2018-2019

THÈSE

pour le

DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

Qualification en MEDECINE GENERALE

Concentration sérique en vitamine D et contrôle cognitif de la marche : résultats de la cohorte MERE

Serum vitamin D and cognitive gait control: The French MERE cohort study

BANNIER Adeline

Né le 12 Avril 1991 à ANGERS (49)

Sous la direction de M. DUVAL Guillaume

Membres du jury

Monsieur le Professeur GARNIER François	Président
Monsieur le Docteur DUVAL Guillaume	Directeur
Monsieur le Professeur ANNWEILER Cédric	Membre
Monsieur le Professeur ABRAHAM Pierre	Membre

Soutenue publiquement le :
11 Avril 2019

FACULTÉ DE SANTÉ
UNIVERSITÉ D'ANGERS

ENGAGEMENT DE NON PLAGIAT

Je, soussigné(e) BANNIER Adeline
déclare être pleinement conscient(e) que le plagiat de documents ou d'une partie d'un document publiée sur toutes formes de support, y compris l'internet, constitue une violation des droits d'auteur ainsi qu'une fraude caractérisée.
En conséquence, je m'engage à citer toutes les sources que j'ai utilisées pour écrire ce rapport ou mémoire.

signé par l'étudiant(e) le **11/04/2019**

LISTE DES ENSEIGNANTS DE LA FACULTÉ DE SANTÉ D'ANGERS

Doyen de la Faculté : Pr Nicolas Lerolle
Vice-Doyen de la Faculté et directeur du département de pharmacie : Pr Frédéric Lagarce
Directeur du département de médecine : Pr Cédric Annweiler

PROFESSEURS DES UNIVERSITÉS

ABRAHAM Pierre	Physiologie	Médecine
ANNWEILER Cédric	Gériatrie et biologie du vieillissement	Médecine
ASFAR Pierre	Réanimation	Médecine
AUBE Christophe	Radiologie et imagerie médicale	Médecine
AUGUSTO Jean-François	Néphrologie	Médecine
AZZOUZI Abdel Rahmène	Urologie	Médecine
BAUFRETON Christophe	Chirurgie thoracique et cardiovasculaire	Médecine
BENOIT Jean-Pierre	Pharmacotechnie	Pharmacie
BEYDON Laurent	Anesthésiologie-réanimation	Médecine
BIGOT Pierre	Urologie	Médecine
BONNEAU Dominique	Génétique	Médecine
BOUCHARA Jean-Philippe	Parasitologie et mycologie	Médecine
BOUVARD Béatrice	Rhumatologie	Médecine
BOURSIER Jérôme	Gastroentérologie ; hépatologie	Médecine
BRIET Marie	Pharmacologie	Médecine
CAILLIEZ Eric	Médecine générale	Médecine
CALES Paul	Gastroentérologe ; hépatologie	Médecine
CAMPONE Mario	Cancérologie ; radiothérapie	Médecine
CAROLI-BOSC François-xavier	Gastroentérologie ; hépatologie	Médecine
CHAPPARD Daniel	Cytologie, embryologie et cytogénétique	Médecine
CONNAN Laurent	Médecine générale	Médecine
COUTANT Régis	Pédiatrie	Médecine
COUTURIER Olivier	Biophysique et médecine nucléaire	Médecine
CUSTAUD Marc-Antoine	Physiologie	Médecine
DE BRUX Jean-Louis	Chirurgie thoracique et	Médecine
DE CASABIANCA Catherine	cardiovasculaire Médecine Générale	Médecine
DESCAMPS Philippe	Gynécologie-obstétrique	Médecine
DINOMAIS Mickaël	Médecine physique et de réadaptation	Médecine
DIQUET Bertrand	Pharmacologie	Médecine
DUBEE Vincent	Maladies Infectieuses et Tropicales	Médecine

DUCANCELLE Alexandra	Bactériologie-virologie ; hygiène hospitalière	Médecine
DUVAL Olivier	Chimie thérapeutique	Pharmacie
DUVERGER Philippe	Pédopsychiatrie	Médecine
EVEILLARD Mathieu	Bactériologie-virologie	Pharmacie
FANELLO Serge	Épidémiologie ; économie de la santé et prévention	Médecine
FAURE Sébastien	Pharmacologie physiologie	Pharmacie
FOURNIER Henri-Dominique	Anatomie	Médecine
FURBER Alain	Cardiologie	Médecine
GAGNADOUX Frédéric	Pneumologie	Médecine
GARNIER François	Médecine générale	Médecine
GASCOIN Géraldine	Pédiatrie	Médecine
GOHIER Bénédicte	Psychiatrie d'adultes	Médecine
GUARDIOLA Philippe	Hématologie ; transfusion	Médecine
GUILET David	Chimie analytique	Pharmacie
HAMY Antoine	Chirurgie générale	Médecine
HUNAULT-BERGER Mathilde	Hématologie ; transfusion	Médecine
IFRAH Norbert	Hématologie ; transfusion	Médecine
JEANNIN Pascale	Immunologie	Médecine
KEMPF Marie	Bactériologie-virologie ; hygiène hospitalière	Médecine
LACCOURREYE Laurent	Oto-rhino-laryngologie	Médecine
LAGARCE Frédéric	Biopharmacie	Pharmacie
LARCHER Gérald	Biochimie et biologie moléculaires	Pharmacie
LASOCKI Sigismond	Anesthésiologie-réanimation	Médecine
LEGENDRE Guillaume	Gynécologie-obstétrique	Médecine
LEGRAND Erick	Rhumatologie	Médecine
LERMITE Emilie	Chirurgie générale	Médecine
LEROLLE Nicolas	Réanimation	Médecine
LUNEL-FABIANI Françoise	Bactériologie-virologie ; hygiène hospitalière	Médecine
MARCHAIS Véronique	Bactériologie-virologie	Pharmacie
MARTIN Ludovic	Dermato-vénéréologie	Médecine
MENEI Philippe	Neurochirurgie	Médecine
MERCAT Alain	Réanimation	Médecine
MERCIER Philippe	Anatomie	Médecine
PAPON Nicolas	Parasitologie et mycologie médicale	Pharmacie
PASSIRANI Catherine	Chimie générale	Pharmacie
PELLIER Isabelle	Pédiatrie	Médecine
PETIT Audrey	Médecine et Santé au Travail	Médecine
PICQUET Jean	Chirurgie vasculaire ; médecine vasculaire	Médecine
PODEVIN Guillaume	Chirurgie infantile	Médecine
PROCACCIO Vincent	Génétique	Médecine
PRUNIER Delphine	Biochimie et Biologie Moléculaire	Médecine
PRUNIER Fabrice	Cardiologie	Médecine
REYNIER Pascal	Biochimie et biologie moléculaire	Médecine

RICHARD Isabelle	Médecine physique et de réadaptation	Médecine
RICHOMME Pascal	Pharmacognosie	Pharmacie
RODIEN Patrice	Endocrinologie, diabète et maladies métaboliques	Médecine
ROQUELAURE Yves	Médecine et santé au travail	Médecine
ROUGE-MAILLART Clotilde	Médecine légale et droit de la santé	Médecine
ROUSSEAU Audrey	Anatomie et cytologie pathologiques	Médecine
ROUSSEAU Pascal	Chirurgie plastique, reconstructrice et esthétique	Médecine
ROUSSELET Marie-Christine	Anatomie et cytologie pathologiques	Médecine
ROY Pierre-Marie	Thérapeutique	Médecine
SAULNIER Patrick	Biophysique et biostatistique	Pharmacie
SERAPHIN Denis	Chimie organique	Pharmacie
SUBRA Jean-François	Néphrologie	Médecine
UGO Valérie	Hématologie ; transfusion	Médecine
URBAN Thierry	Pneumologie	Médecine
VAN BOGAERT Patrick	Pédiatrie	Médecine
VENIER-JULIENNE Marie-Claire	Pharmacotechnie	Pharmacie
VERNY Christophe	Neurologie	Médecine
WILLOTEAUX Serge	Radiologie et imagerie médicale	Médecine

MAÎTRES DE CONFÉRENCES

ANGOULVANT Cécile	Médecine Générale	Médecine
ANNAIX Véronique	Biochimie et biologie moléculaires	Pharmacie
BAGLIN Isabelle	Chimie thérapeutique	Pharmacie
BASTIAT Guillaume	Biophysique et biostatistique	Pharmacie
BEAUVILLAIN Céline	Immunologie	Médecine
BELIZNA Cristina	Médecine interne	Médecine
BELLANGER William	Médecine générale	Médecine
BELONCLE François	Réanimation	Médecine
BENOIT Jacqueline	Pharmacologie	Pharmacie
BIERE Loïc	Cardiologie	Médecine
BLANCHET Odile	Hématologie ; transfusion	Médecine
BOISARD Séverine	Chimie analytique	Pharmacie
CAPITAIN Olivier	Cancérologie ; radiothérapie	Médecine
CASSEREAU Julien	Neurologie	Médecine
CHEVAILLER Alain	Immunologie	Médecine
CHEVALIER Sylvie	Biologie cellulaire	Médecine
CLERE Nicolas	Pharmacologie / physiologie	Pharmacie
COLIN Estelle	Génétique	Médecine
DERBRE Séverine	Pharmacognosie	Pharmacie

DESHAYES Caroline	Bactériologie virologie	Pharmacie
FERRE Marc	Biologie moléculaire	Médecine
FLEURY Maxime	Immunologie	Pharmacie
FORTRAT Jacques-Olivier	Physiologie	Médecine
HAMEL Jean-François	Biostatistiques, informatique médicale	Médicale
HELESBEUX Jean-Jacques	Chimie organique	Pharmacie
HINDRE François	Biophysique	Médecine
JOUSSET-THULLIER Nathalie	Médecine légale et droit de la santé	Médecine
LACOEUILLE Franck	Biophysique et médecine nucléaire	Médecine
LANDREAU Anne	Botanique/ Mycologie	Pharmacie
LEBDAI Souhil	Urologie	Médecine
LEGEAY Samuel	Pharmacocinétique	Pharmacie
LE RAY-RICHOMME Anne-Marie	Pharmacognosie	Pharmacie
LEPELTIER Elise	Chimie générale	Pharmacie
LETOURNEL Franck	Biologie cellulaire	Médecine
LIBOUBAN Hélène	Histologie	Médecine
MABILLEAU Guillaume	Histologie, embryologie et cytogénétique	Médecine
MALLET Sabine	Chimie Analytique	Pharmacie
MAROT Agnès	Parasitologie et mycologie médicale	Pharmacie
MAY-PANLOUP Pascale	Biologie et médecine du développement et de la reproduction	Médecine
MESLIER Nicole	Physiologie	Médecine
MOUILLIE Jean-Marc	Philosophie	Médecine
NAIL BILLAUD Sandrine	Immunologie	Pharmacie
PAILHORIES Hélène	Bactériologie-virologie	Médecine
PAPON Xavier	Anatomie	Médecine
PASCO-PAPON Anne	Radiologie et imagerie médicale	Médecine
PECH Brigitte	Pharmacotechnie	Pharmacie
PENCHAUD Anne-Laurence	Sociologie	Médecine
PIHET Marc	Parasitologie et mycologie	Médecine
PY Thibaut	Médecine Générale	Médecine
RINEAU Emmanuel	Anesthésiologie réanimation	Médecine
RIOU Jérémie	Biostatistiques	Pharmacie
ROGER Emilie	Pharmacotechnie	Pharmacie
SAVARY Camille	Pharmacologie-Toxicologie	Pharmacie
SCHMITT Françoise	Chirurgie infantile	Médecine
SCHINKOWITZ Andréas	Pharmacognosie	Pharmacie
SPIESSER-ROBELET Laurence	Pharmacie Clinique et Education Thérapeutique	Pharmacie
TANGUY-SCHMIDT Aline	Hématologie ; transfusion	Médecine
TESSIER-CAZENEUVE Christine	Médecine Générale	Médecine
TRZEPIZUR Wojciech	Pneumologie	Médecine

AUTRES ENSEIGNANTS

AUTRET Erwan	Anglais	Médecine
BARBEROUSSE Michel	Informatique	Médecine
BRUNOIS-DEBU Isabelle	Anglais	Pharmacie
CHIKH Yamina	Économie-Gestion	Médecine
FISBACH Martine	Anglais	Médecine
O'SULLIVAN Kayleigh	Anglais	Médecine

PAST

CAVAILLON Pascal	Pharmacie Industrielle	Pharmacie
LAFFILHE Jean-Louis	Officine	Pharmacie
MOAL Frédéric	Pharmacie clinique	Pharmacie

ATER

FOUDI Nabil	Physiologie	Pharmacie
KILANI Jaafar	Biotechnologie	Pharmacie
WAKIM Jamal	Biochimie et chimie biomoléculaire	Médecine

AHU

BRIS Céline	Biochimie et biologie moléculaire	Pharmacie
CHAPPE Marion	Pharmacotechnie	Pharmacie
LEBRETON Vincent	Pharmacotechnie	Pharmacie

CONTRACTUEL

VIAULT Guillaume	Chimie organique	Pharmacie

REMERCIEMENTS

Je remercie tous les membres du jury, les Professeurs GARNIER et ABRAHAM, pour le temps et l'attention qu'ils ont pu porter à mon travail.
Je remercie particulièrement le Professeur ANNWEILER, Doyen de la Faculté de Médecine d'Angers et Chef de service du Département de Médecine Gériatrique, de m'avoir offert cette opportunité de travail de recherche.

Un grand merci à mon directeur de Thèse, le Docteur Guillaume DUVAL, pour avoir passé de très nombreuses soirées à travailler sur ce projet.
Merci à Jennifer GAUTIER, biostatisticienne au département de Médecine Gériatrique, pour son implication et sa grande disponibilité.

Je remercie toute l'équipe médicale, paramédicale et scientifique du service de Gériatrie du Centre Hospitalier Universitaire d'ANGERS pour son aide et accompagnement dans ce projet.

Je remercie chaleureusement l'équipe médicale et paramédicale du service de Gériatrie du Centre Hospitalier du Mans pour son soutien.

Et bien sûr je remercie ma famille et mes amis, tout particulièrement mon mari, François, de m'avoir soutenue et de me soutenir encore pendant toutes ces heures et années de travail.

Liste des abréviations

25OHD:	25-hydroxyvitamin D
MMSE:	Mini Mental State Examination
STV:	Stride time variability
BMI:	Body Mass Index
IADL:	Instrumental Activities of Daily Living
PTH:	Parathyroid Hormon
FAB:	Frontal Assessment Battery
SD :	Standard Deviation
CI :	Confidence Interval

Plan

Serum vitamin D and cognitive gait control:

The French MERE cohort study

Adeline Bannier, BS [2]

Pierre Abraham, MD, PhD [1,3]

Mickaël Dinomais, MD, PhD [1,4]

Cedric Annweiler, MD, PhD [1,2,5]

Guillaume T Duval, MD, MSc [1,2]

On behalf of the SOCOS group

1: School of Medicine, University of Angers, France; 2: Department of Geriatric Medicine and Memory Clinic; Research Center of Autonomy and Longevity; UPRES EA 4638, Angers University Hospital, Angers, France; 3: Laboratory for Vascular Investigations; University Hospital, Angers, France. 4: Laboratoire Angevin de Recherche en Ingénierie des Systèmes (LARIS) - EA7315; University of Angers, France; 5: Robarts Research Institute, Department of Medical Biophysics, Schulich School of Medicine and Dentistry, the University of Western Ontario, London, ON, Canada

ABSTRACT

Background. Previous studies showed that hypovitaminosis D was associated with poor physical and gait performances. The association between vitamin D concentration and muscle capacities remains controversial. We suggested that hypovitaminosis D may influence gait performances through an action on the central cognitive component of gait control and especially executive functions. The objective of the present study was to determine whether hypovitaminosis D was associated with increased (i.e. worse) stride time variability while dual-tasking among older adults.

Methods. A subset of 1 566 subjects from the unicentric French 'MERE' cohort of 4865 subjects were used for this analysis. Serum 25OHD concentration was measured and stride-to-stride variability of stride time was defined by the coefficient of variation of stride time. The dual task was a verbal fluency task when walking. Age, gender, Body Mass Index, disability assessed by Instrumental Activities of Daily Living, number of co-morbidities, polymedication, use of vitamin D and psychotropic drugs, and biologic covariables such as creatinine level, parathyroid hormone concentrations, albuminemia, calcemia were used as potential confounders.

Results. Mean serum 25OHD concentration was 58.8±27.9nmol/L and the mean STV was 11.73±14.30%. The stride time variability (STV) during dual task and serum 25OHD concentration were significantly and inversely associated (β=-0.034, 95%CI [-0.062;-0.006], p=0.0169) in the multivariate linear regression model,.

Conclusions. Serum 25OHD concentration was inversely associated with STV during dual task walking as a marker of central cognitive component of gait control involving executive function. These results help to improve knowledge about the involvement of vitamin D in gait brain motor control.

INTRODUCTION

At least one billion people experiences hypovitaminosis D worldwide (1), with increasing prevalence with aging and reaching 70-90% in older adults (2). The clinical relevance is linked to the onset of various adverse health manifestations accompanying hypovitaminosis D, whether skeletal or non-skeletal such as motor disorders.

In particular, an association with gait performance has been reported repeatedly. Observational studies have shown that the lower the serum 25-hydroxyvitamin D (25OHD) concentration, the lower the gait velocity and the acceleration capacity (3,4). Interventional studies have reported a significant increase in walking distance after 6 months of vitamin D supplementation among older women with vitamin D deficiency at baseline (5,6). Several randomized clinical trials have also reported that such gait improvement in older adults resulted in a 15-20% reduction of the fall risk following vitamin D supplementation (5,7). The whole question is to understand how vitamin D, which is a secosteroid hormone classically involved in phosphocalcic bone metabolism (2,8), is able to influence gait performance.

Common proposed explanation is based on possible muscular action of vitamin D (9). It is yet noticeable that an association between vitamin D and muscle strength remains controversial as it is inconstantly described; some studies having reported an association between hypovitaminosis D and muscle weakness (10,11), while others did not (12). Therefore, we suggested that vitamin D may actually influence gait through an action on the central cognitive component of gait control (13); an assumption consistent with the recent finding of neurosteroid properties of vitamin D (14).

We hypothesized that hypovitaminosis D could be involved in impaired cognitive motor control, illustrated by gait disturbances while dual-tasking, a potent marker of cognitive motor control (15). We had the opportunity to examine the association of serum 25OHD concentration with gait variability under single- and dual-task in older participants with memory complaint from the

French MERE cohort. Our objective was to determine whether hypovitaminosis D was associated with increased (i.e. worse) stride time variability while dual-tasking among older adults.

MATERIALS AND METHODS

1. Study population

Data were collected from the 'Alzheimer's Disease and Related Disorders study' (MERE study) between December 2008 and March 2013 (ClinicalTrials.gov number, NCT01315704). The MERE study is an observational cohort study designed to examine gait changes in older adults with memory complaint visiting the University Memory Center of Angers, France. The sampling and data collection procedures have been described elsewhere in detail (16). In summary, subjective memory complaint was documented using the Subjective Memory Complaints Questionnaire (17), and the main exclusion criteria were Mini-Mental State Examination (MMSE) score ≤10 (18), inability to walk independently, history of any acute medical illness in the preceding 3 months, poor vision, inability to understand or answer the study questionnaires, and refusal to participate in research. Participants received a full medical examination, which consisted of structured questionnaires, a clinical examination, a blood test, and a gait analysis.

2. Explanatory variable: Serum vitamin D concentration

Blood samples were collected from resting participants. Serum 25OHD concentration, which effectively reflects the vitamin D status (3), was measured using radioimmunoassay (DiaSorin Inc., Stillwater, MN) in nmol/L (to convert in ng/mL, divide by 2.496) locally at Angers University Hospital. The intra- and interassay precision was 5.2% and 11.3% respectively. In contrary to other methods of analysis such as chromatography, with radioimmunoassay method of 25OHD concentration measuring, there is no lipids interference.

3. Dependent variable: Stride-to-stride variability of stride time

Stride time variability (STV, coefficient of variation of stride time = [mean/standard deviation] x 100) were measured using a computerized walkway with embedded pressure sensors (GAITRite®,

972 cm long, active electronic surface area 792x610 cm, with a total of 29,952 pressure sensors, scanning frequency 60 Hz, software version 3.8, CIR System, Havertown, PA). The GAITRite® system is a reliable tool for gait analysis that has been validated for several gait protocols, including gait variability assessment (19). Two walking conditions were successively measured in non-randomized order: walking at self-selected pace (i.e., single-task condition), and then walking while enumerating animal names (i.e., dual-task condition). Before each condition, a trained evaluator gave standardized verbal instructions to the participants. Participants walked in a quiet, well-lit room wearing their own footwear according to a validated protocol published elsewhere (19,20). To avoid acceleration and deceleration effects, participants started walking one meter before reaching the electronic walkway and completed their walk one meter beyond it.

Standard STV in healthy population is defined by a threshold under 5 percent.(4)

4. Covariates

The following clinical variables were included as potential confounders in the statistical models: age, sex, nutrition status, disability, number of co-morbidities, polymedication, use of psychoactive drugs and use of vitamin D drugs.

Nutrition status was evaluated with the Body Mass Index (BMI = weight in kg/size in m^2) using the same balance. Sub-groups were classified according to World Health Organization criteria. Disability was defined by Instrumental Activities of Daily Living (IADL) with a score ≤3/4 assessed at inclusion. Number of co-morbidities defined as diseases lasting ≥3months and running a course with minimal change, were recorded by the patient's history and using the computerized medical file. Polymedication (use of 5 medications or more) was recorded by independent investigator the same way as use of psychoactive drugs (use of antidepressants or benzodiazepines or neuroleptics or hypnotics) and the use of vitamin D drugs.

Biological covariates were also assessed such as: calcemia (mmol/L), creatinine level (µmol/L), parathyroid hormone (PTH) concentrations (pg/mL).

Executive functions were evaluated with the Frontal Assessment Battery (FAB) with a maximum score of 18.

Stride time variability during walk in simple task, expressed in percentage, has been used as covariate.

5. Statistical analysis

Characteristics of participants were summarized using medians and standard deviation (SD) or frequencies and percentage as appropriate. First, simple linear regression was performed to identify whether 25OHD could be associated with STV during dual-task. Second, multiple linear regression analyses were performed to specify the association between STV during dual task and serum 25OHD after adjusting on covariates. P-values less than 0.05 were considered statistically significant. All statistics were performed using Statistical Package for Social Sciences (version 15.0, IBM Corporation, Chicago, IL).

6. Ethics

Participants were included after having given their informed consent for research. The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983). The study protocol was approved by the local Ethical Committee (2009/15).

RESULTS

4 865 patients were received in consultation at the Memory Center of Angers from September 2009 to December 2018. One thousand five hundred and sixty-six patients were included in the present cohort after exclusion of patients with MMSE<10/30 or missing score (n=360) and exclusion of patients received in follow-up consultation (n=1 667), corresponding to exclusion criteria of the MERE protocol. Participants with one or more missing data were also excluded (n=1 272). (Figure 1) Among the 1 566 included patients, mean age was 79.48±7.2years and 56.77% were women. In the whole cohort, the mean serum 25OHD concentration was 58.8±27.9nmol/L and the mean STV was 11.73±14.30%. (Table 1) 42.4% presented disability, 51.21% suffered from polymedication and 36.21% used psychotropic drugs, 24.9% were treated with vitamin D supplementation, and the average of comorbidities was 3.01±2.0.

Calcemia was measured with an average concentration of 2.34±0.1mmol/L and mean serum 25OHD concentration was 58.82±27.90nmol/L. (Table 1)

As indicated in Table 2, the association between serum 25OHD concentration and STV during dual task in the univariate linear regression model was not significant but p-value was <0.2 (β=-0.018, 95%CI [-0.043;0.008], p=0.1695). In univariate linear regression model, STV in dual task was significantly and positively associated with age (β=0.343, 95%CI [0.245;0.440], p<0.0001), disability (β=4.605, 95%CI [3.189;6.022], p<0.0001), polymedication (β=2.373, 95%CI [0.959;3.786], p=0.0010), use of psychoactive drugs (β=2.666, 95%CI [1.197;4.136], p=0.0004), use of vitamin D drugs (β=2.253, 95%CI [0.618;3.889], p=0.0070) and number of comorbidities (β=0.947, 95%CI [0.596;1.298], p<0.0001). STV in dual task was higher in patient with undernutrition than patients with normal BMI (β=0.343, 95%CI [0.245;0.440], p<0.0001). STV during dual task was significantly and negatively associated with Frontal Assessment Battery (FAB) (β=-0.613, 95%CI [-0.823;-0.403], p<0.0001).

In the multivariate linear regression model, STV during dual task and serum 25OHD concentration were significantly and inversely associated (β=-0.034, 95%CI [-0.062;-0.006], p=0.0169).

(Table 2) STV during dual task was positively associated with age (β=0.134, 95%CI [0.013;0.255], p=0.0305), use of vitamin D drugs (β=2.330, 95%CI [0.530;4.130], p=0.0112), the number of comorbidities (β=0.482, 95%CI [0.102;0.863], p=0.0130), and STV during walk in simple task (β=0.602, 95%CI [0.459;0.745], p<0.0001). STV in dual task was higher in patient with undernutrition than patients with normal BMI (β=-2.936, 95%CI [-5.619;-0.254], p=0.0319).

DISCUSSION AND CONCLUSION

The main result of this study in 1 566 older people was the finding of an inverse association, after adjustment on potential confounding factors, between serum 25OHD concentration and STV while dual-tasking. Since STV is a potent marker of high-level gait control together with a marker of fall risk (22,23), the present finding suggests a link between vitamin D and gait control, with potential interesting clinical implications on fall and disability prevention.

In the past decade, some previous studies have already found a relationship between vitamin D and gait performance (9,24). In animal studies, Kalueff et al. showed that vitamin D receptor knockout mice exhibited major motor control disorders (25). In humans, the most studied link is between vitamin D and gait velocity (26). Most studies have reported a positive association between serum 25OHD concentration and gait velocity (3,26), whether at usual or fast pace. These results were important because confirming vitamin D involvement in motor performance (27). Of note, an association was also retrieved between serum 25OHD concentration and STV (27), a marker of high-level gait control, confirming that vitamin D is associated not only with muscle power but also with brain motor control. However, to our knowledge, previous studies did not evaluate such link while dual-tasking. Thus, our results support new information by showing that vitamin D is associated with STV sensitized by the dual task, which highlights even more clearly the involvement of vitamin D in gait control at the cortical level.

Exactly how vitamin D and cortical gait control are associated and if this association is causal remains not fully elucidated. On one hand, it can be assumed that gait disorders lead to a lack of sunlight exposure, which in turn result in low serum 25OHD concentrations. However, this first assumption needs to be mitigated by the fact that experimentation supports a role for vitamin D in Central Nervous System. Animal experiments have shown that vitamin D has neurotrophic, neuroprotective and immunomodulating properties and is involved in neurotransmitter metabolism and the synthesis of certain growth factors (14,28,29). A scenario of reverse causation is thus plausible and should be considered. Supporting this second assumption,

previous studies have reported a link between hypovitaminosis D and incidental dysexecutive decline (18). Executive functions are cognitive processes that include heterogeneous afferents required to execute complex tasks such as walking (30). The dual-task solicits executive functions by recruiting additional attention capacities when a secondary task is added to a primary task such as gait control (22). Thus, finding an association between serum 25OHD and STV while dual-tasking in the present study is fully consistent with previous studies reporting associations between serum 25OHD and executive functioning, and reinforces the assumption that vitamin D influences the biology of gait control. Similarly, a previous study by Lopez et al. also reported a decline in the performance of the second task in the case of hypovitaminosis D (31).

Our result also showed that dual-task STV was positively associated with advance in age, a greater number of comorbidities and with single-task STV, and was higher in the case of undernutrition. These results are consistent with previous literature (32), which strengthens the credibility of our primary result.

However, our study has some limitations. First, it took place in one single memory center and included only community-dwellers with subjective memory complaint. Thus, the studied population may be not representative of the general population of older adults. Second, although we were able to control for many characteristics likely to modify the association between vitamin D and STV while dual-tasking, residual confounders might be still present, such as the listing of arthritic manifestations (33). Third, the cross-sectional design did not allow any causal inferences. For instance, higher dual-task STV may lead to a loss of independency with low dietary intakes of vitamin D and a lack of sunlight exposure, which in turn leads to low vitamin D status. Hence, further longitudinal studies are needed to follow up on our initial promising results to address issues of causality. Fourth, although we assessed the main components involved in gait control, residual components of gait control could be missed.

Lower serum 25OHD concentrations were associated with higher dual-task STV, which is a potent measure of cortical gait control. Thus, older adults with gait disorders while dual-tasking should

be checked for hypovitaminosis D and substituted if necessary. Our results add a new orientation of research into understanding how vitamin D affects motor coordination and locomotion.

REFERENCES

1. Holick MF. Vitamin D Deficiency. N Engl J Med. 2007 Jul 19;357(3):266–81.

2. Annweiler C, Souberbielle J-C, Schott A-M, de Decker L, Berrut G, Beauchet O. Vitamine D chez la personne âgée: les 5 points à retenir. Geriatr Psychol Neuropsychiatr Vieil. 2011;9(3):259–267.

3. Annweiler C, Schott A-M, Montero-Odasso M, Berrut G, Fantino B, Herrmann FR, et al. Cross-sectional association between serum vitamin D concentration and walking speed measured at usual and fast pace among older women: The EPIDOS study. J Bone Miner Res. 2010 Aug;25(8):1858–66.

4. Suzuki T, Kwon J, Kim H, Shimada H, Yoshida Y, Iwasa H, et al. Low Serum 25-Hydroxyvitamin D Levels Associated With Falls Among Japanese Community-Dwelling Elderly. J Bone Miner Res. 2008;23(8):1309–17.

5. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, Orav JE, Stuck AE, Theiler R, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ. 2009 Oct 1;339(oct01 1):b3692–b3692.

6. Verhaar HJ, Samson MM, Jansen PA, de Vreede PL, Manten JW, Duursma SA 2000. Muscle strength, functional mobility and vitamin D in older women. Aging (Milano) 2000; 12: 455-60.

7. Kalyani RR, Stein B, Valiyil R, Manno R, Maynard JW, Crews D. Vitamin D Treatment for the Prevention of Falls in Older Adults: Systematic Review and Meta-Analysis. J Am Geriatr Soc. 2010 Jul;58(7):1299–310.

8. Bischoff-Ferrari HA, Willett WC, Wong JB, Stuck AE, Staehelin HB, Orav EJ, et al. Prevention of Nonvertebral Fractures With Oral Vitamin D and Dose Dependency: A Meta-analysis of Randomized Controlled Trials. Arch Intern Med. 2009 Mar 23;169(6):551–61.

9. Annweiler C, Montero-Odasso M, Schott AM, Berrut G, Fantino B, Beauchet O. Fall prevention and vitamin D in the elderly: an overview of the key role of the non-bone effects. J NeuroEngineering Rehabil. 2010 Oct 11;7:50.

10. Bischoff HA, Stahelin HB, Urscheler N, Ehrsam R, Vonthein R, Perrig-Chiello P, et al. Muscle strength in the elderly: Its relation to vitamin d metabolites. Arch Phys Med Rehabil. 1999 Jan;80(1):54–8.

11. Mowé M, Haug E, Bøhmer T. Low Serum Calcidiol Concentration in Older Adults with Reduced Muscular Function. J Am Geriatr Soc. 1999;47(2):220–6.

12. Annweiler C, Schott-Petelaz AM, Berrut G, Kressig RW, Bridenbaugh S, Herrmann FR, et al. Vitamin D Deficiency–Related Quadriceps Weakness: Results of the Epidémiologie De L'ostéoporose Cohort. J Am Geriatr Soc. 2009;57(2):368–9.

13. Annweiler C, Beauchet O, Bartha R, Hachinski V, Montero-Odasso M, Knowledge) on behalf of the WT (Working group A-L for. Vitamin D and Caudal Primary Motor Cortex: A Magnetic Resonance Spectroscopy Study. PLOS ONE. 2014 Jan 31;9(1):e87314.

14. Annweiler C, Schott A-M, Berrut G, Chauviré V, Le Gall D, Inzitari M, et al. Vitamin D and Ageing: Neurological Issues. Neuropsychobiology. 2010;62(3):139–50.

15. Annweiler C, Beauchet O, Bartha R, Wells JL, Borrie MJ, Hachinski V, et al. Motor cortex and gait in mild cognitive impairment: a magnetic resonance spectroscopy and volumetric imaging study. Brain. 2013 Mar 1;136(3):859–71.

16. Beauchet O, Launay CP, Allali G, Watfa G, Gallouj K, Herrmann FR, et al. Anti-dementia drugs and changes in gait: a pre-post quasi-experimental pilot study. BMC Neurol. 2013 Nov 21;13:184.

17. Vannier-Nitenberg C, Dauphinot V, Bongue B, Sass C, Rouch I, Beauchet O, et al. Early detection of memory impairment in people over 65 years old consulting at Health Examination Centers for the French health insurance: the EVATEM protocol. BMC Geriatr. 2013 Jun 6;13:55.

18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". J Psychiatr Res. 1975 Nov;12(3):189–98.

19. Montero-Odasso M, Casas A, Hansen KT, Bilski P, Gutmanis I, Wells JL, et al. Quantitative gait analysis under dual-task in older people with mild cognitive impairment: a reliability study. J NeuroEngineering Rehabil. 2009 Sep 21;6:35.

20. Kressig RW, Beauchet O, European GAITRite Network Group. Guidelines for clinical applications of spatio-temporal gait analysis in older adults. Aging Clin Exp Res. 2006 Apr;18(2):174–6.

21. Dubost V, Kressig RW, Gonthier R, Herrmann FR, Aminian K, Najafi B, et al. Relationships between dual-task related changes in stride velocity and stride time variability in healthy older adults. Hum Mov Sci. 2006 Jun 1;25(3):372–82.

22. Olivier Beauchet, Véronique Dubost, Kamiar Aminian, Regis Gonthier, Reto W. Kressig. Dual-Task-Related Gait Changes in the Elderly: Does the Type of Cognitive Task Matter? J Mot Behav. 2005 Jul;37(4):259–64.

23. Sheridan PL, Solomont J, Kowall N, Hausdorff JM. Influence of Executive Function on Locomotor Function: Divided Attention Increases Gait Variability in Alzheimer's Disease. J Am Geriatr Soc. 2003 Nov 1;51(11):1633–7.

24. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, et al. Effect of Vitamin D on Falls: A Meta-analysis. JAMA. 2004 Apr 28;291(16):1999.

25. Kalueff AV, Lou Y-R, Laaksi I, Tuohimaa P. Impaired motor performance in mice lacking neurosteroid vitamin D receptors. Brain Res Bull. 2004 Jul 30;64(1):25–9.

26. Annweiler C, Henni S, Walrand S, Montero-Odasso M, Duque G, Duval GT. Vitamin D and walking speed in older adults: Systematic review and meta-analysis. Maturitas. 2017 Dec 1;106:8–25.

27. Beauchet O, Annweiler C, Verghese J, Fantino B, Herrmann FR, Allali G. Biology of gait control: Vitamin D involvement. Neurology. 2011 May 10;76(19):1617–22.

28. Buell JS, Dawson-Hughes B. Vitamin D and Neurocognitive Dysfunction: Preventing "D"ecline? Mol Aspects Med. 2008 Dec;29(6):415–22.

29. Kalueff AV, Tuohimaa P. Neurosteroid hormone vitamin D and its utility in clinical nutrition: Curr Opin Clin Nutr Metab Care. 2007 Jan;10(1):12–9.

30. Beauchet O, Annweiler C, Montero-Odasso M, Fantino B, Herrmann FR, Allali G. Gait control: a specific subdomain of executive function? J NeuroEngineering Rehabil. 2012 Feb 9;9:12.

31. Lopez J, Campa A, Lewis JE, Huffman FG, Liuzzi JP, Li T, et al. Assessing the Relationship between Vitamin D Status and Impairments in Cognitive and Physical Performance in Older Adults Using a Dual Task Physical Performance Test. J Prev Alzheimers Dis. 2017;4(1):29–36.

32. Montero-Odasso M, Muir SW, Hall M, Doherty TJ, Kloseck M, Beauchet O, et al. Gait Variability Is Associated With Frailty in Community-dwelling Older Adults. J Gerontol Ser A. 2011 May 1;66A(5):568–76.

33. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr. 2008 Apr 1;87(4):1080S-1086S.

FIGURES AND TABLES

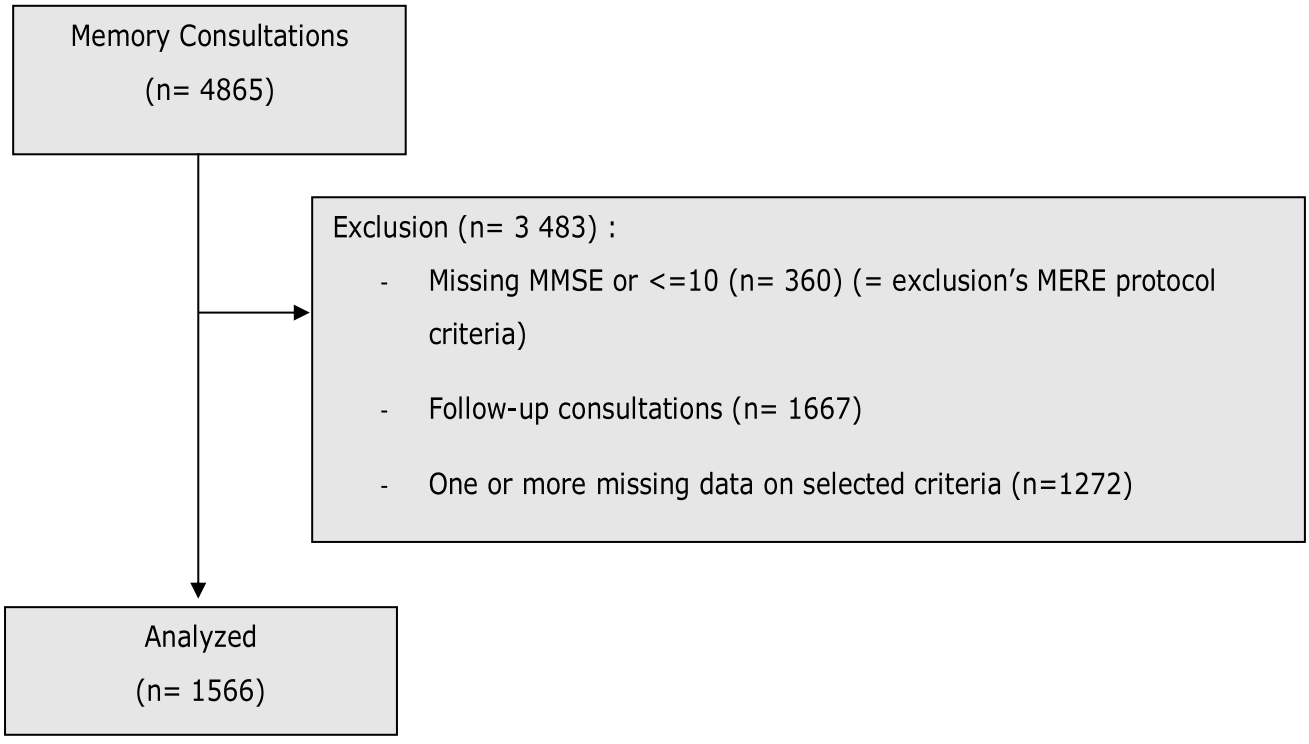

Figure 1. Flow-Chart

Table I. Clinical Characteristics of study participants (n=1 566)

SD: Standard Deviation

%: Percentage

β: Coefficient of regression corresponding to an increase of stride time variability

CI: Confidence interval

BMI: Body mass index

STV : stride time variability

FAB: Frontal assessment battery

*: Defined as IADL score ≤3/4

†: Defined as the use of 5 medications or more

‡: Use of antidepressants or benzodiazepines or neuroleptics or hypnotics

||: Diseases lasting ≥3months and running a course with minimal change

P-values <0.05 were considered statistically significant

	Total cohort (n= 1 566)
Age (years), mean±SD	79,48±7.147
Gender	
Men, n (%)	677 (43.23)
Women, n (%)	889 (56.77)
BMI (ref. <21: undernutrition)* (kg/m^2), n (%)	127 (8.11)
Normal (BMI 21-25)	507 (32.38)
Overweight (BMI 25-30)	621 (39.66)
Obesity (BMI ≥30)	311 (19.56)
Disability†, n (%)	902 (57.60)
Number of comorbidities§, mean±SD	3,01±2.001

Polymedication‡, n (%)	802 (51.21)
Use of psychoactive drugs‖, n (%)	567 (36.21)
Use of vitamin D drugs, n (%)	390 (24.90)
Serum 25OHD concentration (nmol/L), mean±SD	58.82±27.89
Serum calcium concentration (mmol/L), mean±SD	2.34±0.103
Serum creatinine concentration (μmol/L), mean±SD	83.90±30.37
Serum parathormone concentration (pg/mL), mean±SD	28.46±18.23
FAB score, mean±SD	13.19±3.34
STV during walk in simple task, mean±SD	4.44±5.01
STV during walk and verbal fluency dual task, mean±SD	11.73±14.30

Table II. Multivariate linear regression model showing the association between stride-to-stride variability of stride time during walk and verbal fluency task (dependent variable) and serum 25OHD concentrations (independent variable) adjusted on clinical characteristics

β: Coefficient of regression corresponding to an increase of stride time variability

CI: Confidence interval

BMI: Body mass index

STV : stride time variability

FAB: Frontal assessment battery

*: Defined as IADL score ≤3/4

†: Defined as the use of 5 medications or more

‡: Use of antidepressants or benzodiazepines or neuroleptics or hypnotics

||: Diseases lasting ≥3months and running a course with minimal change

P-values <0.05 were considered statistically significant

	STV during walk and verbal fluency dual task					
	Univariate linear regression			Multivariate linear regression		
	β	95%CI	P-Value	β	95%CI	P-Value
Serum 25-hydroxyvitamin D concentration	-0.018	-0.043;-0.008	0.1695	-0.034	-0.062 ;-0.006	**0.0169**
Age	0.343	0.245;0.440	**<0.0001**	0.134	0.068;0.315	**0.0305**
Sex	-0.964	-2.394;0.467	0.1865	1.001	-0.561;2.563	0.2090
BMI (ref. <21: undernutrition)			**0.0008**			**0.0465**
Normal (BMI 21-25)	-3.541	-6.312;-0.770	-	-2.936	-5.619;-0.254	-
Overweight (BMI 25-30)	-1.783	-4.503;0.936	-	-1.620	-4.276;1.036	-
Obesity (BMI ≥30)	0.364	-2.577;3.305	-	-0.578	-3.485;2.329	-
Disability*	4.605	3.189;6.022	**<0.0001**	1.168	-0.561;2.897	0.1852
Number of comorbidities‖	0.947	0.596;1.298	**<0.0001**	0.482	0.102;0.863	**0.0130**
Polymedication†	2.373	0.959;3.786	**0.0010**	-1.446	-3.129;0.236	0.0920
Use psychoactive drugs‡	2.666	1.197;4.136	**0.0004**	1.293	-0.273;2.858	0.1055
Use vitamin D supplements	2.253	0.618;3.889	**0.0070**	2.330	0.530;4.130	**0.0112**
Serum calcium concentration	3.829	-3.025;10.684	0.2734	5.485	-1.307;12.277	0.1134
Serum creatinin concentration	0.019	-0.004;0.043	0.1064	0.021	-0.004;0.046	0.0988
Serum parathormone concentration	0.021	-0.018;0.060	0.2852	-0.018	-0.058;0.023	0.3948
FAB score	-0.613	-0.823;-0.403	**<0.0001**	-0.113	-0.358;0.133	0.3679
STV while single-tasking	0.717	0.580;0.854	**<0.0001**	0.602	0.459;0.745	**<0.0001**

LISTE DES FIGURES

LISTE DES TABLEAUX

TABLE DES MATIERES

ANNEXES

BANNIER Adeline

Concentration en vitamine D et contrôle cognitif de la marche : Résultats de l'étude de cohorte MERE

RÉSUMÉ

Introduction. De précédentes études ont montré que l'hypovitaminose D était associée à une altération des performances physiques et de marche. Une association entre concentration en vitamine D et capacité musculaire reste controversée. Nous avons émis l'hypothèse que l'hypovitaminose D puisse influencer les performances de marche à travers une composante cognitive centrale du contrôle de la marche, notamment les fonctions exécutives. L'objectif de notre étude était de déterminer si l'hypovitaminose D était associée à une augmentation (i.e une aggravation) de la variabilité du temps de pas en double tâche chez des patients âgés.

Méthodes. Un échantillon de 1566 sujets issus de la cohorte monocentrique française 'MERE' de 4865 patients ont été analysées. La concentration sérique de 25OHD a été mesurée et la variabilité du temps de pas a été définie par un coefficient de variation (STV) du temps de pas. La double tâche correspondait à un exercice de fluence verbale pendant la marche. L'âge, le sexe, l'Indice de Masse Corporelle, la dépendance mesurée par le score IADL, le nombre de comorbidités, la polymédication, la supplémentation en vitamine D, et l'usage de psychotropes ; ainsi que des covariables biologiques telles que la créatininémie, la concentration en PTH, l'albuminémie et la calcémie ont été utilisés comme potentiels facteurs de confusion.

Résultats. La concentration sérique moyenne en 25OHD était de 58.8±27.9nmol/L et la STV moyenne de 11.73±14.30%. La STV en double tâche et la concentration en 25OHD étaient significativement et inversement associés β=-0.034, 95%CI [-0.062;-0.006], p=0.0169) lors de l'analyse en régression linéaire multivariée.

Conclusions. La concentration sérique en 25OHD était inversement associée à la variabilité du pas lors de la marche en double tâche, mettant en évidence une composante cognitive centrale du contrôle de la marche impliquant les fonctions exécutives. Ces résultats permettent de mieux comprendre l'implication de la vitamine D dans le contrôle moteur cérébral de la marche.

Mots-clés : Vitamine D, marche, contrôle moteur, double tâche, personnes âgées

Serum vitamin D and cognitive gait control: The French MERE cohort study

ABSTRACT

Background. Previous studies showed that hypovitaminosis D was associated with poor physical and gait performances. The association between vitamin D concentration and muscle capacities remains controversial. We suggested that hypovitaminosis D may influence gait performances through an action on the central cognitive component of gait control and especially executive functions. The objective of the present study was to determine whether hypovitaminosis D was associated with increased (i.e. worse) stride time variability while dual-tasking among older adults.

Methods. A subset of 1 566 subjects from the unicentric French 'MERE' cohort of 4865 subjects were used for this analysis. Serum 25OHD concentration was measured and stride-to-stride variability of stride time was defined by the coefficient of variation of stride time (STV). The dual task was a verbal fluency task when walking. Age, gender, Body Mass Index, disability assessed by Instrumental Activities of Daily Living, number of co-morbidities, polymedication, use of vitamin D and psychotropic drugs, and biologic covariables such as creatinine level, parathyroid hormone concentrations, albuminemia, calcemia were used as potential confounders.

Results. Mean serum 25OHD concentration was 58.8±27.9nmol/L and the mean STV was 11.73±14.30%. The stride time variability during dual task and serum 25OHD concentration were significantly and inversely associated (β=-0.034, 95%CI [-0.062;-0.006], p=0.0169) in the multivariate linear regression model.

Conclusions. Serum 25OHD concentration was inversely associated with STV during dual task walking as a marker of central cognitive component of gait control involving executive function. These results help to improve knowledge about the involvement of vitamin D in gait brain motor control.

Keywords: vitamin D, gait, motor control, dual task, older adults

FACULTÉ DE SANTÉ
UNIVERSITÉ D'ANGERS