Assesment of diabetic nephropathy with Hyperpolarised [1-^{13}C]Pyruvate

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Introduction: Diabetic patients have an increased risk of developing kidney diseases. Diabetic nephropathy is the leading cause of chronic kidney failure and end-stage kidney disease. Early diagnosis and non-invasive monitoring is critical for early intervention. Recent studies using DNP [1] hyperpolarized ^{13}C, that the pyruvate to bicarbonate conversion (Pyruvate dehydrogenase activity) is significantly altered in the heart already at the onset of diabetes [2]. We here investigate the development of diabetic nephropathy in the type-1 STZ induced diabetic rat model. The complex and multifactorial metabolic change induced by prolonged diabetes, can by injection of hyperpolarized [1-^{13}C]pyruvate, map the enzymatic activity of Lactate dehydrogenase (LDH), Alanine Aminotransferase (ALT) ans Pyruvate dehydrogenase (PDH), and thereby give insights to the progression of diabetic nephropathy.

Materials and Methods: Type-1 STZ diabetic and control rats (n = 10, n = 12), where divided into 3 subgroups with different degree of diabetes. The groups where 2, 10 and 12 weeks after onset of diabetes. The animals where placed in a metabolic cage for 72 hours and urine and faeces were sampled during the last 24 hours. The rats had free access to standard chow and water. The rats were anesthetized and a tail vein catheter was inserted for injection of hyperpolarized [1-^{13}C]pyruvate. Temperature and respiration were monitored throughout the experiment. Each animal received two injections of 2 mL hyperpolarized [1-^{13}C]pyruvate over 10 s with 1 hour separation. In both cases a dynamic slice selective sequence, covering both kidneys was used. NP = 1024, SW = 8 kHz, TR = 1 s, TE = 530 us. The MRI spectroscopy data were analyzed by integration of the respectively metabolite signals. The blood glucose level was measured pre and post scanning.

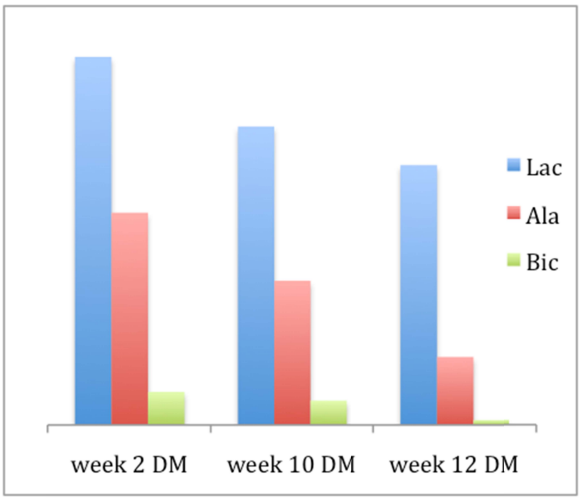

Figure 1. The plot shows the reduction in metabolic activity of ALT, LDH and PDH with increasing diabetes (DM) and diabetic nephropathy.

Results and discussion: The diabetic rats had increased lactate (LDH) and alanin (ALT) levels compared with the controls, while the bicarbonate production (PDH), was reduced with the progression of diabetes and hence reduced kidney function. In conclusion, the study shows a significantly altered metabolic profile with reduced kidney function, in the diabetic rat.

Table 1: The blood glucose level, kidney size and urine secretion is increasing significantly with increasing diabetes and diabetic nephropathy.

Control / Diabetes	Glucose [mmol / L]		Mass [g]		Urin [mL]		Kidney [g]	
2 Weeks	**9.1**	**18.7**	**251**	**233**	**23.8**	**33.1**	**0.93**	**1.05**
10 Weeks	**8.3**	**29.5**	**268**	**257**	**15.5**	**88.5**	**0.91**	**1.22**
12 Weeks	**11.2**	**31.7**	**278**	**214**	**18.0**	**89.1**	**0.89**	**1.15**

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[2] M.A. Schroeder, L.E. Cochlin, L.C. Heather, K. Clarke, G.K. Radda, and D.J. Tyler, In vivo assessment of pyruvate dehydrogenase flux in the heart using hyperpolarized carbon-13 magnetic resonance. Proceedings of the National Academy of Sciences 105 (2008) 12051-12056.