Impact on basal and maximal ATP turnover of structured physical activity counselling in type 2 diabetes: a ^{31}P MRS study

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Introduction: Defects in mitochondrial function may be central to the development of insulin resistance and type 2 diabetes. It has been hypothesised that impaired mitochondrial function reduces the ability of muscle to metabolise fatty acids. The associated accumulation of fatty acids in skeletal muscle, in turn, impedes insulin action through inhibition of insulin receptors in skeletal muscle [1]. Increased physical activity has been shown to improve glucose control, fatty acid oxidation and helps prevent weight gain in people with type 2 diabetes [2]: the mechanisms by which glucose control improves are poorly characterised. To better understand the relationship between diabetes, physical activity and mitochondrial function, the present study observed whether there were differences in basal and maximal mitochondrial activity in people with well controlled type 2 diabetes and people without diabetes. We then observed the influence of 8 weeks of increased physical activity upon basal and maximal mitochondrial activity, resting metabolism and body weight.

Table 1 : Subject characteristics

	Control *n = 10*	T2D *n = 10*	P
Age (yrs)	56 (2)	59 (2)	n/s
Weight (kg)	88 (4)	91 (4)	n/s
Daily energy expenditure (cal/day)	2876 (114)	2888 (218)	n/s
HbA1c (%)	5.6 (0.1)	6.6 (0.3)	< 0.01
FPG (mmol/l)	5.7 (0.1)	7.1 (0.4)	< 0.01
Insulin (μU/l)	8 (1)	14 (4)	n/s

Methods: *Patients:* 10 controls (CON) and 10 patients with type 2 diabetes (T2D) were recruited, matched for age and sedentary physical activity. All subjects were counselled to add 1 hour of brisk walking to their daily routine for a period of 8 weeks. Physical activity, indirect calorimetry and MRS measurement of basal and maximal ATP synthesis were made at baseline and after 8 weeks of the exercise intervention. Blood samples were taken to characterise glucose control by HbA1c (a measure of medium-term blood glucose), fasting plasma glucose (FPG) and fasting insulin level. (Table 1). *Physical activity*: Physical activity was assessed over 3 days using a SenseWear Body Monitoring System (Bodymedia, Pittsburgh, USA). Data are presented as the mean daily number of steps and mean daily calorie expenditure. *Indirect Calorimetery*: Expired gases were collected from a constant-flow hood calorimeter (Deltatrac, Datex Ohmeda, Hertfordsire, UK) whilst the volunteer lay awake quietly for 30 minutes. Substrate oxidation rates and energy expenditure were calculated from oxygen consumption and carbon dioxide production values using stoichiometric equations [3] over the final 20 minutes. *MRS acquisition*: MRS data were acquired using a 3T Intera Achieva scanner (Philips, Best, NL) with a 14cm diameter surface coil for acquisition of phosphorus data. *ATP synthase flux*: A saturation transfer was used to measure transfer between γ-ATP and inorganic phosphate in the gastrocnemius and soleus. The steady-state magnetization of P_i was measured during selective continuous irradiation of the γ-ATP resonance, M_z, and compared to the equilibrium Pi magnetization with the selective irradiation placed symmetrically downfield from the P_i frequency, M_o (TR = 25s). The fractional reduction of Pi magnetization upon saturation of γ-ATP, $(M_o\text{-}M_z)/M_o$, was used to calculate the pseudo-first order rate constant using the Forsen-Hoffman equation, $k_1 = [(M_o\text{-}M_z)/M_o](1/T_1^*)$ where T_1^* is the spin-lattice relaxation time for P_i during saturation of γ-ATP. *Phosphorus measurement during exercise*: A purpose-built in-magnet exercise apparatus was developed. Subjects performed an exercise protocol consisting of 3 minutes rest, 3 minutes of plantar flexion at 0.5Hz and 3 minutes of rest to measure recovery to equilibrium. The exercise used a fixed load of 30% of the maximum voluntary contraction to accurately measure oxidative metabolism in recovery whilst changing pH levels as little as possible [4]. Phosphorus spectra were collected at 10s intervals throughout the exercises. Quantification of phosphocreatine (PCr), inorganic phosphate and pH was performed using AMARES. Standard methods were used to derive the half-time for PCr recovery [4].

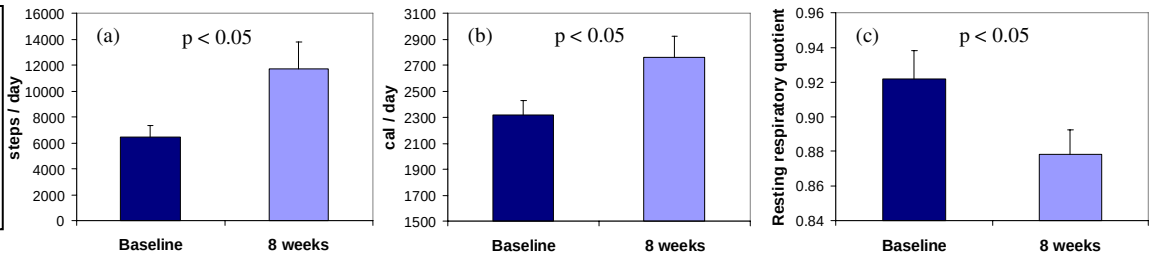

Fig 1: T2D subject (a) steps per day, (b) daily calorie expenditure and (c) resting respiratory quotient at baseline and after 8 weeks of the physical activity intervention

Results: (i) At baseline it was found that there was no significant differences between the CON and T2D groups in either basal ATP turnover (CON: 12.0 ± 1.4 vs T2D 11.7 ± 1.2 μmol/g/min tissue, ns) or maximal ATP turnover, as represented by the half-time for PCr recovery (CON: 30.8 ± 4.8 vs T2D 29.2 ± 3.1s, ns).
(ii) Following physical activity counselling, people with T2D were able to sustain an increase in physical activity for the 8 weeks period, shown by an increase in the number of steps per day ($p < 0.05$, fig 1a) and daily energy expenditure ($p < 0.05$, fig 1b). The resting respiratory quotient was significantly reduced ($p < 0.05$, fig 1c), indicating enhanced lipid oxidation. The weight of the T2D group fell by an average of 1.2 ± 0.6 kg after the physical activity ($p < 0.05$, fig 2a).
(iii) Neither the basal ATP turnover (fig 2b) or the maximal ATP turnover (fig 2c) was altered by the physical activity in the T2D subjects, suggesting that the benefits of increased physical activity were achieved independent of change in mitochondrial activity.
(iv) It was found that there was no correlation between the basal ATP demand (saturation transfer) and maximal ATP demand as measured by recovery from aerobic exercise ($\kappa = 0.04$; $p = 0.752$): it is believed that this is the first human study in which both have been measured.

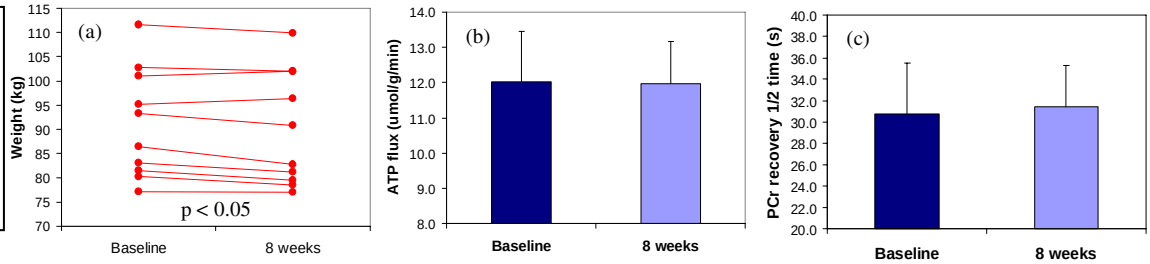

Fig 2: (a) Change in T2D subject weight (b) Basal ATP flux and (c) PCr recovery half time at baseline and after 8 weeks of the physical activity intervention

Conclusion: (i) There are no differences in resting or maximal ATP turnover, assessed using ^{31}P-MRS, in people with and without type 2 diabetes matched for physical activity, age and sex. (ii) People with type 2 diabetes can sustain a more physically active lifestyle following activity counselling. (iii) Increased physical activity may assist long term glucose control by increasing lipid oxidation, independent of changes in resting or maximal mitochondrial activity.

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