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Ambulatory measurement of cortisol: Where do we stand, and which way to follow?

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A B S T R A C T

Accumulating evidence supports the harmful effects of stress on health, including the development and progress of psychopathology (e.g. anxiety disorders), metabolic disorders (e.g. diabetes type II), inflammatory disturbances, and cardiovascular disease. These harmful effects are often expressed as disturbances in cortisol levels, patterns, or responses. Unfortunately, at present, cortisol assessment is only performed in the laboratory. This hinders rapid quantification, let alone being determined by individuals themselves, with self-testing devices or sensors. More accurate and timely detection of cortisol may have important implications for the prevention, diagnosis, and treatment of stress-related disorders as well as for those suffering from adrenal insufficiencies. The present review provides an overview of the most promising and challenging technologies for cortisol measurement. An important first conclusion might be that almost all reviewed technologies were at the proof-of-concept stage, meaning it was premature to interpret the findings in light of regulatory requirements for in vitro diagnostics. Nevertheless, several promising proto-types, including electrochemical sensors with wearable potential, were found and are consequently discussed. Overall the findings suggest that with significant additional investments and research efforts in the coming years, accurate, rapid, and repeated cortisol assessment in everyday life can become reality.

1. Introduction

Ever since the development of the Trier Social Stress Task 25 years ago (TSST: [31]), considerable progress has been made in our knowledge of neuro-endocrine processes related to psychological stress. Specifically aimed at inducing hormonal stress responses under controllable conditions (e.g. [32]), research with laboratory-based stress-tests like the TSST has emphasized a crucial role for cortisol in the adaptation to stress (e.g. [33]). A finding that has been confirmed in more naturalistic settings as well (e.g. with students, nurses, police officers, and athletes - [3,17,26,56,64,78]). However, conventional cortisol assessment requires the involvement of a laboratory and trained personnel. This is time-consuming and therefore restrictive when timely detection of disturbances in cortisol levels may have important implications for the diagnosis, treatment or even prevention of cortisol-related disorders.

A pressing example for the need of immediate assessment of cortisol are patients who develop adrenal insufficiency, for whom timely detection of an adrenal crisis caused by insufficient levels of cortisol is of life-saving importance [54]. Further, reactive hypothalamus-pituitary-adrenal (HPA)-axis responses in itself (e.g. the Cortisol Awakening Rise, CAR) are suggested to indicate the potential presence or development of particular types of psychopathology [1,2,7]. Ideally, detecting cortisol disturbances in real-time could be used to confirm or disconfirm stress-related psychopathology. Efforts continue to form reference ranges for specific cortisol metrices such as diurnal salivary cortisol profiles [44], although reference ranges for cortisol that can be used for individual psychopathology diagnostics are yet to be determined. Nevertheless, technological advancements that allow easy and real-time cortisol assessment could definitely stimulate the formation of such reference values for psychopathology.

A completely different example of the usefulness of immediate assessment of cortisol refers to athlete performance management. Cortisol has been associated with both training load as well as recovery [26,41]. With short recovery periods between training sessions, immediate assessment of cortisol may provide valuable information to optimize the balance between training load and recovery, thereby optimizing performance and avoiding overtraining or insufficient recovery.

Nowadays, the interplay of endocrine processes with other stress-related functions – such as the autonomic nervous system (ANS) and cognitive processes or mood (Fig. 1) becomes ever more evident [4,6,16,69]. Due to chronic stress that strains many biological systems, the interplay between endocrine processes and the ANS, as well as cognitive, psychological, and other physiological processes may become dysregulated [21]. This maladaptive process is referred to as allostatic load [40] and it can have detrimental effects on physical and mental health [16,22,49].

Several studies underline the prognostic value of endocrine information on top of other relevant allostatic parameters, for example

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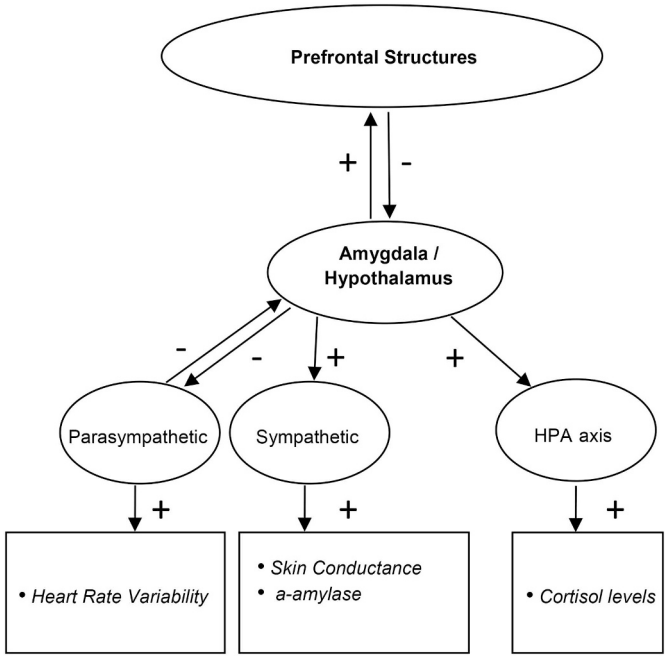


Fig. 1. A schematic view of the interaction of multiple biological systems related to stress.

electrocardiography derivatives or variability in mood [14,29,67,68,70,71,74]. These psychological and physiological parameters can be obtained directly via self-report and wearables, respectively. However, corticosteroid assessment may be regarded as the "missing link" in ambulatory assessment. Hence, for the successful incorporation of endocrine data into real-time prognostic models of somatic and psychological disorders or – for instance – real-time feedback applications [25], the time-resolution delay caused by consumer-to-lab interactions should be considerably shortened, if not solved [24]. With the aim of underlining the development of cortisol self-testing technology, we will review the status of ambulant cortisol measurement and analytics, as well as the technological directions for accelerating progress towards reliable lab-independent instant cortisol assessment.

2. Commonly used analytical techniques to quantify corticosteroids concentrations

Corticosteroids can be derived from a variety of biological sources. Assessments for both clinical and experimental purposes have been reported using blood (serum or plasma), urine [9], sweat [58], hair [65,73], fingernails [20], interstitial fluid [76], and most prominently, saliva [11,23,31,34,45,77]. Shetty and Yamaguchi [62] propose that multiple biosensing platforms might be used for biosample analytical purposes using antibodies. Methodology can be based on either antigen/antibody binding (immunoassays); nucleic acid interactions (DNA, RNA); chemical or enzymatic interactions (Ellman method, [59]), which combined with the biomarker of interest more or less prescribes the specimen of preference and the way to collect these [62]. However, even while using the appropriate binding (anti) agent, most samples nevertheless need to be preprocessed (i.e. generally centrifuged) in order to isolate large bulk molecules from the to be assessed sample. According to Yager et al. [79] building in an H-filter might tackle this necessity as such filters limit the size of the molecules that proceed downstream through the measuring device. Cellular and blood components, which might hinder reliable assessment, can be removed in this way. To accommodate such technologies, most ambulatory assessment devices (e.g. glucose assessment; pregnancy tests; and the method described by [45,63]) use disposable strips that exhibit robustness as they are stored and transported under ambient temperatures and applied under uncontrolled circumstances.

While a comprehensive discussion of measurement techniques for cortisol in specific biosubstrates is beyond the scope of this review and is discussed elsewhere (see [19,42], and [27]), we briefly discuss common analytical techniques including immunoassays (IA's) and mass spectrometry analyses. The most frequently used IA's are Enzyme-Linked Immuno Sorbent Assay (ELISA). Other types of immunoassays are Chemiluminescent Immuno Assays (CLIA) or the nowadays rarely used Radio Immuno Assays, which is unsuitable for ambulatory assessment and diagnostics due to the use of radioactive material. In immunoassays, antibodies are used to generate a signal and thus to measure the concentration of the compound of interest (i.e., the analyte); in ELISA one of the antibodies used is modified (enzyme conjugated) to be capable of generating an optical signal after administration of the substrate; in competitive CLIA the antigen (e.g. cortisol or cortisone) is labeled by chemiluminescent tracer substance. When a specific antibody is added to the labeled antigen, they will bind to each other. When a biosample is added, the non-labeled antigen present in the biosample will compete with the labeled antigen in order to bind to the antibody. After some incubation time and a final washout of all unbound antigen, a signal can be obtained that depends on the fraction of labeled and non-labeled antibody-bound antigens, that reflects the analyte concentration in the specimen.

Another immunoassay methodology is the Lateral Flow Immuno Assay (LFIA). It is usually used for qualitative analyses in resource-poor environments [53]. Specifically, a liquid (e.g. urine, saliva) is applied on a strip, which moves over a test strip through different compartments. In short, the analyte is conjugated, e.g. with an antibody, and in the next compartment bound to a colored particle. If the analyte is present, a colored strip will be seen. While initially used for qualitative assessments, recent technological advances in LFIAs combined with smartphone-based imaging allow for accurate and quantitative biomarker assessment, including cortisol as will be discussed later (see also [45,55]). Lastly, it is worth mentioning that, due to the structural similarity between cortisol and cortisone, immunoassays might also detect cortisone, producing an overestimation of the total cortisol level [42], although some more new assays claim to be better capable of discriminating between cortisol and cortisone [51].

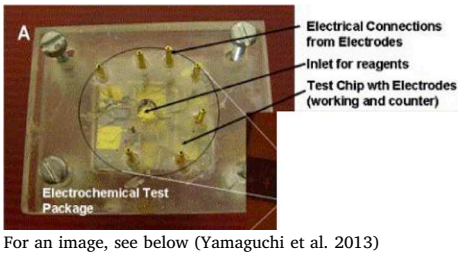
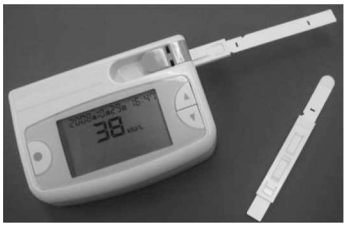
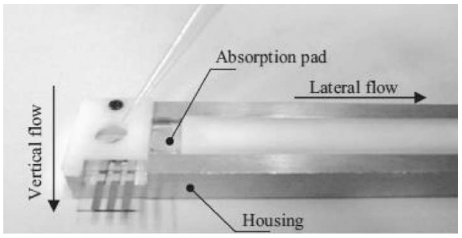
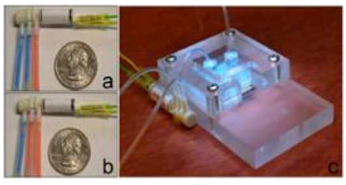
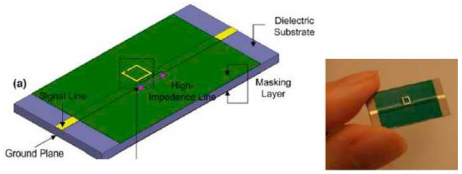
Alternative to optical detection, electrochemical immunosensing is based on the principle of measuring the changes in electrical properties of a conductive material due to the absorption of an analyte on the surface functionalized with antibodies. It provides high sensitivity and low detection limits and (nano)technological advancements have driven efforts towards more miniaturized electrochemical sensing platforms [27].

A totally different methodological approach is mass spectrometry (MS), which is a technique that separates substances based on their polarity and detects them based on their mass and charge. It is considered the gold standard for cortisol assessment because of the technique's high specificity and sensitivity [5,42,51]. However, specific disadvantages are that trained personnel is needed and specific equipment requirements have to be met, e.g. related to the high temperature and/or energy expenditure and gasses needed to conduct the analysis. As compared to conventional IA's, the MS methodology is consequently not suited for the development of ambulatory analytic applications in its present form.

3. Prototypes of instruments to assess cortisol in ambulatory settings

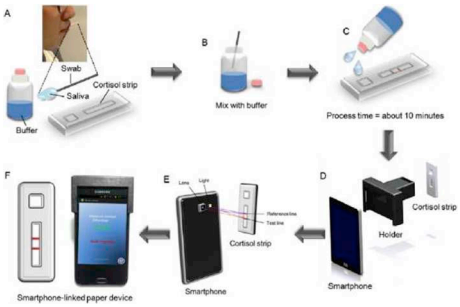
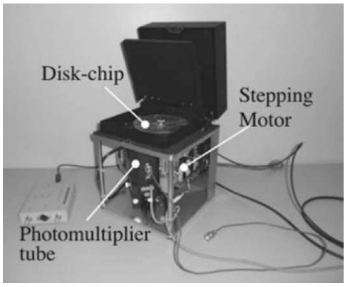
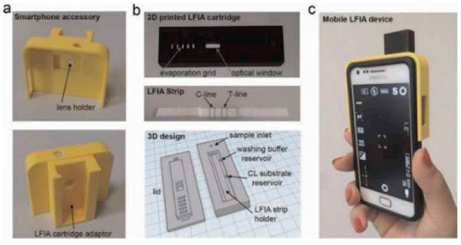
Our literature investigation into ambulatory cortisol assessment methods and devices provides at least some ongoing technological developments with either the ability or potency to provide real-life assessment capabilities, now or in the near future. It is noteworthy however, that almost all technologies or devices were at the proof-of-

Table 1
Overview of published cortisol point of care assessment technology.

Device	Properties	Remarks	Image (if available)	Reference
IM: platinum electrode DT: electrochemical immunosensor IB: competitive binding of endogenous corticosteroid and a corticosteroid-peroxidase conjugate with antibodies (undisclosed) TA: cortisol in saliva and skin exudate using ultrasound	DR: 0.1–100 ng/mL RT: 14 min, including a 10 min preparation (gel)	Portable and hand held device; For 2 min, 9 V is applied to the skin; Gel is applied to the skin 10 min prior to measurement; Parameters are in physiological range; High correlation with plasma constituents; Repeat measures can be done within 5 min		[12]
IM: nitrocellulose membrane DT: LFIA with a reader instrument IB: anti-cortisol-IgG TA: Cortisol in plasma	DR: 3.5–1280 ng/mL RT: 5 min	Portable, rapid, and hand held Test strips can be stored at room temp. For quantification, a personal analyzer for rapid tests reading instrument is required Parameters are in physiological range		[37]
IM: Au nanowires DT: Electrical IB: anti-cortisol antibodies labeled with hydroxysteroid dehydrogenase TA: cortisol	DR: 3.7–12 μg/mL RT: unknown	Parameters are outside physiological range		[35]
IM: immune-chromatographic chip DT: calorimetric chromatography IB: glucose oxidase (GOD)-cortisol conjugated labeled sensor. TA: cortisol/glucose	DR: 1–10 ng/mL RT: 25 min	Portable, rapid, and hand held. Parameters are in physiological range. Proposed method is an indirect detection of cortisol	For an image, see below (Yamaguchi et al. 2013)	[80]
IM: none DT: colorimetric assay platform, color intensity of the enzymatic reaction is measured photometrically IB: none TA: α-amylase in saliva	DR: 10–230 U/mL RT: < 1 min	Hand held reader and disposable test strips; can be stored at room temp. No preparation of the sample (e.g. centrifugation) before measurement. Data is stored with a time stamp Accurate and repeatable High correspondence with clinical chemistry analyzer (R^2 0.99).		[63]
IM: SAM DT: electrochemical immunosensor IB: glucose oxidase (GOD)-cortisol conjugated labeled sensor. TA: cortisol in saliva	DR: 0.1–10 ng/mL RT: 35 min	Sensor can be reused. Parameters are in physiological range. High correspondence with ELISA (R^2 0.92). System requires multiple steps demanding accuracy which may undermine compliance.		[81]
IM: SAM modified IDE DT: electrochemical immunosensor IB: monoclonal anti-cortisol AB TA: cortisol	DR: 0.036–36 ng/mL RT: 30 min	Parameters are in physiological range. Automated and label free Portable biosensor prototype, not yet suitable for user-friendly ambulatory application.		[75]
IM: Asymmetric split-ring resonator as a biosensing transducer DT: Universal test fixture IB: Competitive reaction of cortisol-BSA and free cortisol to the cortisol AB TA: cortisol/a-amylase	DT: 1–10 ng/mL RT: unclear, multiple steps	Simple, direct, cost-effective scheme Label free Sensor prototype, not yet suitable for user-friendly ambulatory application. System requires multiple steps		[36]
IM: nitrocellulose membrane DT: colorimetric LFIA integrated in a	DR: 0.01–100 ng/mL RT: 10 min	Parameters are in physiological range.		[10]

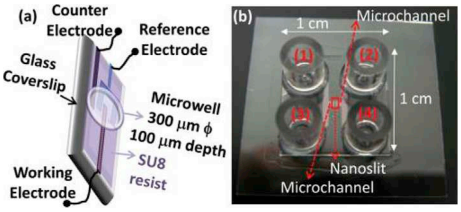
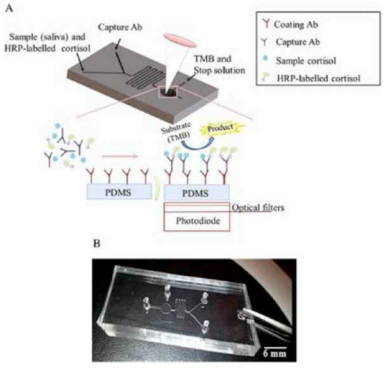
(*continued on next page*)

Table 1 (*continued*)

Device	Properties	Remarks	Image (if available)	Reference
smartphone adapter IB: goat anti-mouse IgG TA: Cortisol in saliva		Good estimation of cortisol concentration. Suitable for ambulatory use. Buffer is required to mix with sample. Unclear if assay can be stored at room temp.		
IM: SAM modified IDE DT: electrochemical immunosensing using a miniaturized potentiostat interfaced with an LTCC microfluidic manifold IB: monoclonal anti-cortisol AB TA: Hydrocortison (cortisol) in phosphate buffered saline	DR: 10 pM to 500 nM RT: 30 min	Parameters are in physiological range. Automated, low cost and label free. Portable biosensor prototype, not yet suitable for user-friendly ambulatory application.	For an image, see above [75]	[13]
IM: polystyrene pad DT: electrochemical immune-sensing and optical detection IB: monoclonal anti-cortisol AB TA: cortisol in saliva	DR: 0.4–11.3 ng/mL RT: < 15 min	Automated and rapid system. Sensor can be reused. Parameters are in physiological range.		[82]
IM: SAM modified IDE DT: electrochemical immunosensing using a miniaturized potentiostat interfaced with an LTCC microfluidic manifold IB: monoclonal anti-cortisol AB TA: Cortisol in plasma	DR: 10 pM to 500 nM RT: 35 min	Not tested with saliva but parameters are in physiological saliva range. Fully integrated and optimized electrochemical sensing device. Automated, low cost, and label free. Portable biosensor prototype, not yet suitable for user-friendly ambulatory application. Actual study involving human subjects. Validated against ELISA (high correlation).	For an image, see above [75]	[28]
IM: nitrocellulose membrane DT: LFIA with a fluorescent LFIA cassette reader IB: AB undisclosed TA: Cortisol in saliva (an absorbent pad that collects up to 2 mL of saliva, ~150 s collection time)	DR: 0.9 to 25 ng/mL DT: 20 min	Good agreement (r = 0.8) with ELISA. Reader connects to smartphone via Bluetooth. Reader is portable but still quite large. Validity results need independent replication. Assay strips and reader are commercially available.		[84]
IM: nitrocellulose membrane DT: chemiluminescent LFIA integrated in a smartphone adapter IB: rabbit anti-cortisol AB TA: Cortisol in saliva	DR: 0.3 to 60 ng/mL RT: 30 min	Parameters are in physiological range. Method is simple and portable and suitable for ambulatory use. Adapter and cartridge were 3d printed and can be adapted to any mobile phone. Good agreement between with ELISA results		[83]
IM: none DT: quantitative aptamer-functionalized nanoparticle-based cortisol assay in bonded microfluidic	DR: 30 pg/mL to 10 µg/mL RT: 2.5 min	Parameters are in physiological range. No interference with other glucocorticoids.		[60]

(*continued on next page*)

Table 1 (*continued*)

Device	Properties	Remarks	Image (if available)	Reference
and nanoslit device IB: no antibody or immobilization required TA: Cortisol in saliva and plasma		Correlates well with ELISA and radio immunoassays. Proof-of-concept, not yet suitable for ambulatory assessment.		
IM: SAM modified IDE DT: electrochemical immunosensing using a miniaturized potentiostat interfaced with an LTCC microfluidic manifold IB: monoclonal anti-cortisol AB TA: Cortisol in saliva	DR: 0.01–20 ng/mL RT: 35 min	Parameters are in physiological range. Not yet validated. A miniaturized and reusable pump, mix and control system is necessary for ambulatory use		[52]
IM: none DT: MIP-based organic electrochemical transistor IB: no antibody or immobilization required TA: Cortisol in sweat	DR: 0.01 to 10.0 uM RT: < 1 min	Sensor integrated in wearable patch allowing natural range of motion High selectivity against cortisol's structural analogs Strong correlation with ELISA Transmission of the results to a user interface remains to developed		[50]

AB = antibody; IM = immobilizing matrix; DT = detection techniques; IB = immobilizing biomolecule; TA = target analyte; DR = detection range; RT = response time; LTCC = low temperature co-fired ceramix; LFIA = lateral flow immunoassay; MIP = molecularly imprinted polymer.

concept stage, rather than ready to be used by end-users or lay persons in a home environment. It was therefore premature to interpret the findings in light of regulatory requirements for in vitro diagnostics. Nevertheless, several prominent examples will be discussed in the text. A more exhaustive overview is given in Table 1, including (1) the detection technique and its properties (i.e. biological analyte, detection time and range, sensitivity and specificity, repeatability); (2) user-friendliness (i.e. portability, ease of use, invasiveness) and images or pictures of the devices.

3.1. Immunoassays with optical read-out

Zangheri et al. [83] developed a chemiluminescent imaging system to quantify cortisol in human saliva using a LFIA with an analytical membrane enclosed in a cartridge that is placed in a smartphone adapter in front of the smartphone camera. The method is simple and relatively fast (30 min from saliva collection to quantification), provides values within the physiological relevant range and there was good agreement with ELISA results, though in a very small sample (n = 11 healthy volunteers, samples collected at 8 am).

[84] report the development and testing of a system capable of measuring salivary cortisol within 20 min of sample collection. The system involves a saliva collection device, a lateral flow test strip, and a fluorescent LFA cassette reader to quantify cortisol. When the system was compared against ELISA for cortisol quantification, good agreement was found (r = 0.8) and parameters were within the relevant physiological range. The reader conveniently connects to smartphone via Bluetooth. Though portable - with the size comparable to a common bread toaster - it remains quite large, especially compared to handheld ambulatory assessment technology such as glucose meters. Lastly, it is noteworthy that, although the researchers appear to collaborate with Oasis Diagnostics (Vancouver, WA, USA), at the time of writing the device was not yet commercially available.

3.2. Electrochemical sensing

Several studies provide examples of electrochemical immunosensing. The research by Cruz et al. [13] and Kaushik et al., [28] describes the development and testing of an electrochemical sensing method to detect plasma cortisol in human subjects. They employed a miniaturized potentiostat (reconfigured LMP91000 chip) interfaced with a microfluidic manifold containing a cortisol immunosensor. Detection range was high and detection limit sufficiently low for cortisol detection, including detection in saliva (see Table 1). A comparison with ELISA yielded a high correspondence.

Sanghavi et al. [60] presented a quantitative nanoparticle-based sensor for cortisol using an aptamer, a single-stranded nucleic acid molecule. Their approach employs a detection strategy that surpasses the need for antibody or target labeling, immobilization on the detection surface, or wash steps prior to readout. Cortisol levels were quantified using square wave voltammetry in a microfluidic or nanoslit device. Salivary cortisol could be detected with 2.5 min, well in the physiological range, and no interference with other glucocorticoids was observed. Further, a first validation step involving only three serum samples showed good comparison with ELISA and radio immunoassays, though further validation is clearly needed, also involving saliva samples. Thus far this appears to be a promising methodology, however it is a first laboratory based proof of concept and it is unclear when the

technology is ready to be applied on a larger scale in routine monitoring of cortisol.

3.3. Cortisol sensors with wearable potential

Continuous monitoring of cortisol would innovate the diagnostics and treatment of cortisol-related diseases, or of dysfunctional cortisol levels due to stress in otherwise healthy individuals. Sensors with wearable potential could be an important step towards continuous monitoring of cortisol. Munje et al. [46] demonstrated a nano-technology-driven biosensor for the detection of cortisol in human sweat. Cortisol was detected and quantified electrochemically, based on impedance changes. In sweat, cortisol has a physiological meaningful range of 8 ng/mL to 140 ng/mL. A detection limit 1 ng/mL was reported in low volumes corresponding to ambient sweat ($< 5\,\mu L$; a drop of water is 50 μL). Further, specificity was demonstrated in synthetic sweat using cytokine IL-1β. Though the measurement was yet a point measurement instead of repeated measurement over time and although further development and testing are clearly required, with the size of a penny, the authors suggest application potential for wearable devices, particularly to detect fatigue during exercise as well as during military training and missions.

A recent study actually demonstrated such a wearable approach. Parlak et al. [50] describe the development of a wearable biosensor patch for the selective detection of cortisol in sweat. They combined an artificial recognition membrane based on a molecularly imprinted polymer (MIP) with an organic electrochemical transistor into a skin-mounted patch (see Table 1 for a picture). With rapid, continuous, sensitive and specific detection (see Table 1) this could be a promising example. However, it must be stressed that the in-vivo test was only performed with one participant, and this person was exercising. It remains to be determined how the sensor performs under resting or non-exercise conditions and when tested by more than one participant. Other aspects that remain unclear are battery life and charging possibilities. The authors state that future efforts will be aimed at miniaturization, processing and transmission of the results to a user interface, and harvesting energy directly from bodily fluids to power the device, among others.

4. Where do we stand?

With growing insight in the role of corticosteroids in (allostatic) processes associated with stress, performance, health and disease, the relevance for potential ambulatory assessment methods is increasing. Our literature search resulted in several promising technologies to proceed with towards cortisol assessment in daily life. Many technologies demonstrated good specificity of cortisol sampling, showed accuracy that was comparable to more conventional or gold-standard detection techniques, and were portable (of which some even hand-held), relatively easy to use, and stored data on a smartphone (e.g., [83]; [84]). However, given that, at the time of writing, none of the discussed technologies is commercially available, this field appears novel and relatively immature. Furthermore, while many prototypes report good agreement with ELISA testing, validity results require independent replication. Lastly, none of the discussed studies examined how sensitive the technique is to small but meaningful fluctuations in cortisol (e.g. < 1 nmolL in saliva) such as those occurring in response to stressful events.

At the moment, there is no single best analytical approach for the development of ambulatory cortisol assessment technology. Some used immune assay methodology ([83]; [84]), a technique that is also used in already available self-testing devices for other molecules such as glucose. However, using Enzyme Immuno Assays implies the use of anti-bodies, which are vulnerable to changes in temperature or humidity and have to be either refilled or applied using a disposable analytical platform. Alternative approaches, like electrochemical sensors, may circumvent these issues. For example, the electrochemical aptamer sensor developed by Sanghavi et al. [60] or the MIP-based wearable organic electrochemical device developed by Marrazza et al. (2017) [39].

Nevertheless, almost all of the reviewed technologies seem yet to be at the proof-of-concept stage. It will be exciting to see when technological advancements and production allow application on a larger scale (e.g. for routine monitoring of cortisol) and which analytical method(s) will by then have been proven fruitful.

5. Which way to follow?

As stressed previously, ambulatory assessment technology will be relevant for assessing state-related (changes in) cortisol levels. To accurately capture cortisol reactivity in the absence of laboratory practices, technology has to be sufficiently sensitive to detect minimal changes in cortisol concentrations. This is relevant when measuring in saliva where meaningful changes of close to or even < 1 nmolL have been reported [30,72]. While many studies report that their technology is sensitive to detect concentrations as they physiologically occur (see Table 1), none of the studies also tested whether small fluctuations such as those close to 1 nmol/L can be detected. This is an important knowledge gap and needs to be addressed in future studies.

In addition to technical challenges related to measurement specificity and sensitivity, which will require lab-dependent validation, another challenge is valid sampling and interpretation of the collected data. These protocols have to be followed precisely to collect meaningful data. Further, specific corticosteroid characteristics have to be taken into account. Numerous studies indicate that there are considerable intra and inter-individual differences across daily cortisol profiles [34,66]. These may be related to a number of factors, ranging from quality of sleep to daily activities to virus infections. Fortunately, recommendations have been published regarding sampling protocols, covariate accounting, quantification strategies as well as reporting and interpreting for specific cortisol metrices [34,43,61,66]. These recommendations need to be translated to easy-to-understand instructions and accompany cortisol assessment technology to ensure reliable data, promote user compliance and (consumer) enthusiasm.

Further, there are important data-analytical challenges, including modeling approaches based on theoretical assumptions. Fekedulegn et al. [15] provided a comprehensive overview about derivative variables for repeated corticosteroid assessment. However, it is relevant to mention that most variables (e.g. the CAR and time- or event-locked difference scores) show considerable inter-individual differences in the timing of the corticosteroid response. In scientific research this has to be taken into account when trying to quantify the (average) maximum corticosteroid response to a challenge across multiple individuals. Interestingly, novel analytical methods are being developed that are based on the timing of maximum corticosteroid reactivity, i.e. corticosteroid-peak locked as opposed to time or event locked (e.g. [38]). In addition to group-based approaches, high frequency-sampling techniques based on (multiple) $N = 1$ approaches provide ways to interpret the collected data on an individual level, focusing on *intra*-individual variance over time instead of *inter*-individual variance [8,47,48,57]. Cortisol assessment techniques allowing quick and repeatable assessment are likely to stimulate this $N = 1$ approach.

What is of direct relevance for the demands and specifications of potential ambulatory assessment devices is that all of the above mentioned analytical approaches rely on rather data driven formalizations of derivative variables. Consequently, it is important to note that their utility on the individual level (i.e., their diagnostic value) depends crucially on the reliability of the underlying data. Fortunately, the reliability of predictive derivative variables can be greatly enhanced by introducing theoretical assumptions into the utilized statistical models, which rest on well documented findings about the kinetics of glucocorticoids. Although the reception of such modeling techniques (see

[18], for an overview) has been comparably sparse in the field of psychoneuro-endocrinology and biobehavioral research, their adequate incorporation would yield much potential with regard to the diagnostic value of corticosteroid ambulatory assessments.

6. Conclusion

Accurate cortisol self-testing technologies will be of vital importance to people with Addison's Disease, as well as highly relevant to many others, ranging from professional athletes to individuals suffering from stress-related psychopathology. Furthermore, it will stimulate research to increase our understanding of intra- and inter-individual differences in cortisol concentrations and how this relates to other health outcomes. Recent research efforts have provided novel analytical procedures and technical designs that hold great promise for the development of reliable ambulatory corticosteroid assessment equipment. With significant additional investments and research efforts in the coming years the remaining technological and procedural hurdles can be overcome, making truly ambulant corticosteroid diagnostics on a large scale a reality.

Conflict of interest

The authors declare no conflict of interest or biomedical financial interests.

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