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Telemedicine for Ketogenic Dietary Treatment in Refractory Epilepsy and Inherited Metabolic Disease: State of Play and Future Perspectives

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Abstract. Ketogenic dietary therapies (KDT) are diets that induce a metabolic condition comparable to fasting. All types of KDT comprise a reduction in carbohydrates whilst dietary fat is increased up to 90% of daily energy expenditure. The amount of protein is normal or slightly increased. KDT are effective, well studied and established as non-pharmacological treatments for pediatric patients with refractory epilepsy and specific inherited metabolic diseases such as Glucose Transporter Type 1 Deficiency Syndrome. Patients and caregivers have to contribute actively to their day-to-day care especially in terms of (self-) calculation and (self-) provision of dietary treatment as well as (self-) measurement of blood glucose and ketones for therapy monitoring. In addition, patients often have to deal with ever-changing drug treatment plans and need to document occurring seizures on a regular basis. With this review, we aim to identify existing tools and features of telemedicine used in the KDT context and further aim to derive implications for further research and development.

Keywords. ketogenic diet, telemedicine, refractory epilepsy, inherited metabolic disease

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1. Introduction

Ketogenic dietary therapies (KDT) are diets that bring on a metabolic condition comparable to fasting and comprise a reduction in carbohydrates whilst dietary fat is increased up to 90% of daily energy expenditure. The amount of protein is normal or slightly increased. These dietary adaptions yield in a metabolic switch from the utilization of glucose as primary energy source for the central nervous system to liver ketogenesis and thus utilization of ketone bodies as primary energy substrate [1]. KDT are effective, well-studied and established non-pharmacological treatments for pediatric patients with refractory epilepsy and specific inherited metabolic diseases (IMD) such as Glucose Transporter Type 1 Deficiency Syndrome (GLUT1DS) [2,3]. Further, the evidence for KDT in adolescents and adults is growing in recent years [4]. Patients and caregivers have to contribute actively to their day-to-day care especially in terms of (self-) calculation and (self-) provision of dietary treatment as well as (self-) measurement of blood glucose and ketones for therapy monitoring. Patients also have to deal with ever-changing drug treatment plans and need to document occurring seizures. Thus, KDT lead to a significant amount of paper based documentation as well as frequent e-mail and telephone contact with health care professionals (HCP).
However, complexity of treatment, low rates of participation and poor retention rates seem to be barriers that have to be overcome in the future [5,6]. Especially during the COVID 19 pandemic, interest in telemedicine aspects in the monitoring and treatment of patients with refractory epilepsy increased strongly [7]. In addition, the International League Against Epilepsy (ILAE) calls for action to promote telemedicine for individuals with epilepsy [8]. Currently, there is a lack of telemedicine solutions for the purpose of therapy monitoring and therapy management of patients with refractory epilepsy or IMD undergoing KDT although that might reduce complexity and contribute to facilitate access, adherence and quality of KDT. Hence, we want to outline the current role of telemedicine in KDT management and present a conceptual framework with regard to the requirements from a clinical and digital health point of view for future research and development.

2. Methods

A systematic literature review in MEDLINE was conducted in December 2023 to identify existing telemedicine strategies for the treatment of patients with refractory epilepsy and IMD undergoing KDT. PICO criteria (Population, Intervention, Comparator, Outcome) were defined as follows: Population (refractory epilepsy, glucose transporter type 1 deficiency), Intervention (ketogenic diet); Comparator (none); Outcome (feasibility). Derived keywords and MeSH (Medical Subject Heading) terms were combined using the Boolean operators “OR” and “AND”. As we were primarily interested in telemedicine methods applied in clinical settings for treatment of refractory epilepsy or IMD with KDT and further wanted to increase the sensitivity of our search, we focused on the criteria Population and Intervention. Considering the predefined inclusion and exclusion criteria, a title- and abstract screening was performed, followed

by an assessment of the remaining articles, focusing on specific telemedicine methods and addressed requirements. Articles were included for full text assessment if original data or a specific concept were reported.

3. Results

Our search in the MEDLINE database identified 11 articles eligible for title and abstract screening. As two articles did not provide original research data or specific concepts, further assessment was performed for 9 studies that were published between 2012 and 2023 and originated from Argentina (n=2) [9,10], USA (n=2) [11,7], Italy (=3) [12,13,14], Brazil [15], and the United Kingdom [16].

Armeno et al. published an observational study with the aim to explore feasibility, effectiveness and safety of online guided KDT initiation and follow up versus standard outpatient KDT. They included children (n=37) between 0 and 18 years of age with drug resistant epilepsy who started KDT between January 2020 and April 2021. 18 patients received online treatment and 10 patients received standard outpatient treatment. The use of Zoom™, WhatsApp™, e-mail and telephone was considered as telemedicine approach in the intervention group. Telemedicine was considered feasible and there was no difference between both groups regarding safety and effectiveness [9].

Semprino et al. conducted a questionnaire-based survey to assess parent satisfaction with telemedicine guided KDT management. The survey did address parents of children between 8 months and 18 years with refractory epilepsy (n=54), treated at a secondary-care center in a region with limited financial resources. The use of messaging and video call via WhatsApp™ was considered as telemedicine approach. Parent's satisfaction was evaluated using a 13-item questionnaire. High parent satisfaction (96.3%) and recommendation-rate (72.2%) as well as easy access and helpfulness of professional coordinated social-network support groups (90%) were reported [10].

Kossoff et al. reported data on their experience with KDT initiation and monitoring during the coronavirus disease 2019 pandemic. Experience from the pediatric and adult ketogenic diet centers at Johns Hopkins University was described on the basis of four respectively 38 patients receiving KDT due to refractory epilepsy or GLUT1DS. Strategies comprising telemedicine aspects included the use of e-mail, telephone, video via Polycom™, Zoom™, Doximity™ (live or prerecorded), SharePoint (a web based Microsoft™ platform for data exchange) and an electronic medical record secure messaging system. Those strategies were applied for initiation, follow-up, patient education, regular visitation and second opinion visits [7].

Cervenka et al. performed a prospective, open-label proof-of-principle study over 3 months investigating the feasibility, safety, and effectiveness of e-mail administered KDT over the course of three months in adults who had refractory epilepsy (n=25). Patients received a manual of instructions on how to self-administer a 20g carbohydrate per day MAD. Unrestricted access via e-mail to the treating neurologist was provided and patients were evaluated at baseline and 3 months. Seizure-frequency, urine ketones and weekly weights were recorded on a provided paper-based calendar and transmitted via e-mail or fax on a monthly basis. Potential adverse effects were also reported in that way. After 1 month, 9 (41%) showed a >50% seizure reduction including one individual (5%) with >90% seizure reduction. After 3 months, 6 (27%) showed a >50% seizure reduction including 3 (14%) with >90% seizure reduction. Median number of e-mails

sent were 6 (IQR 1-19). After one month 95% of patients remained on KDT, after three months 64% remained on the diet [11].

Costa et al. conducted a questionnaire-based survey, to assess the effects of a ketogenic diet management app and web materials in addition to paper-based materials (n=22) compared to paper-based materials only (n=18), designed for caregivers and pediatric patients in the context of KDT. Main features of the "KetApp" were to record and monitor dietary parameters, generate recipes and menus, record blood glucose and ketosis values, record the anthropometric data and monitor them over time, and record epileptic seizure data. Perception and satisfaction were assessed using the Information Satisfaction Questionnaire as well as additional multiple-choice questions with a five-point Likert scale. Overall findings on satisfaction, attitude towards treatment and awareness indicate that web-based materials were beneficial for caregivers of children with refractory epilepsy receiving KDT [12].

Zini et al. published their concept regarding a prototype mHealth application, named "Ketty" for education and monitoring purposes in the treatment of patients with KDT. The main features developed to be supported by "Ketty" were therapy assignment (nutritionist), coaching (dietitian), self-management (patient), and assessment (nutritionist, dietitian). Key roles were patient/caregiver, doctor and dietitian. Patients were not only able to use the application as source of information, but also to access food databases, to generate and calculate recipes, to document their diet history, and to track ketones, glycemia and epilepsy crises. HCP were able to remotely prescribe the dietary regimen, coach the patients, browse data and analyze trends [13].

Ferraris et al 2020. retrospectively evaluated e-mails regarding frequency and content sent to and received from their patients or caregivers (n=34) under KDT during the first year of therapy. Affected patients were 2-17 years old and either diagnosed with drug-resistant epilepsy (n=14) or GLUT1DS (n=20). Median mails sent were 36 (IQR 23.0-64.0) per family. GLUT1DS patients sent more e-mails than patients with refractory epilepsy (median 39.0 (IQR 25.5-56.5) vs. median 26.0 (IQR 19.0-65.0)). Higher e-mail exchange occurred in the group that showed increase in its linear growth (median 83.5; IQR 48.0-102.0) [14].

Lima et al. shared their perspective on the challenges of KDT in the public healthcare system in Brazil and provided information on challenges, perspectives, and their experience of telemedicine assisted KDT follow-up in seven patients during the COVID 19 pandemic. Applied telemedicine strategies comprised the use of telephone, e-mail, messaging applications and voice calls. They addressed hazards to treatment such as long travel distances for clinical visits, financial problems as well as anxiety and stress caused by the pandemic and discussed the use of telemedicine strategies to reduce costs and increase feasibility for affected individuals [15].

Bara et al. performed an online survey on patient and caregiver views from five centers in the United Kingdom about video consultations in the context of KDT. Patients and caregivers (n=40) affected by refractory epilepsy or metabolic conditions, where KDT was indicated, were included. The survey comprised 16 items with open and closed questions, including Likert scales. Video consultations were common (57,5%) and seen as at least partly preferential to on-site consultations (45%), whereas 22.5% of participants reported that they would not like to have video consultations. Benefits were reported in terms of saving travel time, reducing stress by not needing parking slots nearby, and not having to take time off work. In addition, the positive effect on the environment was stressed by 30% of participants. Not being able to get blood tests (55%), weight or height check as well as the less personal contact during video

consultation were frequently seen as disadvantages (42.5% each) [16]. Table 1 gives an overview on the tools and features of telemedicine strategies applied in the context of KDT for refractory epilepsy and IMD.

Table 1. Results from the systematic literature review in Medline – Tools and features

Study	Tools	Features
Armeno et al. 2022	telephone, e-mail, Zoom™, WhatsApp™	messaging, instant messaging, voice calls, video calls
Semprino et al. 2020	WhatsApp™	instant messaging, voice calls, video calls
Kossoff et al. 2020	telephone, e-mail, video conference, SharePoint (Microsoft™), electronic medical record secure messaging system	messaging, instant messaging, voice calls, video calls, video conference, store, organize, share, and access information
Costa et al. 2021	video, website, app (KetApp)	share, and access information, therapy monitoring, therapy management
Lima et al. 2020	telephone, e-mail, messaging applications and voice calls	messaging, instant messaging, voice calls, video calls
Zini et al. 2018	app (Ketty)	share, and access information, therapy monitoring, therapy management
Bara et al. 2023	video consultation	video calls
Ferraris et al. 2020	e-mail	messaging
Cervenka et al. 2012	e-mail	messaging, share, and access information

4. Discussion

Telemedicine for KDT is feasible and might be necessary during a pandemic. Further, it certainly bears potential benefits for patients, caregivers and the society with regard to stress reduction, cost savings, increased efficiency and the reduction of carbon emissions. Two studies included only adult patients [11,15] whereas six studies included caregiver-child dyads [9,710,12,14,16]. In one study, the concept of a specific app is described [13]. Published strategies primarily target the use of communication tools as add-ons or alternatives to on-site clinical visits [9,10,14,15,16]. Most commonly, telephone, e-mail and different types of messaging tools were applied. Four centers used several channels in parallel to communicate and provide information. Five centers relied on only one channel. Further, published efforts also aim at facilitating therapy management via online provision of information and providing easy-access to professional expertise via e-mail management [7,11]. Preliminary experiences from two centers exist regarding the use [12] and development [13] of specific applications trying to enable comprehensive therapy monitoring and management features such as seizure documentation, blood glucose and ketone monitoring, dietary prescription, calculation and tracking. Table 2 maps general, disease and KDT specific requirements for future digital health applications in therapy monitoring and management of patients treated with KDT based on our preliminary review and the authors extensive clinical experience. Additional benefits might be gained within the setup of clinical registries and the support of clinical studies. Telemedicine in the KDT context might not be suitable for all patients and reveals challenges such as technical difficulties (e.g. poor internet connection, inability to connect to virtual platform), necessity of training for patients, caregivers and HCP,

remuneration, data safety, cyber and legal security. At the same time opportunities like reduced travel time, easier planning of follow-up visits, multidisciplinary meetings and educational sessions as well as easier access to KDT will result from digital health innovation within this field. [9,10]

5. Conclusion

Feasibility of telemedicine in KDT was shown and further research might firstly need to assess existing requirements from patients, caregivers, and HCP dealing with KDT. In combination with a comprehensive workup of all existing literature and developments in the medical device sector, this might lead to the creation of potential multi-channel tools to facilitate KDT implementation, increased adherence and increased efficacy. From a clinical point of view it appears of utter importance, that patients planned for KDT receive upfront diagnostic workup that requires on-site visitation to a certain extent. A single messaging tool might not match the quality of personal contact between HCP and patients, respectively caregivers, but advanced telemedicine strategies will certainly have an important role in the future of KDT. However, the impact of telemedicine on feasibility, adherence and effectiveness has to be studied in future clinical trials in comparison to standard treatment.

Table 2. Requirements for telemedicine applications in the context of Ketogenic Dietary Treatment

Directly dietary therapy associated issues and requirements	
Issue	**Requirements**
Blood glucose monitoring	Documentation, visualisation, sensor integration
Blood ketone monitoring	
Breath ketone monitoring	
Dietary prescription	Wizard for calculation of energy and nutrient requirements Interface to database for foods for special medical purposes
Dietary tracking	Food protocol
Diet facilitation	Interface to food databases Wizard for recipe calculation
Growth and weight monitoring	Documentation, visualisation
Directly disease associated issues and requirements	
Seizure frequency	Documentation, visualisation
Medication prescription and monitoring	Documentation, visualisation Interface to medication database
Drug level monitoring	Documentation, visualisation
Quality of life	Integration of standard questionnaires
Cognition	Integration of standard questionnaires
General issues and requirements	
Patient registration	Basic data registration Registration of contact person
Patient management	Appointment- and task management
Communication	Unidirectional communication (HCP→Patient/Caregiver) (e.g. push messages, reminder) Bidirectional communication tools (HCP↔Patient/Caregiver) (e.g. messaging, video call) Interprofessional communication (HCP ↔ HCP)
Reporting	Generation of ad hoc and standard reports
Data safety and protection	Data storage at non-profit health care provider

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