ISPAD-JDRF Research Fellowship Report

Project Title: Myocardial complications of diabetic ketoacidosis

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1. **Backround**

   Diabetic ketoacidosis (DKA) is a severe acute complication in patients with T1D. It is the result of an insulin deficiency with successive lipolysis and ketogenesis with resulting acidosis. The severe metabolic derailment can lead to organ dysfunction with cerebral damage, pancreatitis and kidney damage. In adult medicine, an association between DKA and myocardial damage is not uncommon.

   Such cardiac impairment represents an additional cardiovascular risk factor alongside the diabetes itself and is associated with a poorer long-term cardiac outcome [Eubanks 2012]. Patients with T1D generally have a greatly increased risk of cardiovascular disease, which is associated with a loss of life of 17 years in women and 14 years in men if the manifestation of T1D occurs before the age of 10 [Rawshani 2018].

   In the context of DKA, patients of different age groups show cardiac involvement through an increase in cardiac biomarkers such as troponin, CK-MB or NT-proBNP [Atabek 2004; Al-Mallah 2008; Japitana 2013]; ECG changes such as QT prolongation and ST elevation [Kaefer 2019; Moller 2015; Odubanjo 2018]. Echocardiographic changes, in particular left ventricular dysfunction and reduced contractility, have also been described [Shim 2021; Roberts 2009; Moller 2015].

   In a preliminary study, we investigated cardiac involvement in the context of DKA in 10 children and adolescents with T1D. The cardiac biomarkers troponin I and NT-proBNP were measured at 0, 12, 24, 48 and 72 hours after the start of therapy. 70% showed elevated NT-proBNP values, 20% an additional troponin I elevation. The standard echocardiographic examination of the patients with elevation of both cardiac enzymes showed inconspicuous or unspecific findings. There were no clinical symptoms.

   Cardiac diagnostics such as ECG, echo-KG and cardiac biomarkers are usually part of the standard examination in adult medicine; in pediatrics, these examinations are only performed if there are strict clinical or anamnestic indications. In order to be able to assess cardiovascular complications in the context of DKA, there is therefore a lack of sufficient systematically collected data on cardiac biomarkers and dysfunctions, particularly in the pediatric field. The clinical significance also results from the stable frequency of DKA with T1D manifestation in childhood and adolescence in Germany: one third of children and adolescents experience the manifestation of their T1D in the DKA stage [Holl 2023].

   Rationale: Early detection enables regular check-ups, can influence treatment targets for other cardiovascular risk factors such as hyperlipidemia and can lead to early therapeutic consequences in order to delay or even prevent complications and life-shortening secondary diseases.

Aim: By means of a clinical observational study, we would like to detect cardiac impairment in children and adolescents in the clinical state of ketoacidosis at the time of manifestation of T1D and record its longer-term course.

Study design: A monocentric, prospective, clinical observational study with case-control groups over two years is planned. Both recruitment and observation of the patients are planned for 12 months.
Study population: 55 children and adolescents aged 0 - 17 years who are hospitalized with diabetic ketoacidosis with manifestation of T1D in the children's and adolescent hospital AUF DER BULT (cases) and 35 children and adolescents aged 0 - 17 years who are treated without DKA with manifestation of T1D in the children's and adolescent hospital (controls) are to be included in the study.
Control parameters: These include demographic data such as gender, age, weight and previous illnesses on the one hand, and laboratory parameters and cardiac function diagnostics on the other.
The following laboratory parameters are recorded: pH, bicarbonate, base excess, pCO2, sodium, potassium, calcium, osmolarity, glucose, phosphate, magnesium, HbA1c, creatinine, CRP, troponin I, NT-proBNP.
We will use the following examination methods for cardiac function diagnostics:

1. Echocardiography using an ultrasound machine from Philipps with special software (TOMTEC AutoStrain LA and RV,Affiniti Rev. 9.0 SW).

- Determination of basic anatomical and hemodynamic parameters using standard 2D and Doppler sonographic examinations including apical 4-, 5- and 2-chamber views, as well as parasternal long and short axis.
- Assessment of valve function and cardiac function using Doppler sonography. Calculation of the ejection fraction according to Simpson and Bullet
- Determination of FAC (Fractional Area Change), FS (Fractional Shortening), TAPSE (Tricuspid Annular Plane Systolic Excursion) and MAPSE (Mitral Annular Plane Systolic Excursion).
- Extended analysis of diastolic function using tissue Doppler/TDI (Tissue Doppler Imaging). Investigation of regional, i.e. longitudinal, radial and circumferential motion/contractility disorders using speckle tracking/2-D-strain analysis.
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2. ECG: The following cardiac functions should be recorded here:

- Basic rhythm, position type,
- PQ, QRS and QT duration, course of ST segment and T wave
- Morphology of the QRS complex

Conduct of the study:
The study includes a baseline examination for each study group as well as 4 follow-up examinations for the case group and one follow-up examination for the control group.
The baseline examination takes place for each study group as part of the manifestation treatment on admission. It includes the information interview and obtaining consent, the collection of demographic data and the initial blood sample after diagnosis, but before the start of treatment.
The follow-up examinations take place 24 hours after hospitalization for both study groups and especially for the case group (patients with DKA) also after 48 and 72 hours. They primarily include the determination of laboratory parameters. Cardiac functional diagnostics

with ECG and echo are performed approx. 24 hours after admission for patients in both groups and additionally 5-7 days after admission for patients with DKA (case group). In the case of pathological functional diagnostics, further outpatient checks are carried out as specified by the pediatric cardiologist.

Current status of the first 11 months (January 2024 – November 2024):
We received the positive ethics vote on 22.08.2023 with the corresponding application number 11049_BO_K_2023.
The study initiation was in December 2023 and recruitment started in January 2024.
Since January 2024 we have had 78 patients with onset of type 1 diabetes.

Recruitment numbers to date

- So far 56 patients have been included
- 30 with DKA
- DKA-Severity:
    - 12 severe DKA
    - 5 moderate DKA
    - 13 mild DKA

Of the 22 patients who were not included in the study, the majority were transferred from peripheral clinics after 2-3 days, so that no more data could be collected. Others had language barriers.

Next steps:

- An interim evaluation will take place in January 2025.
- Recruitment will continue until the number of subjects reaches 90
- The entire data analysis is expected to take place from May to July
- A publication is planned for November/December

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