Evaluating the impact of physical exercise on mild Alzheimer's disease in a randomized clinical trial: quantification with 18F-FDG and 11C-AcAc PET imaging

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PRINCIPAL INVESTIGATORS and CO-INVESTIGATORS:

Stephen Cunnane, PhD
Nancy Paquet, MD, FRCPC
Christian Bocti, MD, FRCPC
Guy Lacombe, MD, FRCPC
Hélène Imbault, PhD

CONTRIBUTORS

Éric Lavallée, tim
Stéphanie Dubreuil, research assistant
Maxime Gravel, MD
Eric Turcotte, MD, FRCPC
Tamas, Fulop, MD
Dionne, Isabelle, PhD
Catherine Brodeur, MD, FRCPC
Marie-Maxime Lavallée, student
Christian-Alexandre Castellano, PhD, research assistant
Mathieu Maltais, kinesiologist
Mélanie Fortier, research assistant
Esteban Espinosa, nuclear medicine technologist
Etienne Croteau, PhD, nuclear medicine technologist
Christine Brodeur-Dubreuil, research nurse

Centre d'imagerie moléculaire de Sherbrooke (CIMS) ; Centre de recherche clinique (CRC) ; Centre Hospitalier Universitaire de Sherbrooke (CHUS) ; Centre de recherche sur le vieillissement (CDRV) ; Centre de santé et de service sociaux – Institut universitaire de gériatrie de Sherbooke (CSSS-IUGS)

Participants

This study was conducted with the informed written consent of all the participants and was approved by the appropriate ethics committees (Health and Social Services Center – Sherbrooke University Geriatrics Institute and the Centre hospitalier universitaire de Sherbrooke). The original research protocol included two groups: a Walking group and a sedentary Control group. Patients were diagnosed as having probable or possible AD dementia using conventional NINCDS-ADRDA criteria. They were referred to this study by a geriatrician or a neurologist from the Memory Disorders Clinic at Health and Social Services Center – Sherbrooke University Geriatrics Institute or a physician from the Sherbrooke University Hospital Center (CIUSSS de l'Estrie - CHUS) between January, 2010 and September, 2015. All prospective participants had to normally be sedentary *e.g.* not following a structured physical activity or training more than 30 min twice a week. Exclusion criteria included an MMSE score <20/30, drug addiction, alcohol use disorder, depression, smoking, diabetes, evidence of overt heart, liver or renal disease, and uncontrolled hypertension, dyslipidemia, or thyroid disease. All participants were taking an acetylcholinesterase inhibitor (Donepezil, Galantamine or Rivastigmine) for at least 3 months prior to study enrollment. Six were medicated for hypothyroid disorder (Levothyroxine) and eight for dyslipidemia (Pravastatin, Simvastatin, Rosuvastatin or Atorvastatin).

Walking program

Participants were trained to walk on motorized treadmills 3 days/wk for 12 weeks. Most of the walking sessions were conducted at the exercise facility at the Research Centre on Aging, under the supervision of a kinesiologist. For 3 participants, some training sessions were conducted from home, in which case a Polar FT2 watch with T31 heart rate sensor strap (Polar Electro, Kempele, Finland) was used to monitor exercise intensity and duration. The walking program was divided into two phases: phase one lasted 6 wks and consisted of a gradual increase of the duration of the training from 15 min per session in Week 1, to 40 min per session in Week 6 (adding 5 min weekly); phase two lasted 6 wks and consisted of 40 min training sessions. The objective of each training session was to achieve 60% of maximum heart rate (pulse of 120 beats/min [bpm]) and a perceived exertion at level 12-14 on the Borg scale, e.g. mild shortness of breath while still being able to speak during exercise. Heart rate reserve was determined during the pre-intervention visit.

Neuroimaging protocol

To measure brain 18F-FDG and 11C-AcAc uptake, a previously described dynamic PET imaging protocol was chosen. Participants underwent a T1-weighted magnetic resonance image (MRI; scan duration = 9.14 min, TR = 16.00 ms, TE = 4.68 ms, field of view = 256 x 240 x 192 mm, matrix size = 256 x 256 x 164, flip angle = 20° and 1 mm isotropic voxels) on a 1.5 Tesla scanner (Sonata, Siemens Medical Solutions, Erlangen, Germany). All participants also underwent a brain dynamic acquisition (2 mm isotropic voxels, field of view = 25 cm and axial field = 18 cm) on a dual PET-CT Philips Gemini TF scanner (Philips Medical System, Eindhoven, The Netherlands). The PET scans were done twice, once at the beginning (Baseline) and once at the end of the 3-month aerobic training period (Walking). Briefly, for each scan, after a fasting period of 6-7 h after breakfast, the participant was positioned in the PET-CT scanner in the early afternoon in a dark quiet environment. After intravenous administration of 248 ± 89 MBq of 11C-AcAc via a forearm vein catheter, dynamic scans were obtained over a total duration of 10 min (time frames 12 x 10 sec, 8 x 30 seconds, and 1 x 4 minutes). After a 60 min wash-out period, an IV dose of 189 ± 26 MBq of 18F-FDG was administered and PET images were acquired over 60 min (time frames = 12 x 10 sec, 8 x 30 s sec, 6 x 4 min, and 3 x 10 min).

Quantification of cerebral acetoacetate and glucose consumption

Cerebral 11C-AcAc and 18F-FDG PET images were analyzed using PMOD 3.7 (PMOD Technologies Ltd., Zurich, Switzerland) as previously described. Briefly, cerebral metabolic rate (CMR; [µmoles/100 g/min]) of acetoacetate and glucose (CMRacac and CMRglu, respectively) were quantified according to the graphical analysis method developed by Patlak et al.[26] based on the plasma time-activity curves determined from the blood samples obtained during the 11C-AcAc and 18F-FDG PET scans. The following equation was used: CMR = K*Cp/LC , where K is the rate constant for net uptake of the tracer, Cp is the plasma tracer, and LC is the lumped constant ; The LC of CMRacac and CMRglu were set to 1.0 and 0.8, respectively[18, 27]. Brain segmentation was defined by Freesurfer parcellation labels (Freesurfer Suite 5.0). Brain 3D projections of parametric maps of CMRacac and CMRglu were visualized using MIM Neuro (MIM Software Inc., Cleveland, OH, USA).

Biochemical analysis

Most plasma metabolites were measured using an automated clinical chemistry analyzer (Dimension Xpand Plus; Siemens Healthcare Diagnostics, Deerfield, IL, USA). Plasma concentrations of homocysteine were analyzed by high performance liquid chromatography (Agilent technologies Santa Clara, CA, USA). Plasma insulin was analyzed by commercial enzyme-linked immunosorbent assay (Alpco, Salem, NH, USA) with a Victor X4 multi-label plate reader (Perkin Elmer, Woodbridge, ON, Canada). The homeostasis model assessment method was used to estimate insulin resistance (HOMA-IR) from fasting plasma glucose and insulin.

Statistical methods

We established from our previous work and from others that with an increase of blood ketones of 2-fold, a sample size of n=10 would provide the required 80% power ($p < 0.05$) to detect a pre- to post-walking difference in the primary outcome - global CMRacac. Data are presented as mean ± SD. All statistical analyses were carried out using SPSS 24.0 software (SPSS Inc, Chicago, IL, USA). A Wilcoxon signed rank test was used to compare difference between the pre- and the post-walking measurements with a statistical threshold of $p \leq 0.05$.

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