ISPAD-Breakthrough T1D Fellowship – Progress Report

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Planned time of research fellowship: from summer 2024 (postponed due to maternal leave)

Start of fellowship was 1st of September 2024 part time only 7.4 hours/week due to clinical specialization at other clinical departments for the rest of working hours.

Background

The importance of near normalization of the glucose level in PWD1 is indisputable in securing both short and long-term physical and mental health(1,2). Not achieving glycemic targets is associated with an increased risk of short (e.g. hypoglycemic or ketoacidosis events) and long-term complications (e.g. nephropathy, retinopathy, neuropathy and cardiovascular disease)(3–5). However, achieving strict control is challenging and only a minority obtain the current treatment goals even when equipped with insulin pumps and continuous glucose monitoring (CGM)(6,7). Modern technology including automated insulin delivery systems, where CGM values are the basis for an algorithm that adjusts insulin delivery, constitutes an important therapeutic tool that helps PWD1 obtain treatment goals and prevents short and long-term complications(8–13).

The pre-requisite for using the technology is a *well-functioning infusion set and CGM*. Nevertheless, a major obstacle is the evolvement of contact dermatitis (CD) and in some cases, an allergy towards the components in the adhesive material or housing of the infusion set and CGM(14,15). CD is seen in 25-33% of children and adults and persists over time(16–18), highlighting the lack of proper treatment options. Importantly, skin complications negatively impact mental health(19,20). The CD can be separated in allergic or irritative CD, where allergic CD is a type IV hypersensitivity reaction which can be diagnosed by a positive skin patch test to a potential allergen, whereas irritative CD is an exclusion diagnosis(14). A key challenge here is that full declaration of device constitutes are not required from authorities(21).

We have shown how a skin care program prevents some skin problems but not effectively the CD(22), indicating that there are still allergic and irritative components of the CD-reactions that aren't solved yet. In clinical practice treatment options are therefore typically blind "try-as-you-go" with different barriers and under-patches also indicated in the recent ISPAD Guidelines(23), although consequently increasing the burden and costs of skin problems(24). Besides long-term effects of using steroid creams or sprays on the skin to reduce reactions and the potential steroid-induced skin atrophy have not been investigated(25,26). The potential healing properties of patches has been studied in some smaller studies where hydrocolloid patches seemed to accelerate healing of the skin and prevent eczema(27).

Skin barrier defects may be inherited and mutations in the filaggrin gene contribute to a substantial part of those with CD(28). Our recent study of non-lesional skin in PWD1 though demonstrated similar skin barrier(29), but knowledge on skin barrier in the device sites are still not investigated. Natural moisturizing factors (NMF) are a major part of the skin barrier and are shown to be reduced in reactions of CD and atopic dermatitis(30,31), and can be investigated by the in dermatology well-known tape stripping method(32). NMF is a sensitive method of skin barrier impairment and can therefore also see smaller differences which are not seen visually yet; therefore it is a very important method for investigating the consequence of occlusion from and content in diabetes devices.

Children and adolescents are an important age group to study, when it comes to skin problems caused by diabetes devices since they are known to have more reactions than adults(16), are more likely to have atopic dermatitis(33), have less skin surface for insertion of devices, are more likely to use diabetes technology in Denmark due to organizational priorities and have higher demands for the adherence of diabetes devices, especially in the young ones.

Objectives and aim

The overall **goal** of this project is therefore to ensure CD is not prohibiting any person with diabetes the access to the optimal treatment by the following specific aims:

Aim 1: Describe contact dermatitis caused by diabetes devices by patch test results, allergens, discontinuation of devices, and handling of contact dermatitis in clinical practice

Aim 2: Investigate skin barrier as a function of occlusion time, skin resting time and type of device

Aim 3: Explore new methods for prevention and treatment of contact dermatitis

This research thereby enables better handling of CD in clinical practice, increases knowledge on skin barrier impairment and importance of rotation, type of device and wear-time to create optimal prevention guidelines. Secondly, guide device industry in important allergens to avoid in future diabetes devices and thereby achieving the **goal** to let all PWD1 use diabetes devices without CD.

WP1 – Study design and current status

Study design

Description of 8-years of referrals of contact dermatitis

Work package (WP) 1 will solve Aim 1: *describe contact dermatitis caused by diabetes devices by patch test results, allergens, discontinuation of devices, and handling of contact dermatitis in clinical practice.* The rationale behind the study is to systematically report and describe the referrals of CD caused by diabetes devices to dermatologist and patch testing.

The study design is therefore a retrospectively observational longitudinal study by using both information from patch testing and medical files to collect data on allergens, causes, treatment, prevention, and consequences of CD.

Study population: All referrals to Department of Dermatology at Gentofte Hospital of CD caused by diabetes devices will be included depending on the ethics and data protection regulations.

Data variables: Each included patient will be pseudo anonymously handled with the following data variables which are already available: Sex, Age, Patch test results, allergens, medical device with reaction, duration of use of diabetes device prior to CD, history of other diabetes devices prior to CD, additional tape or patch used, treatment with steroid including duration, other comorbidities, consequence of CD (discontinuation etcetera) and methods for handling of CD in clinical practice.

Expected outcomes: The primary outcome is to describe individual allergens and their relation to different diabetes devices and patches**,** which can also guide in relevant allergens to be included in “Diabetes Device Patch Test Screening series”. The secondary outcome is to obtain knowledge on discontinuation rate and handling of these CD in clinical practice.

Current status

The study design needed to be changed a bit since the intention was to include the first 100 referrals from 2015 to 2023, but after carefully looking into all regulations in Denmark this would need consent from all participants and since this can be very difficult to obtain and there by resulting in selection bias, we have chosen another strategy. From 2015 to 2019 38 referrals were seen and summarized in a study by Ulrik Ahrensbøll-Friis et al(14), which have shed light on important allergens and which devices contained each allergen. This study will therefore be a national extension with inclusion of more clinical perspectives. We have decided to do it as a cross-sectional quality improvement project to evaluate the quality of the handling of CD in clinical practice among both pediatric, endocrinologic and dermatologic departments. This type of project is though limited to the last 5 years of data collection and resulted in data from 01-01-2020 to 31-12-2024 where all participants denying access to electronic patient records to ensure quality improvement was omitted. All data collection is manually into a RedCap Server. By writing, all applications for the project are approved and the data collection is estimated to be done by 1st of September 2025.

Next steps here will then be Statistics and Manuscript Writing where the first manuscript is expected to be finalized before the end of 2025.

WP2 – Study design and current status

Study design

Skin Barrier, Prevention and Treatment of Contact Dermatitis

WP2 will address both Aim 2: *Investigate skin barrier as a function of occlusion time, skin resting time and type of device* and Aim 3**:** *Explore new methods for prevention and treatment of contact dermatitis.* The rationale is to focus within the subgroup of children and adolescents with CD caused by diabetes devices and explore both important measures of their skin barrier in lesional and non-lesional skin and to include them in a randomized controlled trial (RCT) with the aim to prevent CD. In addition, we are including known study methods with the use of tape stripping techniques, patches, the skin care program, and ultrasound as our previous studies.

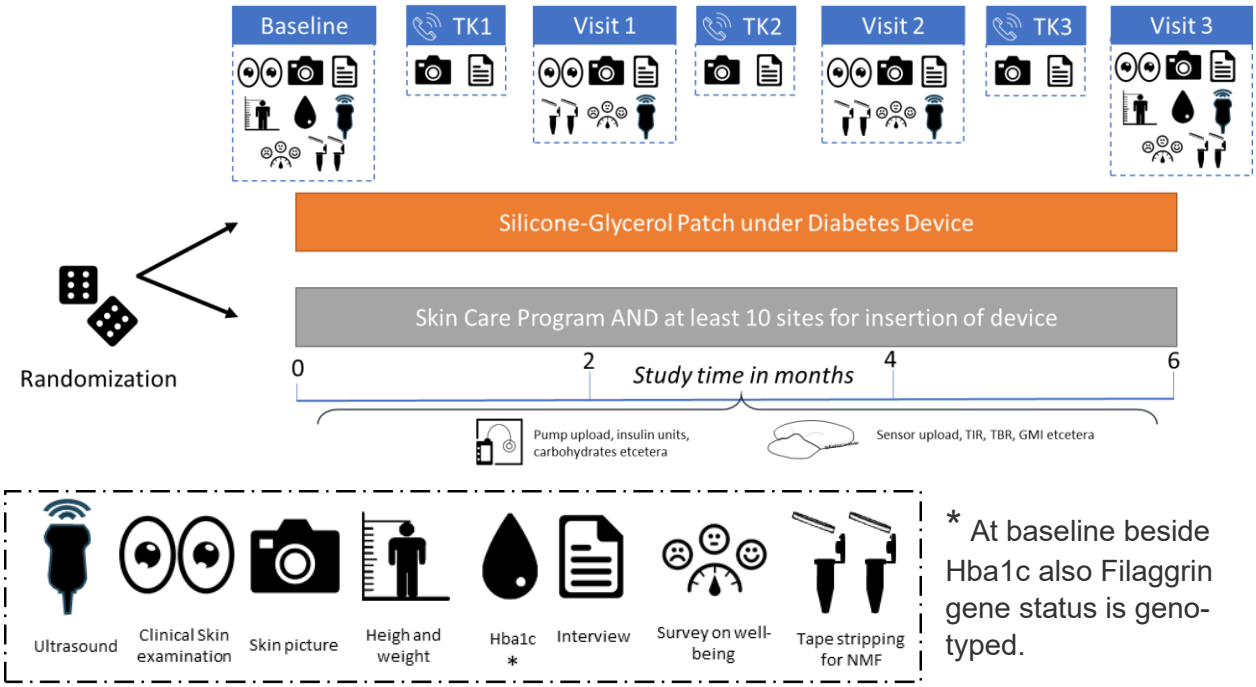
The study design is an explorative and hypotheses generating RCT with the following two arms:

a) Insertion of a silicone-glycerol patch by Glysious® underneath the diabetes device
b) Use of the skin care program and identify at least 10 sites for insertion of each diabetes device to ensure appropriate healing time

If not sufficient to overcome CD in a period of 4 weeks, liquid barrier, acrylic-based, hydrocolloid-based or silicone-based patches are included underneath device in that order with each tried for 4 weeks before going to the next type as the present standard of care. A silicone-based patch is already used in clinical practice, but the Glysious patch is different since it is even more skin friendly and moisturizes the skin, has higher breathability and absorbs sweat due to the inclusion of glycerol(34). In addition, it is less costly and with smaller environmental footprint compared with regular silicone-based patches(35). If participants have been using steroid lotion or spray prior to inclusion in the study, a sub-study on steroid-induced skin atrophy will be incorporated based on the skin barrier measures.

Study population: Children and adolescents with CD caused by diabetes devices from Steno Diabetes Center Copenhagen are invited.

Study design: This is a prospective study with four physical and three remote visits in a period of 6 months to be able to see reappearance or prevention of CD. An overview of study methods and investigations are seen in the figure.



* At baseline beside Hba1c also Filaggrin gene status is genotyped.

Expected outcomes: This study will not only give new knowledge on a possible alternative patch to use under the diabetes device or the use of ultrasound, but also insights of the skin barrier after different number of days with occlusion of different patches. The study is explorative in its nature and will guide and refer on future important clinical studies to be performed or implemented in clinical practice since estimated incidences of CD with the new un-proven patch is too uncertain. A clear risk is therefore a null finding of no significant differences between the two arms due to limited power, however results will be compared to reappearance rates of CD from earlier studies of 35%.

Current status

There are many economic expenses related to this clinical study, so some economic additional funding has been needed but is now ensured with the Danish diabetes associations research grant in early 2025. While this has been ensured the first many months of the fellowship have been used on contracting with the company to be able to do this study with agreement ensured in Q1 of 2025 postponed due to new rules for contracting with companies at SDCC. During this period the protocol have been finalized and the application for approval of study initiation for the ethics committee have been submitted in July 2025.

Next steps will therefore be inclusion of participants and follow-up visits where more staff have been employed to let this project be possible to be finalized in less than 1 year. After that statistics and manuscript writing are next steps. And the ambition is to submit an abstract for ISPAD 2026 with the results from this study.

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