mean (SD). N=33 for each state. **** indicates *P*<.001. RER: respiratory exchange ratio.



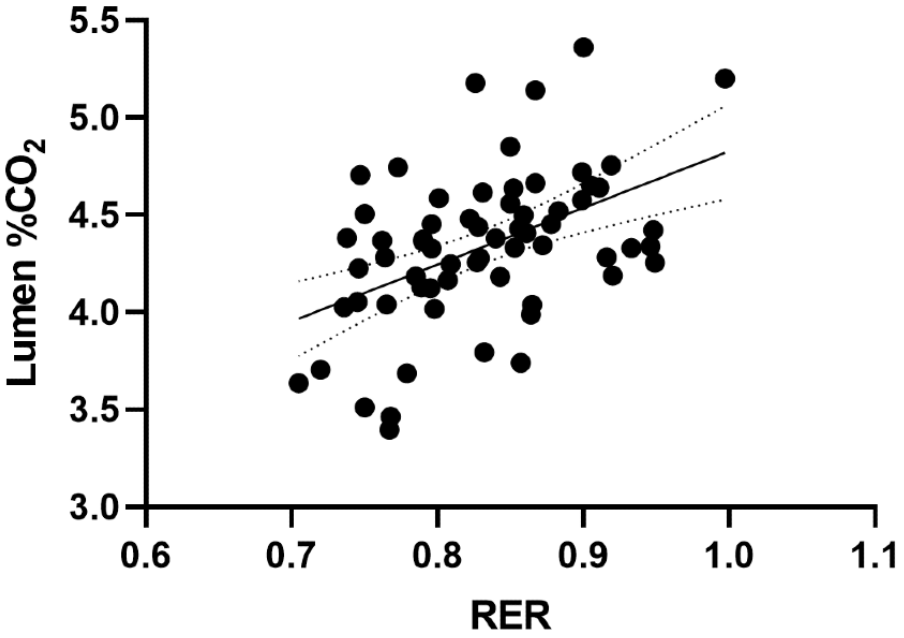
To test for agreement between RER units from the metabolic cart and % CO_2 from Lumen, reduced major axis regression was performed [9]. It revealed a significant relationship between RER and Lumen % CO_2 ($F_{1,63}$=18.54, *P*<.001, y=6.111x–0.7445, x-intercept=0.1218; Figure 4). This analysis confirmed the agreement between Lumen % CO_2 and metabolic cart RER, with a systemic bias as a result of the nature of the different units.

Figure 4. Reduced major axis regression of RER from the metabolic cart and Lumen % CO_2 measurements for metabolic activity. N=33 for each state. RER: respiratory exchange ratio.



To determine the ability of metabolic cart RER to predict Lumen % CO_2, ordinary least squares regression was performed to estimate Lumen values from RER measures, with the assumption that RER is an accurate independent measure, to predict Lumen % CO_2. A significant model effect was present ($F_{1,63}$=18.54, *P*<.001, R^2=0.2274; Figure 5). The RER parameter estimate indicated that for every 1-unit increase in RER, a 2.914-unit increase (SE 0.6767) in Lumen % CO_2 is expected. Since a full unit increase in RER is not a plausible outcome, this parameter estimate can be interpreted similarly by a 0.1-unit increase in RER (eg, 0.7 to 0.8) to produce a 0.2914-unit increase in Lumen % CO_2.

Figure 5. Ordinary least squares regression of RER and Lumen % CO_2. N=33 for each state. RER: respiratory exchange ratio.



Discussion

Principal Findings

This study evaluated the ability of the Lumen device to assess changes in the body's metabolic fuel utilization in healthy young adults compared to the indirect calorimetry metabolic cart measurement. Our results show that Lumen CO_2 levels are in agreement with RER values from the metabolic cart, which correspond to relative changes in metabolic fuel utilization.

Both Lumen CO_2 levels and metabolic cart RER showed significant increases in metabolic levels as a result of glucose intake in healthy individuals in resting conditions (Figure 3). These results can be expected, as cells using more carbohydrates as fuel produce more CO_2 relative to O_2 consumption compared to cells metabolizing fat. The ratio between CO_2 production and O_2 consumption in this process is known as the respiratory quotient (RQ) or RER. RQ and RER vary depending on the energy source of the cell (carbohydrate versus fat), and the acronyms are commonly used interchangeably [2,10,11]. In resting conditions, oxygen consumption is fairly stable [12,13], meaning that participants' changes in RQ are due to changes in CO_2 production. This is the underlying concept of the Lumen device, enabling it to track changes in metabolic fuel utilization. For that reason, it was important to ensure that participants in this study were at rest before and during their measurements.

Reduced major axis regression revealed an agreement between RER and Lumen CO_2 levels (Figure 4). This analysis enables us to test for agreement between methods with different units and verify the validity of the Lumen device with a metabolic cart. It demonstrates the ability of the Lumen device to provide equivalent results to the metabolic cart in assessing metabolic fuel utilization.

Furthermore, the results from the simple linear regression predicting Lumen % CO_2 using RER values suggest that, while there is measurement agreement between the Lumen % CO_2 and RER, the proportion of variance remains low (Figure 5). Thus, Lumen can be seen to be an effective instrument for monitoring individual changes in metabolic responses (within-subject consistency), rather than a substitute for the metabolic cart (between-subject precision).

Evidence suggests that the assessment of RER can be beneficial for multiple applications, such as nutrition, diabetes prevention, or weight management [14]. It has previously been shown that RER could be a prognostic marker of weight loss and a predictor of weight gain [15,16]. Moreover, minute-to-minute RER measured in a respiratory chamber calorimeter showed that the slopes of RER were different in response to different dietary interventions [17]. However, although RER is currently the preferred method for determining metabolic fuel, it is a time-consuming, uncomfortable, and costly and impractical tool for real-time day-to-day assessments of metabolic activity. In contrast, the Lumen device is small, mobile, user-specific, and relatively cheap, and delivers the outcome immediately to the user and enables real-time decisions.

Limitations

This study is the first to show agreement between Lumen % CO_2 and RER. However, it is important to note that participants in this study were young (mean age 22.4 years) and healthy individuals. With increasing age, metabolism changes, as can be seen in various metabolic cart studies [18-20]. Future studies will need to examine whether RER metabolic cart levels correspond to Lumen CO_2 levels in older subjects and those with metabolic conditions.

Unlike the metabolic cart, the Lumen device does not measure oxygen consumption. Accordingly, the Lumen measurement should be performed under resting conditions with stable VO_2, allowing the correct interpretation of changes of % CO_2 as changes in metabolic state.

In addition, results from this study showed a high peak of blood glucose levels 45 minutes after glucose intake (5 minutes after the third drink), whereas both RER and Lumen % CO_2 showed a more moderate increase in levels. It is possible that the metabolic cart and Lumen measurements were performed too early, as it may be that in some of our participants, the peak glucose levels occurred more than 45 minutes after ingestion; thus, it was not yet fully metabolized [21].

Conclusions

In summary, Lumen can provide valid information regarding an individual's metabolic state, and in agreement with results from the metabolic cart. Unlike the metabolic cart, Lumen measurement can be performed anywhere, anytime, without the need for a specialized laboratory, equipment, and technical staff. The Lumen device is able to detect changes in metabolism due to dietary intake, similarly to the metabolic cart. The capability of taking metabolic measurements continuously outside of laboratory settings can provide new insights about the metabolic state of an individual so as to obtain further knowledge and understanding about metabolism and nutrition.

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Authors' Contributions

KAL and SY analyzed the data and prepared the manuscript. RA and JO coordinated the project and collected the data. JRB reviewed and edited the manuscript. MM and MK conceived, designed, and supervised the study as well as reviewed and edited the manuscript. All authors approved the manuscript before submission.

Conflicts of Interest

SY and MM are employees of Metaflow Ltd, and contributed to the design and analysis of the study as well as the preparation of the manuscript. The other authors declare no conflicts of interest.

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Abbreviations

RER: respiratory exchange ratio
RQ: respiratory quotient
VCO_2: carbon dioxide production
VO_2: oxygen consumption

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