Cerebral metabolite biomarkers of Type 2 Diabetes Mellitus, blood glucose measures, and cognitive decline

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Target audience: Investigators interested in neuroimaging and Type 2 Diabetes Mellitus.

Introduction: Type 2 Diabetes Mellitus (T2DM) is a common chronic metabolic disorder, characterized by chronic hyperglycemia. In addition to (cardio)vascular disease, T2DM is associated with cerebral abnormalities, accelerated cognitive decline, and dementia. A high-normal glucose level, a T2DM risk factor, is associated with an increased risk of developing dementia even among participants without T2DM[1]. Additionally, the plasma glucose related glycated hemoglobin (HbA1c) is indicative of glycaemic regulation for the previous 2-3 months. Magnetic resonance spectroscopy (MRS) provides the opportunity to study cerebral metabolites, including neurotransmitters. Altered cerebral metabolic concentrations may be associated with neurodegeneration. The aim of this study is to examine if cerebral metabolites constitute a MRI biomarker for i) T2DM, ii) blood glucose measures (fasting blood glucose and HbA1c), and/or iii) cognitive status.

Methods: *Subjects and MRI*: 40 non-T2DM (age 59.1±9.0 y, 15 male, BMI 24.7±2.8 kg/m^2) and 44 T2DM (age 64.9±6.0 y, 33 male, BMI 29.5±3.9 kg/m^2) participants were included in this study. Cognitive performance was assessed using three tasks (memory, fluency and executive function), subsequently expressed as the sum of the Z-scores. 3D T1-weighted fast field echo and ^{1}H-MRS (PRESS and MEGA-PRESS) data were obtained at 3T (Philips Achieva TX). ^{1}H-MRS spectra were acquired from a 3x3x3 cm^3 voxel located in the occipital lobe (Fig. 1A), using a single voxel PRESS sequence (TE/TR= 38/2000ms, 128 averages, MOIST water suppression). Additionally, a spectrum (16 averages) was recorded of unsuppressed water. For γ-aminobutyric acid (GABA), a MEGA-PRESS sequence (TE/TR=68/2000ms, 320 averages, editing pulses at 1.9 (ON) and 7.46 ppm (OFF) interleaved in 40 blocks, MOIST water suppression) was used. *Analysis*: PRESS spectra were analyzed using LCModel (Version 6.2-2B) with a simulated basisset. Metabolites include glutamate (Glu), myo-inositol (mI), total N-Acetylaspartate (tNAA), total creatine (tCr) and glutamate / glutamine (Glx). MEGA-PRESS spectra were analyzed in Matlab with Gannet[2], yielding GABA+ estimates (with potential macromolecule contamination). Metabolite ratios are reported relative to total water. *Statistics:* Linear regression was performed (IBM SPSS statistics v20), with each metabolite concentration as dependent, and T2DM, cognitive performance, T2DM*cognitive performance, age, and gender as independent variables (*model 1*). Additionally, T2DM risk factors (fasting blood glucose (*model 2*) and HbA1c (*model 3*)) were added separately to *model 1*. Furthermore, group characteristics were tested using independent samples t-test and Chi-Square tests.

Results: T2DM participants scored significantly worse on cognitive performance than non-T2DM participants (Z-score: -1.3±2.9 vs 0.8±2.3, p≤0.001). Furthermore, age, gender, fasting blood glucose (7.8±1.6 vs 5.1±0.4 mmol/l), and HbA1c (6.8±0.5 vs 5.7±0.4%) were significantly different between both groups (p<0.001). Good-quality spectra (SNR range of 11-25) were acquired for ^{1}H-MRS (Fig. 1BC). Linear regression revealed increased GABA+ concentrations with higher HbA1c levels (*model 3*, Table 1.). tCr and tNAA were increased in female participants and tNAA and Glu decreased with age. No significant results were found regarding diabetic status, cognitive performance, mI, or Glx.

Table 1.

Metabolite	Model	Independent variable	β	95% CI	p-value
GABA+	3	HbA1c	0.233	0.037 – 0.428	0.020
		T2DM	-0.126	-0.434 – 0.182	0.418
		Cognition	0.012	-0.049 – 0.072	0.702

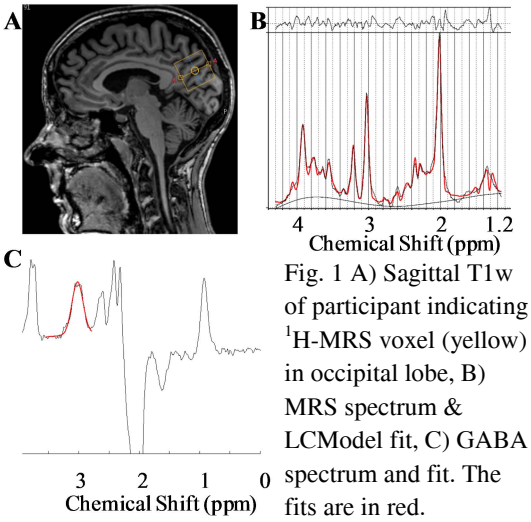

Fig. 1 A) Sagittal T1w of participant indicating ^{1}H-MRS voxel (yellow) in occipital lobe, B) MRS spectrum & LCModel fit, C) GABA spectrum and fit. The fits are in red.

Discussion & Conclusion: In this study we observed significantly higher GABA+ concentrations in participants with a higher HbA1c. This indicates that a high concentration of the inhibitory neurotransmitter GABA is associated with poor blood glucose control, independent of diabetes or cognitive status (Table 1.). Although a direct relation of GABA and glucose control is not straightforward, abnormalities in both cerebral GABAergic and blood glucose homeostasis have been linked to dementia[1,3]. Unfortunately, no relationship with cognitive status was observed in this study, possibly due to the relatively mild cognitive problems of the subjects (in contrast to dementia patients), or the voxel location (occipital), chosen for optimal spectral quality, rather than neuropsychological relevance[4]. Furthermore, our results show that tCr concentration is dependent on gender, which indicates that tCr should not be used as a standard for ratios. Finally, tNAA is a marker for neuronal integrity and decreases with age, which is consistent with literature[5]. To conclude, the current study is the first study to report higher GABA+ levels in participants with poor blood glucose control. In the context of T2DM, it remains to be elucidated whether, in addition to blood glucose level, also elevated GABA levels are associated with an increased risk for developing dementia. Future, larger, longitudinal studies are warranted to explore this interesting topic.

References: [1] Crane, P.K., et al., 2013, N Engl J Med, vol. 369, no.15, pp.540-548. [2] Edden, R.A.E., et al., Gannet: a batch-processing tool for the quantitative analysis of GABA-edited MRS spectra, J Magn Reson Imaging, in press. [3] Mohanakrishnan, P., et al., 1997, J Gerontol, vol. 52, no.2, pp.111-117. [4] Awad, N., et al., 2004, J Clin Exp Neuropsychol, vol. 26, no.8, pp.1044-1080. [5] Angelie, E., et al., 2001, AJNR. Vol. 22, no.1, pp.119-127.