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REVIEW | *Emerging Wearable Physiological Monitoring Technologies & Decision Aids for Health & Performance*

Wearable physiological systems and technologies for metabolic monitoring

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Gao W, Brooks GA, Klonoff DC. Wearable physiological systems and technologies for metabolic monitoring. *J Appl Physiol* 124: 548–556, 2018. First published September 28, 2017; doi:10.1152/japplphysiol.00407.2017.—Wearable sensors allow continuous monitoring of metabolites for diabetes, sports medicine, exercise science, and physiology research. These sensors can continuously detect target analytes in skin interstitial fluid (ISF), tears, saliva, and sweat. In this review, we will summarize developments on wearable devices and their potential applications in research, clinical practice, and recreational and sporting activities. Sampling skin ISF can require insertion of a needle into the skin, whereas sweat, tears, and saliva can be sampled by devices worn outside the body. The most widely sampled metabolite from a wearable device is glucose in skin ISF for monitoring diabetes patients. Continuous ISF glucose monitoring allows estimation of the glucose concentration in blood without the pain, inconvenience, and blood waste of fingerstick capillary blood glucose testing. This tool is currently used by diabetes patients to provide information for dosing insulin and determining a diet and exercise plan. Similar technologies for measuring concentrations of other analytes in skin ISF could be used to monitor athletes, emergency responders, warfighters, and others in states of extreme physiological stress. Sweat is a potentially useful substrate for sampling analytes for metabolic monitoring during exercise. Lactate, sodium, potassium, and hydrogen ions can be measured in sweat. Tools for converting the concentrations of these analytes sampled from sweat, tears, and saliva into blood concentrations are being developed. As an understanding of the relationships between the concentrations of analytes in blood and easily sampled body fluid increases, then the benefits of new wearable devices for metabolic monitoring will also increase.

glucose; lactate; personalized medicine; potassium pH; real-time; sodium; sweat; temperature; wearable devices

INTRODUCTION

Analyte concentrations in the blood can inform physiologists and health care professionals about the state of metabolic physiology in health and during exercise, as well as metabolic pathophysiology associated with metabolic diseases. Recent advances have been made in development of sensors for noninvasive and minimally invasive continuous analyte monitoring. Bloodless wearable devices have been developed to automatically measure physiological limits of performance in sports and extreme environments, as well as diagnose and monitor diseases characterized by metabolic analyte imbalances, such as diabetes mellitus and cystic fibrosis. In this article, we reviewed the available literature on wearable technologies used to *1*) sample various body compartments for monitoring analyte concentrations in sweat, tears, and saliva; *2*) monitor interstitial fluid (ISF) for glucose concentrations; and *3*) monitor analytes other than glucose in ISF for detection and monitoring of various physiological and pathophysiological states. Many of the historical challenges for body fluid analysis can be resolved by sampling and sensing key biomarkers in these fluids through novel wearable devices.

MONITORING ANALYTE CONCENTRATIONS IN SWEAT

As an important body fluid, sweat contains a number of important metabolic biomarkers, which could provide insightful physiological information:

Sweat glucose. Glucose concentration in sweat is in the micromolar (μM) range, nominally <100 μM, which is much

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lower than in blood. With the advent of a wearable device it has been possible to observe that glucose concentration in sweat first rises, and then falls during constant-rate exercise (17). How sweat and blood glucose concentrations correlate over time under various conditions will need to be determined if wearable devices are to find applicability for monitoring people with diabetes or athletes without diabetes.

Sweat sodium. Whether measured by conventional methods or by wearable device technology, the sodium concentration in sweat ($[Na^+]$) is ~55% of that in plasma. Both plasma and sweat concentrations tend to rise in response to increments in exercise duration and intensity. More work will be necessary to demonstrate whether the plasma $[Na^+]$ can be reliably predicted from determinations of sweat $[Na^+]$ by wearable devices. Approximately 20% of marathon runners have been noted to produce sweat with a high concentration of sodium. For such athletes, measurement of sweat rate and sweat electrolyte concentration could inform recommendations for salt intake during endurance activities (35). Recent evidence suggests that the measurement of sweat sodium concentration in athletes is impacted by the type of analyte technology used to analyze the sample, and results from different assays should not be used interchangeably (21). There is a need for novel noninvasive tools to detect dehydration in firefighters and soldiers. Although salivary osmolality can be measured as an indicator of dehydration, it is likely that measurement of a sweat analyte or other body fluid analyte will eventually become established as a valid clinical marker for dehydration (23).

Sweat potassium. Of metabolites detectable in sweat by wearable devices, perhaps most intriguing is potassium, because the absolute levels correspond to those determined by conventional methods, and at least in one study sweat $[K^+]$ tracked plasma aldosterone (41). In a Belgian child with elevated sweat sodium concentrations, a diagnosis of cystic fibrosis was initially made and later rejected, in part, because of very low sweat potassium levels. The sodium results were attributed to falsification of testing, in part, because of very low sweat potassium levels (37). The sweat potassium levels in this patient were below the usual physiological range for both patients (6–17 mmol/l) and nonpatients (14–30 mmol/l). The patient's physicians concluded that filter papers used to collect sweat in this child had been contaminated with a potassium-free, sodium and chloride-enriched solution, such as saline. Again, studies are needed to determine if the $[K^+]$ responses in sweat track those in blood in human subjects engaged in exercises of graded intensities and durations under various environmental conditions.

Sweat lactate. The lactate concentration in sweat is in the same millimolar range as in blood, but it is higher, nominally ~5 mM (10, 17), a value higher than the typical lactate threshold (43). From previous work, we know that lactate excretion in sweat rises depending on exercise intensity (10), and events of high blood lactate and increasing lactate with exercise intensity can be identified with observations made with wearable devices (17).

However, the relationship between blood and sweat lactate responses over time at constant exercise power output (PO) is less certain because blood lactate may remain constant, or decrease over time (41), whereas sweat lactate tends to rise (17). Studies are needed to determine whether the lactate responses in sweat track those in blood in human subjects engaged in exercises of graded intensities and durations under various environmental conditions. Alternatively, a big data analysis may reveal that some combination or ratio of parameters (e.g., the sweat [lactate]/[glucose] analogous to the VE/$\dot{V}CO_2$ in graded exercise testing (61) may prove to be informative of perturbations in blood metabolites.

Temperature and pH. Classic studies in exercise and environmental physiology (51) show that skin temperature goes through a dynamic range of responses, first dropping in temperate conditions at the start of exercise as sweating commences and then gradually increasing as body temperature increases and volume shifts occur. Wearable devices require accurate assessments of skin temperature because the various analytical features for analysis of glucose, lactate K^+, and Na^+ are all temperature-sensitive, and analytical algorithms require data on skin temperature. Wearable devices can provide accurate, real-time measurements of skin temperature.

Measurement of sweat acidity is also within technical capability of wearable devices. Sweat pH is typically 5.5 (44), which is less than that of arterial blood (~7.4). Wearable devices can provide accurate, real-time measurements of sweat pH, but it remains to be determined how the data can be interpreted with regard to changes in physiological status of the individual being tracked.

Wearable devices to sample sweat. Tremendous progress has been made recently on developing wearable sweat biosensors (Fig. 1) (6, 7, 17–19, 22, 24, 28, 34, 36, 46, 49) These wearable tools have been successfully used to measure the detailed sweat profiles of a wide spectrum of analytes, including metabolites, electrolytes, and heavy metals during various indoor and outdoor physical activities. Wearable sweat biosensors are usually prepared on a flexible substrate that forms conformal contact with the skin, but minimizes the required sweat volume, so that it can properly collect and analyze sweat samples. Various sensing platforms have been developed in the past decade, which include epidermal tattoos, flexible patches, and smart textiles. For example, Wang's group has reported the use of temporary tattoo-based electrochemical sensors for measuring a wide range of sweat analytes (Fig. 1*A*) (6, 7, 24); Heikenfeld and coworkers have reported an adhesive radiofrequency identification (RFID) sensor patch that can measure sweat sodium levels and communicate with a cell phone through wireless radiofrequency (RF) communication (49).

Because sweat secretion is complex, to extract useful and accurate physiological information, simultaneous detection is achieved through merging plastic-based sensors that interface with the skin and silicon-integrated circuits consolidated on a flexible circuit board for complex signal processing (17, 18, 46). The system contains four electrochemical sensors for monitoring sweat glucose, lactate, sodium, and potassium, as well as a temperature sensor for signal calibration. The platform shows the promise for a number of health-monitoring applications (e.g., dehydration monitoring during long-term physical exercise). Lee et al. (36) demonstrated a wearable patch for sweat-based diabetes monitoring and feedback therapy. The patch consists of a heater, temperature, humidity, glucose, and pH sensors for diabetes monitoring and polymeric microneedles that can be thermally activated to deliver drugs transcutaneously. Rogers and colleagues (34) recently developed a colorimetric sweat-sensing system for monitoring sweat

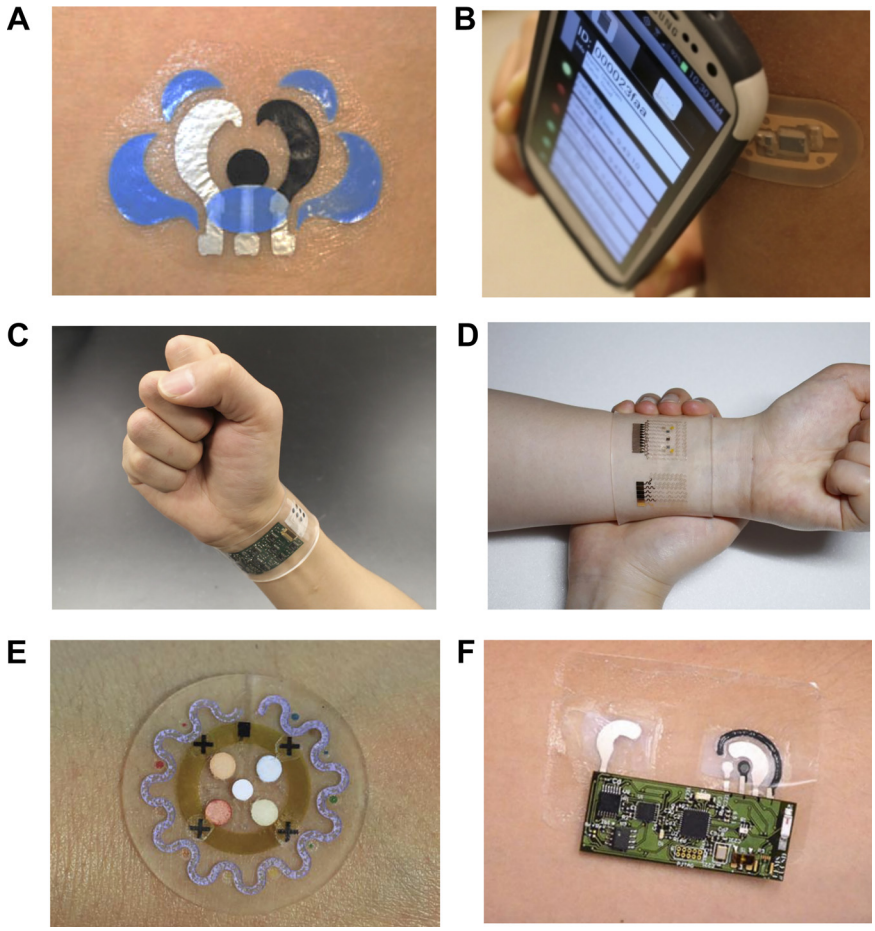

Fig. 1. Skin worn wearable biosensors for in situ sweat analysis. *A*: epidermal temporary tattoo (7) (Reprinted with permission from (62). Copyright 2012, Royal Society of Chemistry). *B*: adhesive RFID sensor patch (reprinted with permission from (49). Copyright 2015, IEEE). *C*: fully integrated flexible sensor band (reprinted with permission from (17). Copyright 2016, Nature Publishing Group). *D*: flexible and stretchable sensor patch (36) (reprinted with permission from (36). Copyright 2016, Nature Publishing Group). *E*: colorimetric sweat-sensing patch (reprinted with permission from (34). Copyright 2016, American Association for the Advancement of Science). *F*: wearable patch for sweat extraction and sensing (reprinted with permission from (28). Copyright 2016, American Chemical Society).

chloride, pH, glucose, and lactate. The system can wirelessly interface to capture digital images for quantitation. Sweat can be extracted not only during physical exercise, but also through local extraction on demand by way of iontophoresis. Wang's group demonstrated a wearable sweat ethanol sensor that integrates an iontophoresis-based sweat extraction system along with a flexible wireless circuit board. These sensors demonstrate clear differences in responses before and after alcohol consumption, reflecting the increase of blood ethanol levels (28).

Similar to the process of extracting sweat to measure glucose, a distillate of interstitial fluid containing transdermal extracted glucose can also be analyzed using noninvasive reverse iontophoresis through wearable devices. This technique led to the development of the GlucoWatch, a commercial wearable noninvasive electrochemical glucose-monitoring device (48). A new glucose monitor, SugarBEAT, which also uses reverse iontophoresis to obtain glucose from ISF, has recently received a Conformité Européene (CE) mark (12a), roughly equivalent (in Europe) to the Food and Drug Administration (FDA) approval (in the United States) to market the product. To minimize the potential skin irradiation caused by reverse iontophoresis, a tattoo-based wearable platform was also recently developed for interstitial fluid extraction and glucose sensing.

Effects of environment on measuring sweat. The process of relating blood and sweat metabolite and electrolyte levels is challenged by characteristics of the sweat response. For individuals studied at rest or in cold environments, normal thermoregulatory mechanisms will dictate that sweating will be minimal, and hence, assessments of comparator blood metabolite levels will not be possible. Similarly, for making measurements on swimmers or those exposed to wet environments, wearable sensor technology for measuring sweat will also be challenged. As well, even for efforts that elicit significant sweating responses there will be a lag between the onset of physical activity and the onset of sweating. From previous efforts of others, we know that sweat composition and amount will vary depending upon environmental conditions, as well as exercise intensity (10), duration, and hydration status (44). Furthermore, there is variability among subjects when the difference between blood and ISF concentrations is calculated. Still, another complication is that sweat volume loss, which could result in a higher concentration of sweat analytes, is not detectable given current wearable device technology.

From recent experience, we know that it is possible to construct wearable devices to track metabolites and electrolytes in sweat (17). While existing as prototypes for experimental research, the devices are highly accurate, but are not yet commercially available. So, what are the challenges?

Current generation of wearable devices have readily been incorporated into wrist and head bands (17). Similarly, as with electrocardiogram (EKG) electrode placement, it should be possible to attach sensors to other body areas of interest for

assessing sweat composition, such as chest, back, arms, and legs. Depending on intended use, ease of device placement may offer particular challenges. Already noted was the issue of contamination by water, but other environmental and skin contaminants could affect sensing. Though not developed yet, suction and other types of collection cups, tabs, adhesive attachments, and sensor needles for determining metabolites in sweat and ISF may be in the offing.

In the rich history of exercise and environmental physiology, there are extensive data on sweat loss due to exertion, the effects of environment on sweat rate, and the contents of metabolites and electrolytes in sweat. However, from the era before the advent of wearable devices there was little apparent need to relate sweat metabolite levels to those in blood. To reiterate, considering the pace of technological developments, it is possible to contemplate tracking ISF and blood metabolite levels in patients, athletes, and others using wearable devices.

MONITORING ANALYTE CONCENTRATIONS IN TEARS AND SALIVA

Saliva and tears, two other complex biofluids containing numerous important constituents, which can be sampled noninvasively, can also serve as excellent candidates for monitoring physiological and metabolic states. The field of wearable salivary and tear sensing has experienced considerable progress, aimed primarily toward the incorporation of sensors within contact lenses and mouth guards.

Soft contact lens-based sensors with integrated electrochemical sensing and wireless electronics have been developed by Parviz and colleagues (38, 57, 63) for monitoring tear analytes, including glucose and lactate. A device embodying this technology is now being developed by Google, as illustrated in Fig. 2*A* (13). Amorphous indium gallium zinc oxide field effect transistors have been shown in vitro to be a promising technology to serve as sensing transducers for glucose. These transistors could potentially become integrated into contact lenses as transparent glucose sensors for tear fluid (14). Other chemical and optical technologies have also been proposed for contact lens measurement of tear glucose (1).

Mannoor et al. (40) demonstrated a dental tattoo for continuous wireless monitoring of bacteria by biofunctionalizing antimicrobial peptides on graphene-modified silk tattoo substrates. Kim et al. (29) reported a wearable noninvasive mouthguard biosensor for continuous salivary lactate detection in undiluted human saliva samples. Recently, the same group reported an integrated mouthguard-based biosensor that can monitor in real time salivary uric acid and wirelessly communicate to the computer (27). Saliva has been explored as a substrate for measuring glucose levels in diabetes. Preliminary studies have shown that saliva could serve as a potentially noninvasive adjunct to monitor glycemic control in diabetic patients (15, 45).

METABOLIC MONITORING OF INTERSTITIAL FLUID GLUCOSE

Basics of continuous ISF glucose monitoring. Wearable continuous glucose monitoring (CGM) systems to measure glucose in the ISF of skin are well established for diabetes, the world's most common metabolic disease. A continuous glucose monitor is a wearable sensor that automatically measures glucose at regular intervals (ranging from every 5 to 15 min) usually from interstitial fluid (ISF) in skin. A CGM typically consists of six components: *1*) a wearable sensor; *2*) a sensor inserter; *3*) a transmitter to send data to a receiver and to the cloud for storage and analysis; *4*) a handheld receiver or monitor; *5*) software (in the receiver and in the cloud); and *6*) (in many systems) a blood glucose monitor for calibrating the system. Such devices follow a series of earlier developments. In the mid-20th century, diabetes patients would test their urine glucose concentration, which is loosely correlated with the blood glucose concentration, but this measurement is insufficiently accurate for fine-tuning treatment. In the late 20th century, patients began to test capillary blood glucose levels usually by pricking the finger with a needle called a lancet to obtain a drop of blood and capture it in a glucose monitor. This method can provide an accurate reflection of the reference blood glucose concentration; however, patients are often reluctant to obtain this information because of pain and a need to dispose of the used lancets and blood waste. In the 21st century, continuous glucose monitoring technology allows patients to use a wearable and painless glucose monitor that automatically measures the glucose concentration in skin ISF (which is proportionate to the blood glucose concentration) and then transmits the data to a hub or to a smartphone. From there, the data can be used by the patient in real time, and the data can also be transmitted, analyzed, and stored on the cloud.

Currently available continuous glucose monitors have been reported to have a mean absolute relative difference (MARD) of around 10%. On the basis of simulation studies, this 10%-or-less threshold is generally felt to be necessary for a continuous glucose monitor product even to be considered by FDA as safe for nonadjunctive use, which means that no confirmatory

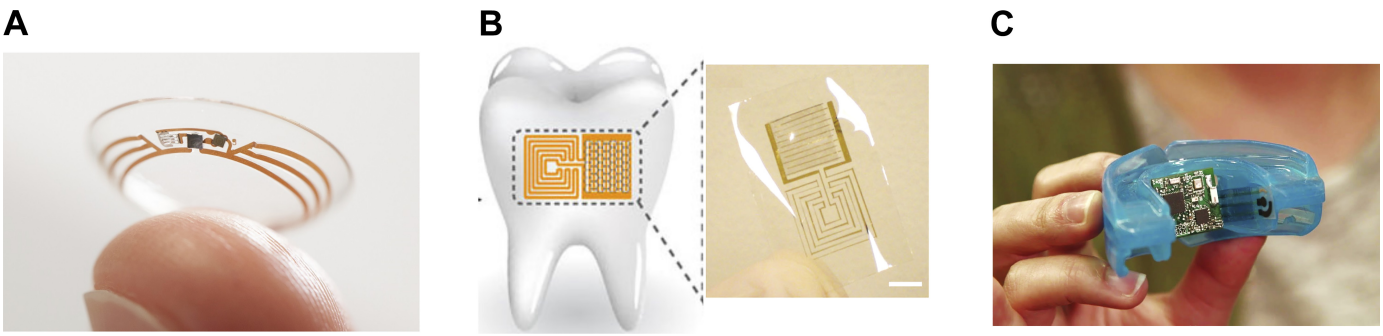

Fig. 2. Wearable sensors for sampling tears and saliva. *A*: Google contact lenses for glucose monitoring (Copyright 2017, Alphabet). *B*: dental tattoo-based sensor for bacteria monitoring (40). *C*: smart mouth guard for monitoring salivary uric acid (Reprinted with permission from (27). Copyright 2015, Elsevier).

fingerstick blood glucose test would be needed before taking action based on the glucose reading (11). In 2016, one continuous glucose monitor with a MARD reported to be 9.0% (4) was approved by FDA for nonadjunctive use (57a). The diabetes community had been uncertain of how the FDA would rule when the question was put to that agency and whether any system's accuracy was deemed sufficient for such an indication. This approval was seen as a vote of confidence in the accuracy of that system. Other products are improving in accuracy, and their manufacturers are hoping to receive similar approvals from FDA in the future.

CGM for diabetes, patients, athletes, and subjects in drug trials. CGM can provide real-time insights into the blood glucose concentration to assist diabetes patients to manage their disease. This tool is used by ~15% of patients with type 1 diabetes in the United States to provide information that can assist with insulin dosing (16), and a small but increasing number of patients with Type 2 diabetes who do not use insulin are also benefitting from this tool (58). Continuous glucose monitoring has been used by athletes to determine how many carbohydrates to load before and during intense competition. Aside from the benefits to patients with diabetes, optimization of an athlete's blood glucose levels through the use of CGM has the potential to improve speed and recovery, and to aid in training. Periodic carbohydrate replacement during high-intensity cycling has been shown to improve subsequent sprint performance (5). This type of monitoring was used by the U.S. women's Olympic cycling team, which won a silver medal at the London 2012 Olympic games (45a). Although CGM has demonstrated that intensive physical training can increase the risk of hypoglycemia (55), in some athletes, physical training can result in a tendency to experience elevated glucose levels (56). Therefore, CGM can be used for physiological research on individual athletes and for optimization of training.

CGM can provide useful information for a clinical trial about the effect of a drug on glucose levels. Information can be gleaned about the effect of the drug on the percent of time the subject spends in in the target glycemic range, in hypoglycemia and in hyperglycemia (as well as the magnitude of the excursions outside of the target range). Glycemic variability is a concept describing the magnitude of fluctuations in blood glucose levels and might predict future complications or even mortality in diabetes (20). CGM can also determine the extent of glycemic variability (GV) associated with the use of a medication, and there is evidence that decreasing GV can result in decreased diabetic complications (20).

TECHNOLOGIES FOR WEARABLE CONTINUOUS GLUCOSE MONITORS

CGMs approved by the FDA for use in the United States use a needle sensor containing an enzyme that breaks down ISF glucose molecules, liberating an electron for each glucose molecule. The electron is then transferred to an electrode where an electric current is generated proportionate to the glucose concentration. In Europe, a CGM is available that measures ISF glucose through fluorescence. Compared with the electrochemistry method (which is used in all continuous glucose monitors currently approved by the FDA), fluorescence glucose-sensing methods are potentially more sensitive to low concentrations of glucose and are not subject to chemical interferences (such as with the use of acetaminophen) that can affect electrochemical sensors. However, some implanted fluorescing chemicals can be toxic, and to read these chemicals, it is necessary to always carry or wear a dedicated light source to interrogate the implanted fluorescing sensor (31).

Additional types of long-term implanted sensors are under development that measure ISF glucose through various enzymatic, optical, or osmotic technologies. Some of the optical methods under development do not insert a needle into the skin or implant a sensor, and these methods are known as noninvasive sensors. Contact lenses to noninvasively measure the glucose concentration of tears and then convert the measured concentration to an estimated blood glucose level have been discussed earlier in this article. Methods for noninvasively measuring glucose in sweat have also been discussed earlier in this article.

Alarms. CGMs can be built to contain an alarm that automatically notifies a user when a glucose level is above or below a preset threshold. CGMs measure not only the absolute concentration of glucose but also the rate of change of this analyte (47). An alarm can be sounded for a rate of change above a preset velocity. Furthermore, a proprietary algorithm can be created to predict a glucose concentration outside of a predefined range and sound a predictive alarm, based on the absolute glucose concentration and the rate of change of the glucose concentration. A patient can respond to an alarm for a currently abnormal glucose level or take a preventative action in response to a predictive alarm. To the extent that all currently available CGMs have lesser point accuracy than the level of accuracy required by the FDA for blood glucose monitors, then the threshold alarms and predictive alarms of CGMs will not always be accurate. An inappropriate alarm for hypoglycemia in the presence of a truly normal glucose value is a false alarm and a lack of a hypoglycemic alarm in the presence of true hypoglycemia is a missed alarm. The incidence of false positive and false negative alarms can cause patients to lose confidence in their sensor. Patients are advised to check their blood glucose level with a capillary finger stick blood glucose test if they suspect that the sensor reading is not correct. In the presence of false positive hypoglycemia alarms, patient responses to these hypoglycemic alarms can eventually decline, and this insensitivity is known as alarm fatigue (54).

While CGM alarms can be helpful, they can be associated with false-positive soundings and false-negative silence because the accuracy of the CGMs is imperfect. The threshold for the alarm to sound can be set higher than the threshold for falling into typical hypoglycemic glucose range to maximize sensitivity or lower than this threshold to maximize specificity. Also, patients frequently do not respond to hypoglycemic alarms, either intentionally (because of alarm fatigue) or because they did not hear the alarm (12). If a patient has hypoglycemia unawareness and is at risk of sleeping through a hypoglycemic episode, then the patient could benefit from a sensor-integrated insulin pump for controlled continuous insulin delivery (rather than multiple discrete injections of this drug). In this case, if a patient becomes hypoglycemic and does not adjust their insulin dose, then the system could temporarily suspend the continuous insulin delivery when the glucose level either approaches or frankly falls below a hypoglycemic threshold. The result would be less nocturnal hypoglycemia (8).

PHYSIOLOGY OF MEASURING GLUCOSE IN ISF

The simultaneous concentrations of glucose in ISF and blood are usually equivalent. The accuracy of a CGM for measuring glucose at a point in time is known as the point accuracy. If the blood glucose concentration changes rapidly, then the change in concentration of glucose in the ISF (compared with the blood glucose level) can lag behind by ~5–15 min behind the change in blood glucose (26). The lag consists of three components: *1*) the physiological lag time, which is affected by blood perfusion to the skin and by the rate of change of the blood glucose concentration); *2*) the sensor reaction time, which is related to the duration of time needed for glucose to diffuse into the sensor; and *3*) the sensor signal processing time, which includes time for digital filtering by software for noise reduction and data smoothing (59). To compensate for potential drift of the sensor measurement, in part, due to accumulation of subcutaneous residues on the sensor, most CGMs require calibration with a capillary blood glucose measurement by a blood glucose monitor two times daily. Greater accuracy of the blood glucose monitor used for calibration will result in greater accuracy of the CGM. The accuracy of the CGM to describe the magnitude and direction of a changing ISF glucose concentration is known as the trend accuracy. In the future, it is likely that some CGMs will provide real-time continuous glucose data without a need for calibration. A real-time or personal CGM reader displays the results in real time, and a retrospective professional CGM stores the information to be downloaded and (along with a diary) interpreted after the sensor has been removed and its data downloaded. The frequency of calibration that is needed (if any) is related to the sensor's properties and not to whether the device is intended for real-time or retrospective data presentation. Real-time CGM data can be sent wirelessly by way of a mobile application or app directly to a patient's smartphone or else wirelessly to the cloud for the patient, healthcare professional, or an authorized caregiver, who can securely view on a computer or reader. One CGM now on the market in the United States and Europe does not require calibration, but in the United States, it is currently only approved by the FDA for retrospective professional use and not for real-time personal use. One CGM now on the market in the United States is approved by the FDA to provide real-time data for making diabetes treatment decisions without a capillary blood glucose test for confirmation (57b).

TECHNOLOGIES FOR DETECTING HYPOGLYCEMIA QUALITATIVELY

Whereas CGMs measure glucose quantitatively and can be used for detecting hypoglycemia, the accuracy of most such devices already on the market and soon to come onto the market is at its lowest in the hypoglycemic range. An alternate paradigm for detecting hypoglycemia is a qualitative sensor that can measure the body's physiological response to hypoglycemia. There are currently no widely used products available for this purpose. On the basis of a response of the autonomic nervous system to hypoglycemia, products have been studied that measure various autonomically mediated responses to hypoglycemia, including the electroencephalogram (EEG) response (50), the EKG response (52), and the skin conductivity response (25). Service dogs can alert their owners to hypoglycemia, and the mechanism is unknown, but it is postulated to be related to an uncharacterized odor emitted by a hypoglycemic person that only a dog can detect. Dogs have been found to be less reliable than CGMs for diagnosing hypoglycemia (39).

TRENDS IN CGM TECHNOLOGY

Future glucose sensors will be bundled with other types of wearable physiological monitors to provide a more complete picture of the wearer's metabolic state. In the future, CGM hardware will become smaller, more accurate, and more energy efficient. Patients will demand that their wirelessly transmitted CGM data be secure (30) and private (33), and they will demand that manufacturers adhere to consensus security standards (32) because greater security leads to greater safety. As CGM data from wearable devices become part of the "Internet of Things", new paradigms for data distribution will be developed so that real-time glucose data and treatment recommendations will be available not only to patients, but (with their permission) to their healthcare professionals, their electronic medical record, and designated relatives and caregivers.

MONITORING ISF ANALYTES OTHER THAN GLUCOSE

The need for metabolic monitoring. With the advent of continuous glucose monitoring and its application to the regulation of glycemia, it has become clear that continuous monitoring of other metabolites and electrolytes in ISF is feasible not only for diabetes, but also for sports medicine, exercise science, and other conditions. Moreover, as shown recently (17), technology has advanced such that there is also the potential for the fabrication of completely noninvasive wearable devices to measure the contents of glucose, lactate, sodium ion, and potassium ion in sweat during exercise. Although there is great potential for such devices, there are significant technical, legal, scientific, and other challenges.

Needle probes to sample ISF. The use of needle sensors to measure ISF levels of analytes could provide athletes, coaches, trainers, and dietitians key information on body energy status of competitors whether they be on the field, mountain, trail, or in outer space. There would be real advantages to the ability to continuously and remotely report on a stressed individual's blood [glucose]. Equally important would be the ability to remotely monitor an athlete's plasma lactate, sodium (Na^+), and potassium (K^+) ion levels. Soldiers and emergency responders are sometimes exposed to extreme conditions that can lead to dehydration, and a sodium monitor can provide a warning that can mandate rehydration. Alternatively, for patients presenting on the sideline or in a medical tent after athletic competitions, the symptoms of dehydration and overhydration are similar. For individuals suffering hyponatremia, hypertonic NaCl treatment rather than isotonic rehydration is called for. Indeed, isotonic hydration could result in volume overload, have little effect on plasma [Na^+], and exacerbate a condition of pulmonary and cerebral edema due to hyponatremia. Consequently, for caregivers, knowing whether plasma and ISF Na^+ are elevated (as in dehydration), or decreased (as in hyponatremia) is an important distinction in delivering care. With regard to the use of wearable devices, in the future, it may be possible to monitor electrolyte and metabolic parameters so that potentially disastrous events could be avoided or the data

would be helpful in managing the recovery process from fatiguing or injurious exercise efforts.

Sodium is abundant in extracellular fluid, and on a molar basis, it is far more plentiful than glucose, lactate, or potassium. Although very much lower than those of sodium (~140 mEq/l), extracellular levels of glucose (~5 mM) and K^+ (~4 mEq/l) are significant, but levels of these analytes are highly regulated within narrow ranges. Hence, during daily life and athletic competition and for individuals under stress, physical/chemical inertia, as well as counterregulatory responses serve to maintain glycemia, blood Na^+, and blood K^+ levels. In contrast, while typically present in much lower concentrations, hydrogen (0.0004 mEq/l)[1] ions and lactate anion (0.5–1.0 mM) concentrations can change rapidly under stress. Hence, while as already mentioned, the monitoring of plasma and ISF glucose K^+ and Na^+ concentrations has the potential to be informative of changes in physiological status, changes in lactate concentration, and pH are better indicators of physiological stress. For this reason, monitoring lactate concentration, and to a lesser extent pH, is widely used in designing exercise training regimens and setting race pace in endurance competitions.

Technology to develop a microneedle probe to monitor ISF [lactate] is within the capability of at least one manufacturer of glucose sensor patches. As yet, there have been a few inadequate financial or other incentives to run the clinical trials necessary to obtain FDA clearance for ISF lactate sensors. But, what if one thinks of ISF lactate sensor applicability for sports and medical conditions with extreme metabolic stress or low cardiac output where lactic acidosis is a risk? Real-time knowledge of whether an athlete is approaching or has exceeded lactate threshold pace (9, 43) could provide imperative information on competitive strategy. Similarly, by using sensors to detect hyponatremia or hyperkalemia (as well as lactatemia and acidosis), health care professionals would have advanced knowledge about patient management should injuries either become imminent or actually occur.

Finally, needle probes to monitor ISF P_{O_2} would provide important information to professional and recreational athletes who are exposed to altitude hypoxia, who are dehydrated, or are who are otherwise at the limit of their aerobic capacity.

SUMMARY

Wearable device technology has great potential in sports medicine, clinical medicine, and real-time physiological investigations. The devices for these purposes are lightweight, nonintrusive in terms of restricting movement, and in many cases, as noninvasive as heart rate monitors. Compared with point of care blood glucose and lactate monitoring devices, wearable devices such as CGMs can provide automatic real-time, continuous monitoring that does not necessarily require a performer to stop for a volitional confirmatory measurement. Gauged against standard reference solutions, many wearable devices provide accurate readings that are sufficient reliability for experimental and clinical purposes. Three trends are driving interest in development of better wearable sensors for metabolic monitoring, medical research, and patient care include: 1) increasing interest in combining physiological data sets from multiple organ systems; 2) increased use of CGMs to measure glucose in diabetes care; and 3) increased interest in development of sensors for monitoring sweat analytes. For applications in emergency medicine, microdevices using similar technology to wearable devices for ISF harvesting, compared with sweat harvesting, have a much better chance of tracking blood metabolic analyte levels. For many prototype wearable systems, commercialization will require *1*) scalable production of reliable devices, *2*) stability of the sensors over long periods of time, and *3*) robust algorithms to accurately predict blood metabolite levels from measurements of alternative body fluids.

[1] At pH 7.4 $[H^+] = 10-^{7.4} \approx 0.0000040 = 4.0 \times 10^{-8}$ M $= 4.0 \times 10^{-5}$ mM.

DISCLOSURES

David Klonoff is a consultant for Ascensia, EOFlow, Lifecare, Novo, Onduo, and Voluntis and has received research funding from Disaome, Lexicon, and Novo. He is an employee of the Diabetes Technology Society.

AUTHOR CONTRIBUTIONS

W.G., G.A.B., and D.C.K. conceived and designed research; W.G. and D.C.K. analyzed data; W.G., G.A.B., and D.C.K. drafted manuscript; W.G., G.A.B., and D.C.K. edited and revised manuscript; W.G., G.A.B., and D.C.K. approved final version of manuscript; G.A.B. prepared figures.

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