

# Clinical Protocol

**Title:** Glucose Measurement Using Microneedle Patches

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## Background

Diabetes is a serious health concern and due to its rapidly increasing incidence, especially in children and adolescents, has been declared a global epidemic by the World Health Organization. It is taking a heavy toll on the US economy - US\$ 376 billion annually that will increase to US\$ 490 billion in 2030 [1-3]. Glycemic control in children and adolescents with diabetes is limited by poor patient compliance. In addition to failing to adhere to appropriate diet and pharmacologic therapy, children and adolescents with diabetes who do not monitor their blood glucose frequently and make adjustments based on those measurements, have poor glycemic control and are at risk for developing long-term complications. The frequent (> 4 times daily) monitoring of blood glucose is an essential component of diabetes management as maintenance of blood glucose near the physiologic range enables the diabetic child to lead a healthy life and avoid long-term complications from diabetes [4, 5].

Commercial blood glucose-monitoring devices (BGMDs) employ a cost-effective biosensor that can be mass-produced and responds rapidly to glucose detection. The BGMDs require an automated lancet device to prick the fingertip for blood sampling, which is painful [6]. The development of BGMDs in the past 2 decades has improved by reducing the amount of blood needed for measurement and reducing the size of the lancet. In the past decade, minimally invasive glucose sensors have been developed that utilize interstitial fluid to determine glucose concentration that correlates well with serum glucose [7, 8]. Despite these improvements, children with diabetes are still apprehensive with these devices and perceive them as painful. Avoidance or non-compliance with current BGMDs places diabetic children at increased risk for long-term complications [6]. The goal of this proposal is to develop microneedle patches as a new method for interstitial fluid collection and subsequent glucose measurement to reduce pain and apprehension in children and adolescents with diabetes.

Microneedles have been developed to create transport pathways for small drugs, macromolecules, and fluid flow in a painless manner. They range in length from 150 – 900  $\mu\text{m}$  and the microscopic length permits appropriate collection of interstitial fluid but limits the extension into the abundant nerve-ending region of the dermis, thereby minimizing pain [9-11]. We have collected interstitial fluid with subsequent glucose measurements using hollow, glass microneedles previously however, it required a two-step process [12]. Hollow, glass microneedles were applied to human skin and suction was required to withdraw the interstitial fluid from the needles. The study showed a strong correlation between glucose levels in interstitial fluid and blood but, the two-step process was time-consuming and cumbersome, making it difficult to translate it into a point-of-care system.

The American Diabetes Association (ADA) recommends that diabetics maintain their plasma glucose in a strict range to prevent long-term complications of diabetes [13]. Children with diabetes who fail to appropriately monitor their blood glucose are not aware of how to adjust their diet and/or pharmacotherapy to optimize their glycemic control. In this project, we propose to target collection of interstitial fluid for glucose measurement from the painless application of solid microneedles in children with diabetes. Because these microneedles and continuous indwelling sensors for interstitial fluid glucose monitoring are both FDA-approved, this is a well-established and accepted medium from which to sample and measure glucose [6, 8].

Needle anxiety prevents ideal glycemic control and up to 50% of children and adolescents fail to monitor their blood glucose consistently [7, 14]. Microneedle patches could eliminate needle anxiety and improve adherence to proper glucose monitoring. Studies show microneedles reduce injection pain [9, 10] and increase patient and clinician acceptance for other injected drugs [15]. We will investigate if microneedle patches can improve adherence and compliance with glucose monitoring in children and adolescents with diabetes.

We have recently developed a simple process, to independently extract interstitial fluid from skin. The microneedles are made from biocompatible polymers or metal. Inserting these microneedles creates on create holes in the skin. These pores are pathways to draw out interstitial fluid out of the skin. The collected fluid is used for analysis. In a future design, the glucose-sensing functionality can be integrated into the patch backing (e.g., integrate a glucose test strip into the patch backing) to create a simple, one-step method of glucose monitoring.

We have used our original glass microneedle design to collect interstitial fluid more than 100 times in rats and in six adult human subjects. We have used stainless steel microneedles for drug/vaccine delivery in hundreds of mice. Polymer microneedles also have been tested in extensive animal studies and there is an ongoing Phase 1 human clinical trial on influenza vaccination using these microneedles.. We have used placebo microneedles of various designs in a number of different studies involving nearly 1000 microneedle insertions in close to 150 human subjects. The process of insertion of the microneedles has been simple and painless.

Overall, there is a need to improve glucose monitoring to prevent the costly long-term complications of diabetes. Existing alternatives have limitations that restrict widespread uptake. This project will provide a first detailed assessment of microneedle patches as an option for improved efficacy and acceptance of glucose monitoring in children with diabetes. Current efforts to develop alternative glucose monitoring methods (e.g., interstitial glucose measurement) have had minimal clinical impact due to the apprehension and discomfort associated with insertion of either a glucose sensor or lancet that requires penetration through the epidermal layer [6]. As a novel approach designed to address the shortcomings of other glucose measuring methods, especially in children, we propose the application of microneedle patches for interstitial fluid collection and subsequent glucose concentration measurement to achieve two improvements: (i) improved safety as a bloodless method with less tissue trauma and (ii) higher acceptance among pediatric patients and clinicians due to the painless and non-threatening patch design.

## **Procedures**

A cohort of 15 children and adolescents with diabetes will be recruited for the study. We hypothesize that glucose concentration collected from interstitial fluid will correlate with both capillary blood glucose (collected from a lancet and measured with a BGMD) and venous glucose (collected from an intravenous

catheter). In this aim, we will measure glucose concentrations collected from children and adolescents with diabetes (type 1 or type 2).

Glucose measurements from all three methods (interstitial fluid - microneedle, capillary blood - lancet, and venous blood - intravenous catheter) will be made simultaneously from each subject every hour from 8:30 AM – 11:30 AM. Suction (up to 500 mmHg) may be applied after microneedle treatment at the skin site for up to 1 hour to withdraw fluid ( $\leq 500 \mu\text{l}$  [microliters]) from the skin. Measurements will be taken every hour for the study period. Subjects will arrive in the morning after an overnight fast and will eat or drink a breakfast during the study visit. Subjects will be asked about the pain and apprehension with each device.

Pain and apprehension will be determined with the use of the visual analog pain scale (VAS) and a questionnaire. Each subject will be asked to rate their apprehension prior to receiving each method for blood or interstitial fluid collection as well as the pain associated with each method immediately after collection. Each subject will receive each method of glucose monitoring simultaneously. Similar to a cross-over study, each subject's apprehension, pain, and glucose with each method will be compared using the paired t-test method. Sample size is determined based on the number of subjects needed to achieve statistically significant differences in pain based on the VAS. In order to detect a pain difference of 20 mm with a standard deviation of 20 at a power of 95% and an alpha of 0.05, 15 subjects will be recruited.

### Expected Outcomes

In this study, we will develop microneedle patches for collection of interstitial fluid for subsequent measurement of glucose concentration in an effort to improve patient compliance and cost (Fig 1). Recent studies have shown that intradermal microneedle insertion is less painful and strongly preferred by patients receiving drug delivery through injections [13-15]. We hypothesize that interstitial fluid collection using microneedle patches can improve glycemic monitoring in being as effective as conventional methods and in a less painful manner, thereby improving patient compliance. The microneedle patches will be fabricated at the Global Center for Medical Innovation at the Georgia Institute of Technology. Prior to use in human subjects, the microneedle patches will be sterilized by an approved sterility center.



**Fig. 1. Microneedle patches for interstitial fluid glucose monitoring. Prototype patches are shown with green dye in the microneedles for visual enhancement (left). Application of microneedle patches to the skin is simple (center). High magnification images of microneedles (right).**

### Collaboration Plan & Leveraging of Resources

*This study will be carried out by a highly interdisciplinary team of physician-scientists and engineers to provide the first in-depth study of glucose monitoring using microneedle patches in children with diabetes.*

This work is led by Eric Felner, a pediatric endocrinologist with extensive insulin delivery and microneedle experience at the Emory University School of Medicine, in collaboration with Mark Prausnitz, an expert microneedle engineer at the Georgia Institute of Technology, who has developed microneedle patches for almost 20 years. Dr. Felner and Dr. Prausnitz have co-authored published studies and co-supervised medical, graduate, and undergraduate students together for almost 10 years.

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