# The impact of type 1 diabetes on the neurochemical profile

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## Introduction

Patients with type 1 diabetes (T1DM) require insulin therapy to regulate their blood glucose levels. As achieving near-normal glucose levels with insulin therapy is difficult, patients experience often hypoglycemic and hyperglycemic events, which may have an impact on the brain. This may be in particular true for patients who often experience hypoglycemia, which eventually leads to impaired awareness of hypoglycemia (IAH).

The concept that T1DM affects the brain is supported by several studies reporting on a lower cognitive performance[1,2] and structural cerebral changes[3,4] in T1DM. The neurochemical mechanism that may underlie these developments are not well studied yet.

Here we evaluate the neurochemical profile of patients with T1DM and IAH, patients with T1DM and normal awareness of hypoglycemia (NAH) and healthy non-diabetic controls.

## Methods

We included 13 healthy controls, 18 subjects with T1DM and NAH and 13 subjects with T1DM and IAH.

$^{1}$H-MRS data were recorded during a hyperinsulinemic-euglycemic glucose clamp on a 3T MR system (MAGNETOM Trio or MAGNETOM Prisma, Siemens). Data were acquired from a single voxel (22.5-25.0 cm$^3$) with a sLASER spectroscopy sequence (TE 30-33 ms; TR 3000 ms; 32 averages). A water-unsuppressed spectrum was used for absolute metabolite quantification and eddy-current correction. Spectra were analysed with LCModel (fig. 1).

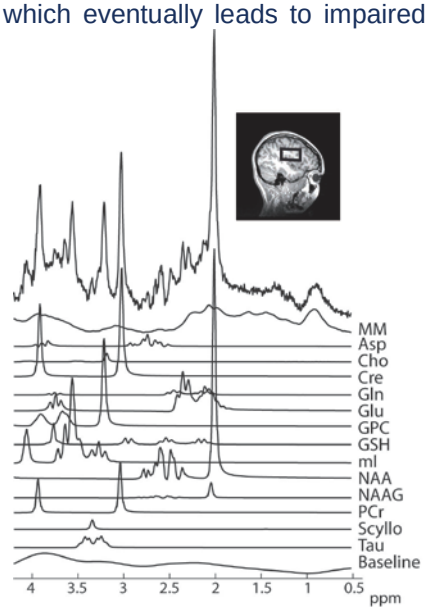


Fig 1. Example of a $^{1}$H-MR spectrum and LCModel analysis

## Results

The subjects were matched for age, gender, BMI, duration of diabetes and $HbA_{1c}$ levels. Plasma glucose levels were well in the euglycemic range (5.3 ± 0.6 mmol/L) during data acquisition.

Glutamate levels were higher in subjects with T1DM, both with NAH (+15%, $p$ = 0.013) and IAH (+19%, $p$ = 0.003), compared to non-diabetic controls. Furthermore, we observed higher aspartate levels in T1DM with IAH (+30%, $p$ = 0.009) compared to non-diabetic controls. All other metabolite levels were not significantly different between groups (fig. 2).

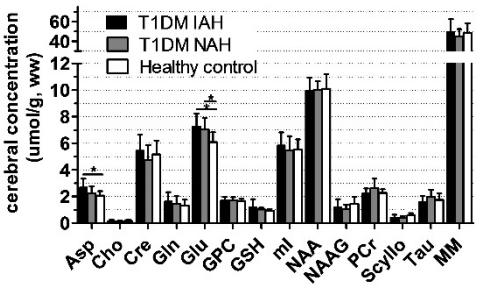


Fig 2. Metabolite levels. * p < 0.05

## Discussion and conclusion

Our main finding is that the brain glutamate levels are elevated in T1DM. Glutamate is one of the most important excitatory neurotransmitters and changes in glutamate levels may be linked to metabolic activity.[5] Alternatively, glutamate itself may act as a metabolic substrate for the TCA cycle. Higher glutamate levels could be the result of a cerebral protection mechanism in response to multiple hypoglycemic insults during a lifetime with diabetes. We also found higher aspartate levels in T1DM with IAH, but are uncertain of its cause.

In conclusion, we showed that there are subtle alterations in the neurochemical profile of patients with T1DM, with limited impact of IAH.

### References

**1**. Cukierman-Yaffe et al., Diabetes 2014 **2.** Kodl et al. Endocr Rev 2008 **3.** Bednarik et al., Front Neurosci 2017
**4.** Hughes et al., J Diabetes Complications 2013 **5.** Rae, Neurochem Res 2014