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Integration of Antibody-Based and Electron-Based Diagnostics into Teledermatology for Skin Microbiome Monitoring

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Abstract

Teledermatology has emerged as a vital technology for remotely delivering medical care and is expected to play an adjunctive role in diagnosing skin diseases in the near future. However, a limitation of teledermatology is the current inability of the medium to assess the changes in the human skin microbiome. Skin infections or microbiome dysbiosis, particularly at early stages, cannot be promptly detected using teledermatology services. Herein, antibody-based and electron-based diagnostics are introduced as complementary tools for teledermatology to examine the infections or microbiome dysbiosis. The lateral or circular flow immunoassay methods as rapid diagnostic tests for detecting microbial antigens or antibodies were presented for patients' self-diagnosis. The electronic skin patch was underlined as an electron-based diagnostic device for monitoring the activities of electrogenic skin microbes. Data derived from antibody-based and electron-based diagnostics can be instantly transmitted to smartphones or computers for dermatologists to track patients' skin conditions and therapy progress.

Keywords: Electrogenic, Diagnostic, Infection, Microbiome, Teledermatology.

Abbreviations

- Artificial Intelligence (AI)
- Bacillus Subtilis (B. subtilis)
- Cutibacterium Acnes (C. acnes)
- Circular Flow Immunoassay (CFIA)
- Coronavirus Disease 2019 (COVID-19)
- Quinone Demethylmenaquinone (DMK)
- Extracellular Electron Transfer (EET)
- Group A Streptococcal (GAS)
- Gold Nanoparticles (AuNPs)
- Herpes Simplex Virus 1 (HSV-1)
- Heptaprenyl Diphosphate Synthase (HepT)
- Immunoglobulin (Ig)
- Lateral Flow Immunoassay (LFIA)
- 1, 4-dihydroxy-2-naphthoic acid (DHNA)
- Prenyltransferase (MenA)
- Microbial Fuel Cells (MFCs)
- Type II NADH hydrogenase (NDH2)
- Nitrocellulose (NC)
- Next-Generation Sequencing (NGS)
- Polyethylene Glycol (PEG)
- Proton Exchange Membrane (PEM)
- Peptide Pheromone Encoding Lipoprotein A (PplA)
- Rapid Diagnostic Test (RDT)
- Ribosomal RNA (rRNA)
- Real Time Reverse Transcription-Polymerase Chain Reaction (RT-PCR)
- Short-Chain Fatty Acids (SCFAs)
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
- Staphylococcus epidermidis (S. epidermidis)
- Staphylococcus hominis (S. hominis)
- Staphylococcus warneri (S. warneri)
- Ultraviolet (UV)

1. Introduction

Teledermatology utilizes technology using smartphones or videoconferencing to deliver dermatological services to patients located at a remote distance [1]. Mounting evidence revealed that patients are generally satisfied with teledermatology, either synchronously or asynchronously [2]. However, compared with traditional face-to-face clinical visits, teledermatology has several disadvantages. These disadvantages include 1) many patients, especially elders, cannot gain access to the required infrastructure (e.g., video-enabled devices) to participate in teledermatology services; 2) poor quality of images taken by patients using non-professional devices hinder physicians' decision-making [3]. 3) insurance reimbursements using teledermatology vary across different regions; 4) high-risk groups including patients with severe infections cannot obtain instant therapies through teledermatology [4]. 5) conflicts of interest, overdiagnosis, and overprescribing may occur if teledermatology services involve selling prescription drugs

directly to patients [5]. and 6) infections, especially infections at the early stage in skin wounds, cannot be rapidly detected by teledermatology [6].

The human skin microbiome is a collection of all microbes, including bacteria, protozoa, fungi, and viruses, that coexist in the skin. It plays a crucial role in regulating human health [7]. It has been reported that the component microbes of the skin microbiome have essential functions in educating both innate and adaptive immunity of the skin [8]. Skin dysbiosis is a term used to describe a microbial imbalance or dysfunction in the skin microbiome, which negatively impacts health [9]. The overgrowth of *Cutibacterium acnes (C. acnes)* in the skin microbiome has been linked to the progress of acne vulgaris [10]. Skin dysbiosis with increased *Staphylococcus aureus (S. aureus)* colonization on the skin is a hallmark of atopic dermatitis alongside an impaired epidermal barrier [11]. Recent studies demonstrated that herpes simplex virus 1 (HSV-1) easily penetrates this impaired epidermal barrier to initiate infection in the setting of atopic dermatitis [12]. The results indicated that the dysbiotic skin microbiome in atopic dermatitis with massive *S. aureus* colonization may increase the susceptibility to skin infections.

Next-Generation Sequencing (NGS) technologies are commonly used to obtain the comprehensive sequence-based interrogation of microbial populations. The 16S ribosomal RNA (rRNA) gene with conserved sequences and specific variable regions among prokaryotes has been used as a molecular signature to identify and quantify microbes in microbial populations using NGS, also referred to as meta-taxonomic analysis [13]. 16S rRNA gene sequencing via NGS analysis is considered a gold standard analytic technique to examine the changes in microbial composition and abundance in healthy individuals and patients with dysbiosis-related skin diseases [14]. Although 16S rRNA gene sequencing for microbes is a high-throughput analysis to understand the linkage between skin homeostasis and dysbiosis, there are significant limitations. The analysis requires many steps and relies heavily on expensive equipment. Furthermore, it is extremely time-consuming and labor-intensive. Patients frequently wait several weeks to obtain their results. Thus, 16S rRNA gene sequencing cannot instantly create a report for diagnosis of skin dysbiosis and infections during the operation of teledermatology, minimizing its clinical utility in this setting.

A rapid diagnostic test (RDT), an antibody-based diagnostic technique including a lateral flow immunoassay (LFIA) is an alternative method of quickly detecting either skin microbial antigens or immunoglobulin (Ig)G/IgM antibodies [15,16]. In addition, electron-based diagnostics, including an electronic circuit mounted on the skin as a patch have been developed to monitor microbial activities in real time [17]. This review will summarize the recent development of antibody-based and electron-based diagnostics for detecting skin microbes. The potential for integrating these two types of diagnostics into teledermatology services will be highlighted.

2. Methods

Teledermatology is conducted in real-time via videoconferencing or store-and-forward procedures when digital images or photographs are submitted with a medical history. The methods applied for teledermatology can be found in detail as previously described [18]. Literature summarizing the LFIA has been published [19]. Many devices, including microbial fuel cells (MFCs) and various electronic sensors for the detection of bacterial electricity have been developed [20,21].

3. Results and Discussion

3.1 Antibody-Based Diagnostics for Teledermatology

The antibody-based RDTs such as LFIA are fast and easy modalities to detect microbial antigens or antibodies induced by microbes in blood and other body fluids. A typical LFIA contains three pads (sample, conjugate, and absorbent pads) and one nitrocellulose (NC) membrane with test and control zones. LFIA is a small handheld device that does not need specialized training or equipment to operate and yields a result within a few minutes [22]. By spotting spike (S) antigen of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on an NC membrane, LFIA has been used to rapidly detect the antibodies induced by SARS-CoV-2 amidst coronavirus disease 2019 (COVID-19) pandemic [23]. Furthermore, by connecting the ends of two LFIAs, where the membrane glycoprotein of SARS-CoV-2 or hemagglutinin of influenza viruses was spotted on NC membranes, the LFIA allows for the synchronic detection of two antibodies in one sample. By dispensing non-conjugated SARS-CoV-2 spike protein-specific goat IgG in the NC membrane and the conjugate pad, the LFIA has been used to detect SARS-CoV-2 [24]. It became a point of care and an alternative method to traditional approaches such as real-time reverse transcription-polymerase chain reaction (RT-PCR).

It has been documented that human blood and body fluids hold the various antibodies developed by exposure to different commensal bacteria [25]. Protein A of S. aureus exhibits a higher affinity for human immunoglobulins, especially IgG (IgG1 and IgG2) [26]. Scientists have utilized S. aureus protein A to conjugate gold nanoparticles (AuNPs) for binding Fc regions of various immunoglobulins in the blood. By spotting the S. aureus protein A-conjugated AuNPs and microbial antigens on conjugate pads and NC membranes, respectively, the LFIA can capture the skin microbes-induced antibodies in the blood. A multiplexed circular flow immunoassay (CFIA) test strip (Figure 1) has been created by improving the components from the LFIAs into a circular array, enabling the simultaneous detection of different circulating antibodies in blood samples using as little as a few microliters of a sample. It has been reported that the profile of circulating antibodies to skin bacteria detected by LFIAs differentially correlated with the abundance of bacteria in the human skin microbiome. Compared to the traditional method using 16S rRNA gene sequencing via NGS, the CFIA can quickly generate results in less than 30 min and establish a profile of the human skin microbiome within a short time. Most importantly, the images of CFIAs associated with titers of circulating antibodies and the abundance of skin bacteria can be quantified and displayed in real-time by a built-in camera. Therefore, CFIA has an immense potential to become a new, specific, multi-target, and quantitative tool for digital and simultaneous monitoring of various antibodies, as an indicator of bacterial abundance in the human skin microbiome during the operation of teledermatology services (Figure 1).

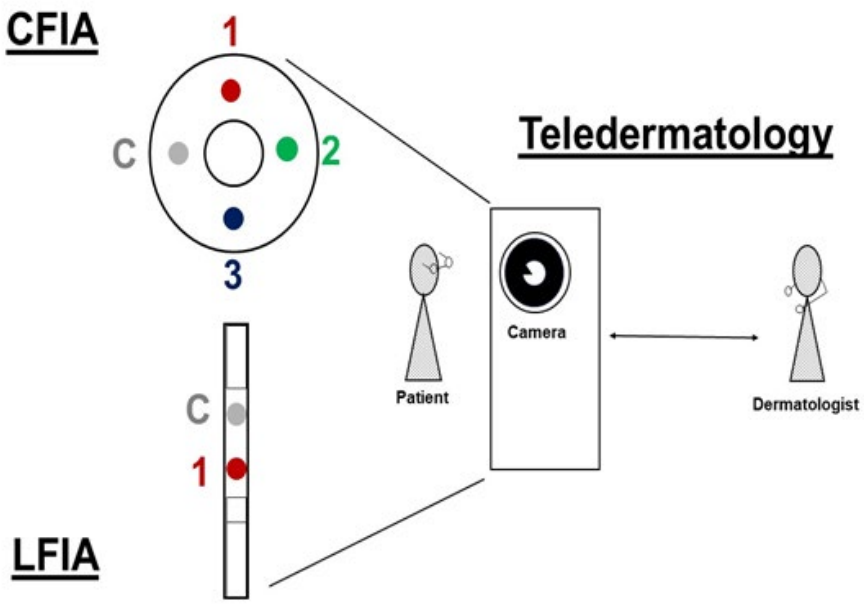

Figure 1: Delivery of LFIA or CFIA images captured with a smartphone or computer camera to a dermatologist during teledermatology service. The levels of microbial antibodies or antigens can be quantified relative to the control (C) antibody or antigen. LFIA detects and quantifies only one antibody or antigen (spot 1). CFIA simultaneously quantifies and differentiates antibodies or antigens (spots 1 to 3) in one assay using one sample. Both LFIA and CFIA yield "ready to read" results in a short time, require little to no skilled training, and do not need specialized equipment for result reading. The results of the quantitative antibodies or antigens on LFIA or CFIA detected by patients can thus be quickly sent to dermatologists using smartphones or videoconferencing for teledermatology.

3.2. Electron-based Diagnostics for Teledermatology

By adopting the principle of LFIA, several rapid antigen (beta-hemolysin) tests have been used in clinic to detect the *Group A streptococcal* (GAS) bacteria [27]. Since rapid antigen tests have been widely used at home during the COVID-19 pandemic, the use of rapid antigen tests by patients at home to detect bacterial infection in skin wounds may help dermatologists prescribe appropriate antibiotics to patients via teledermatology [28,29]. Although antibody-based RDTs, including LFIA and CFIA, can rapidly produce a result for bacterial detection within 10-20 minutes, they cannot dynamically monitor the activity of bacteria in real time. Recent studies have revealed that several skin microbes are electrogenic [30]. These electrogenic microbes, also referred to as exoelectrogens, can intracellularly yield and transfer electrons extracellularly across the cell envelope to electron acceptors, including minerals and electrodes. Electronic sensors with electrodes have been developed to detect the electrons elicited by bacteria [31]. These sensors can be integrated into teledermatology for monitoring the activity of microbes in the skin.

3.3 Electrogenic Skin Bacteria

In Gram-negative bacteria, the haem groups related to the *CymA* gene, encoding membrane-anchored tetraheme cytochrome c, and three genes (*MtrA, MtrB,* and *MtrC*) encoding methyltransferase created a signal pathway for electrons to transport across the periplasm and the outer lipid membrane [32,33]. Through extracellular electron transfer (EET), several Gram-positive bacteria transfer electrons from the bacterial cytosol to the extracellular space [34]. *Listeria monocytogenes (L. monocytogenes)* expresses peptide pheromone encoding lipoprotein A (PplA), which contains two flavin molecules, enabling electrons to exit the membrane to reach the exterior environment [35]. An eight-gene locus associated with electron production in *L. monocytogenes* has been identified. Among these genes, *ndh2*, encoding a unique Type II NADH hydrogenase (NDH2) catalyzes electron exchange from cytosolic NADH to a quinone derivative [36]. The *dmkA* and *dmkB* genes encoding paralogs of the microbial enzymes 1, 4-dihydroxy-2-naphthoic acid (DHNA) prenyltransferase (MenA), and heptaprenyl diphosphate synthase (HepT) are responsible for the formation of the quinone demethylmenaquinone (DMK) [37,38]. Overall, Gram-negative bacteria use multiheme c-type cytochromes for electric production whereas Gram-positive bacteria mediate the pathway of EET for electron transfer. Many bacteria with abundant c-type cytochromes or quinones as electron mediators on their membranes have been recognized as electrogenic bacteria. Additionally, sweat-eating bacteria, which can metabolize components such as lactate and glycerol in skin sweat, have been identified as electrogenic bacteria. These bacteria, including *Staphylococcus epidermidis (S. epidermidis), Staphylococcus capitis,* and *Micrococcus luteus,* are highly abundant on the skin surface. *S. epidermidis and Staphylococcus hominis (S. hominis),* specifically, have been shown to mediate glycerol fermentation to yield electricity. The electricity produced by glycerol fermentation of S. epidermidis may increase the resistance of the bacteria to ultraviolet (UV) light and may impair the growth of C. acnes, an opportunistic bacterium in acne vulgaris [39]. An iron-resistant *Staphylococcus warneri (S. warneri)* bacteria strain also displays high electrogenic potential by using lactate as an electron donor. Some transient bacteria of the skin which originated from the soil can generate electricity

as well. For example, *Nitrosomonas europaea*, a Gram-negative bacterium, can convert ammonia and organic substances in sweat to electricity. The sporulation and germination of *Bacillus subtilis (B. subtilis)* initiated by skin sweat induced a detectable electrical signal [40]. Results in previous studies above demonstrated that several microbes residing on the human skin can metabolize substrates as electron donors to yield electricity.

3.4 Detection of Skin Electricity Produced by Bacteria

MFC is a standard device for the detection of bacterial electricity. It uses bacteria as a catalyst to oxidize organic substrates to convert chemical energy into electrical energy. MFC is composed of the chambers of electrodes (cathode and anode) separated by the presence of a proton exchange membrane (PEM) [41]. Bacteria oxidize organic substrates in an anode to form protons and electrons. PEM accelerates the migration of protons to the cathode, whereas electrons are transferred through an external circuit. Although MFC can detect bacterial electricity in a research laboratory, it requires a bacterial culture in a large chamber, making it inappropriate for operation in the home, outpatient care centers, and hospitals during teledermatology services. In recent years, small semiconductor circuits such as electronic skin patches have been widely developed to detect skin electricity attributable to changes in skin conductance and electrogenic skin bacteria [42,43]. An electronic skin patch imprints an integrated circuit with a cathode and an anode onto a thin, flexible silicon film that can be applied to the skin. Patients can monitor electricity as an indicator of bacterial activity at home through an electronic skin patch. Detected signals can be instantly transmitted to both the patient's cell phone and the clinic during teledermatology services (Figure 2).

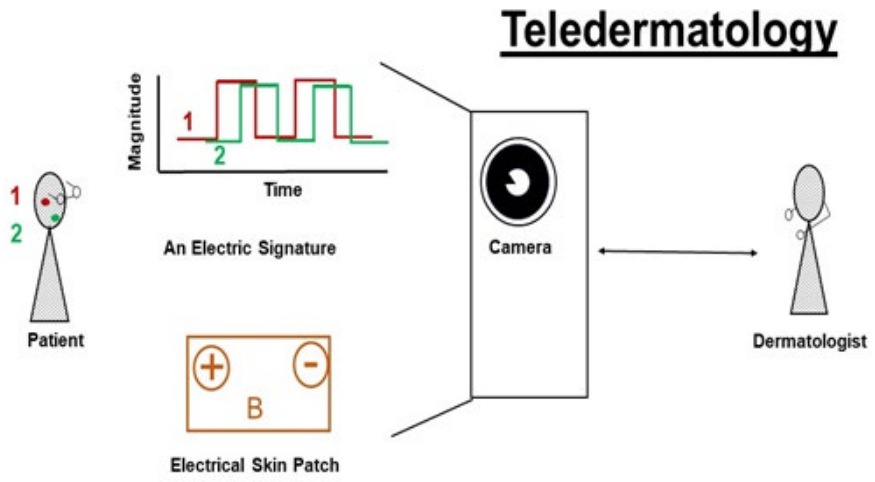

Figure 2: An electric signature derived from the electricity of bacteria on a patient's skin for teledermatology. An electrical skin patch can be fabricated with a cathode (+), an anode (-), and Bluetooth (B). Once it is placed on the skin, it collects, processes, and displays the electrical signals continuously produced by skin bacteria dynamically in real time. The electrical signals (red and green lines) that go up and down with varying magnitudes form differential electric signatures. Different skin bacteria (labelled 1 and 2) generate distinguishable electric signatures, which provide dermatologists with information to remotely monitor the dysbiotic microbiome on skin with/without diseases or before/after treatments.

Electricity-producing bacteria such as Shewanella, Geobacter, and Pseudomonas species in the soil can mediate the formation of biofilms to yield electricity [44]. A recent study has shown that S. epidermidis ATCC 12228, a non-biofilm forming strain of skin bacterium, uses polyethylene glycol (PEG)-8 Laurate as a specific carbon source to produce electricity, clearly illustrating non-biofilm-mediated electricity production. Furthermore, each bacterial species expresses different enzymes to metabolize carbon sources. The study also demonstrated little or no electricity in media containing C. acnes and PEG-8 Laurate. Thus, bacterial electricity signatures can be distinguished by providing bacteria with specific carbon sources [45,46]. All three dominant skin bacteria (S. epidermidis, C. acnes, and S. aureus) can fermentatively metabolize glucose to short-chain fatty acids (SCFAs) [47-49]. SCFAs such as acetate, propionate, and butyrate have been identified as electron donors to intensify bacterial electricity [50]. S. epidermidis, but not S. aureus, can ferment mannose and galactose. S. aureus cannot ferment ducitol and saccharic acid. In fact, previous studies have demonstrated that different electric signatures can be produced by various bacteria, including S. epidermidis and S. hominis, when the bacteria were cultured with the same carbon source: glycerol, an endogenous molecule in human skin. During teledermatology services, patients can use an electronic skin patch to harvest electricity produced by bacteria on the skin. The signatures of bacterial electricity will be established by transmitting electric data to a smartphone or computer for further calculation. Although the signatures of bacterial electricity have been not yet used as disease biomarkers in clinic, the data calculator will synthesize the algorithms which can efficiently transfer data to the current clinical settings in the near future. A dermatologist will be able to diagnose the status of the patient's skin based on the electric signature, which reflects changes in the skin microbiome.

Many skin commensals, including C. acnes and S. epidermidis, have a bidirectional (symbiotic and opportunistic) relationship with their host [51]. LFIAs have been applied for the detection

of opportunistic bacteria in research laboratories or pathogenic GAS in clinic. Literature has demonstrated when CFIA was loaded with antigens from different microbes, it can be used to detect the circulating antibodies to different pathogens such as SARS-CoV-2 and influenza viruses from blood samples in one assay [52]. However, spotting multiple antigens from different microbes on a LFIA can yield results derived from cross-reactions of antibodies due to shared antibody epitopes in antigens of different microbes. Thus, this potential problem of specific antibody and antigen interactions must be overcome before LFIA can be used in clinic in the future. In terms of electron-based diagnostics, although bacterial enzymes metabolize carbon sources as electron donors to generate electricity, different bacteria may share the same carbon sources to produce similar electric signatures. With large amounts of bacterial electric signatures collected from the human skin artificial intelligence (AI) technologies may be able to differentiate the similar electric signatures generated from different bacteria [53].

4. Conclusion

Teledermatology is the remote dermatologic diagnosis of patients in real-time using smartphones or videoconferencing. The challenges of teledermatology implementation include the identification of specific skin microbes causing an infection or a dysbiotic microbiome. Traditional approaches such as RT-PCR or 16S rRNA gene sequencing involve the use of bulky medical equipment and are labor intensive and time-consuming. Antibody-based diagnostics such as LFIA have been widely used as rapid tests during the COVID-19 pandemic for patients at home to detect the antigens or antibodies of SARS-CoV-2. There is increasing evidence that electricity produced by microbes dynamically reflects the real-time activities of microbes in the human microbiome. The electron-based diagnostics such as electronic skin patches have been constructed to sense microbial electricity for wireless connection with a smart device. Thus, antibody-based and electron-based diagnostics have great potential for integration with teledermatology to track infections and dysbiotic microbiomes. However, additional studies are undoubtedly required to further optimize the operation of antibody-based and electron-based diagnostics for both patients and dermatologists during teledermatology services.

Availability of Data and Material

Information comes from the references, which are open for the public.

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Author Contributions

T.Y.H. collected literature and wrote this manuscript. T.Y.H. organized papers related to antibody- and electron-based diagnostics.

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Competing Interests

The authors declare that they have no competing interests

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