Falls, physical limitations, confusion and memory problems in people with type II diabetes, undiagnosed diabetes and prediabetes, and the influence of vitamins A, D and E

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ABSTRACT

Aims: To examine the association between type II diabetes, prediabetes and undiagnosed diabetes with falls, physical limitations, confusion and memory problems, and to evaluate the effects of vitamins A, D and E levels on the associations.

Methods: Data from 37,973 participants of the National Health and Nutrition Examination Survey was analyzed.

Results: The participants’ mean age was 46 ± 17 years, 20% had diabetes of which 17% were unaware of their condition (undiagnosed diabetes), and 21% had prediabetes. Diabetes was significantly associated with falls, difficulties in stooping, crouching, kneeling, completing house chores, getting in and out bed, sitting and sitting for long periods, reaching over head, grasping, holding objects, and attending social events. The association between diabetes and confusion or memory problems was stronger for those diagnosed before age 40. Memory problems were reported only by people with diabetes with lower vitamin D levels. Vitamin A and E levels did not modify the association between diabetes and falls or any of the physical functions, confusion or memory problems. Prediabetes was only associated with difficulty standing for long periods.

Conclusions: Diabetes was associated with falls, difficulties in physical functioning and attending social events. Vitamin D levels modified the effects on confusion and memory problems.

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1. Introduction

Diabetes is “a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both” (Liddle & Gillean, 1995). Type II diabetes is associated with falls and faster decline in physical and cognitive functions due to neuropathy (Hausdorff, Rios, & Edelberg, 2001; Marks, 2014; Vinik, Vinik, Colberg, & Morrison, 2015). Furthermore, diabetes leads to an unfavorable environment for the muscles affecting physical function, mobility and falls risk. Insulin resistance is a key accelerator of loss of muscle mass and function (Miller, Lui, Perry, Kaiser, & Morley, 1999; Rodríguez-Saldaña et al., 2002). Insulin stimulates glucose uptake and metabolism maintaining glucose homeostasis. Skeletal muscles are the primary site of glucose disposal.

Insulin resistance in skeletal muscles is a major factor in diabetes. Muscles are also affected by the availability of vitamin D, which supports the function of type II muscle fibers, preserving muscle strength and reducing functional decline and falls. Low vitamin D levels are also associated with cognitive decline (Soni et al., 2012).

Loss of muscle mass (sarcopenia), decreased strength and falls are also associated with increased oxidative stress. Therefore, vitamins with antioxidant properties such as vitamins A and E may be protective to muscle health (Cerullo, Gambassi, & Cesari, 2012; Khor, Abdul Karim, Wan Ngah, Mohd Yusof, & Makpol, 2014). Vitamin E levels are associated with strength and frailty (Ble et al., 2006; Cesari et al., 2004). Antioxidant mixtures containing vitamins A and E, zinc, selenium and rutin were found to increase muscle anabolic response in animal models (Marzani et al., 2008). As antioxidant enzymes and potent signaling molecule, vitamins A and E are also thought to have an important role in maintaining cognitive function (Morris, Evans, Bienias, Tangney, & Wilson, 2002; Olson & Mello, 2010).

Little is known about which specific abilities are affected by diabetes, and studies evaluating large, representative samples are needed. Therefore, the objective of this study was to evaluate the association between diabetes, pre-diabetes and undiagnosed diabetes...
with falls and specific physical limitations, confusion or memory problems in a large sample, and to identify if vitamins A, D and E levels affect the associations.

2. Subjects

A total of 58,126 participants of all ages of the National Health and Nutrition Examination Survey (NHANES) from the 1999 to 2012 had data on diabetes. Among them, 39,019 aged 20 years and older were interviewed about physical functions, confusion and memory problems. After exclusion of participants with missing data (1,049), the final sample included 37,973 subjects. NHANES protocols were approved by the institutional review boards of the NCHS and CDC, and informed consent was obtained from all participants.

3. Materials and methods

3.1. Data source

The NHANES is an ongoing cross-sectional survey of the US non-institutionalized civilian population selected using a complex multistage sampling design to derive a representative sample of the US population. It is conducted yearly by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). Two-year data cycles were combined for analysis as per the National Center for Health Statistics recommendations.

3.2. Diabetes, undiagnosed diabetes, and pre-diabetes

Participants were classified as having diabetes if they answered yes to the question: “Other than during pregnancy, have you ever been told by a doctor or health professional that you had diabetes or sugar diabetes?”, and presented a fasting plasma glucose \( \geq 126 \) mg/dl, any random glycaemia \( \geq 200 \) mg/dl, or glycohemoglobin \( \geq 6.5 \). Participants were classified as having undiagnosed diabetes if they answered no to the same question, but presented a fasting plasma glucose \( \geq 126 \) mg/dl, any random glycaemia \( \geq 200 \) mg/dl, or glycohemoglobin \( \geq 6.5 \). Participants were classified as having pre-diabetes if they answered no to the same question and presented a fasting plasma glucose between 100 and 126 mg/dl, or glycohemoglobin between 5.7 and 6.5.

3.3. Physical functioning, confusion or memory problems, and falls

Data on physical functioning, confusion or memory problems were collected during home visits using a computer-assisted personal interviewing system. Participants were classified as having physical limitations if they reported at least “some difficulty” when walking for a quarter mile without using any assistive device, or when stooping, crouching, or kneeling, or in completing house chores, getting in and out bed, standing or sitting for long periods, reaching over head, grasping/holding objects, or attending social events. Participants were classified as having confusion or memory problems if they answered yes to the question: “Are you limited in any way because of difficulty remembering or because you experience periods of confusion”. The NHANES Balance questionnaire available from 1999 to 2004 included data on falls in previous year for the participants aged 40 years and older. The question used to assess history of falls was: “Have you had difficulty with falling during the past 12 months?”.

3.4. Covariates

Demographic characteristics including age, gender, race/ethnicity, education level, family income, cigarette smoking, were obtained from the NHANES survey. Height and weight were measured in a mobile examination center. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, and classified as underweight \(< 18.5 \) kg/m\(^2\), normal \(18.5–24.9 \) kg/m\(^2\), overweight \(25–29.9 \) kg/m\(^2\), or obese \(\geq 30 \) kg/m\(^2\). Total cholesterol was enzymatically measured in serum using the Roche Hitachi 717 and 912. Family income to poverty ratio was adjusted for family size, year and state. Cigarette smoking status was determined using the question “Have you smoked at least 100 cigarettes in your life?”.

Health conditions were ascertained based on the question: “Has a doctor or other health professional ever told you that you have diabetes, arthritis, cardiomyopathies (congestive heart failure, coronary heart disease, and/or history of heart attack), stroke, cancer, thyroid or liver disease?” Each condition was asked about separately. Hypertension was defined by self-report or by a mean systolic blood pressure \( > 140 \) mmHg on 4 measurements in 2 separate occasions. Serum vitamins A and E were measured using high performance liquid chromatography with photodiode array detection, and serum vitamin D was essayed using the Diasorin (formerly Incstar) 25-OH-D method. Serum vitamins A and E were measured in NHANES for the years 1999 to 2006, and serum vitamin was measured from 2001 to 2005.

3.5. Statistical analysis

All analyses were performed in STATA (Version 11, STATA Corporation, College Station, TX, USA), and p-values \(< 0.05\) were considered statistically significant. NHANES sampling weights and STATA survey commands, taking into account the multistage and complex survey design, were used in all procedures to adjust for unequal selection probabilities, non-responses, over-sampling, post-stratification, and sampling errors, so that estimates were nationally representative.

Descriptive analyses were performed, and p-values for differences in proportions or means by diabetes/prediabetes status were calculated using chi-square test for the categorical variables and Student’s t-test for the continuous variables. Multivariate logistic regression analysis was performed while adjusting for age, gender, race/ethnicity, family income to poverty ratio, education level, smoking, BMI, hypertension, arthritis, cardiomyopathies, stroke, comorbidities, glycohemoglobin and total cholesterol. Effect modification by serum vitamins A, D and E on the association between diabetes status and the outcomes was investigated by including the interaction or product term in the models. Stratified analyses were subsequently performed at each level of the significant modifying variables. Afterwards, the association between specific physical function limitations, confusion or memory problems, and falls in the previous year among participants with diabetes or prediabetes was assessed adjusting for the same covariates, and vitamin levels were tested for effect modification.

4. Results

Table 1 presents the participants’ characteristics (n = 37,973). The mean (SD) age was 46 ± 17 years; 52% were women; 70% were non-Hispanic Whites; 20% had type II diabetes (n = 7,532) of which 17% were unaware of their condition (undiagnosed diabetes, n = 1280), and 21% had prediabetes (n = 7,933). Among participants with diabetes, 45% were already treated (insulin or diabetes pills), and 74% were diagnosed at age \( \geq 40 \) (diagnostic criteria for type 2 diabetes/“adult-onset diabetes”).

Gender and racial/ethnic distribution significantly differed by diabetes status. Participants with diabetes or prediabetes were older, had lower levels of education, had lower income to poverty ratios, were smokers and obese more often, had more hypertension, arthritis, cardiomyopathies, stroke and other comorbidities, and presented physical limitations and falls in the past year at a higher proportion than participants who did not have diabetes or prediabetes (P < 0.001). Those with prediabetes also had higher total cholesterol levels (P < 0.001).
Diabetes was significantly associated with difficulties in stooping, crouching, or kneeling, house chores, getting in and out bed, standing and sitting for long periods, reaching over head, grasping/holding objects, attending social events, and confusion or memory problems, but not with difficulties in walking a quarter mile (Table 2). The associations between diabetes and difficulties in house chores, attending social events, and confusion or memory problems were stronger for the participants with diabetes who were diagnosed before age 40. The number of years of diabetes was associated with difficulties in walking a quarter mile, stooping/crouching/kneeling, house chores, standing and sitting for long periods, reaching over head, attending social events, and with confusion or memory problems.

Prediabetes was only significantly associated with difficulty in standing for long periods. While, those who were unaware of their diabetes status (undiagnosed diabetes) were more likely to have difficulties in stooping, crouching, or kneeling, standing and sitting for long periods, and attending social events than those without diabetes.

The odds of having confusion or memory problems were higher for the participants with diabetes who had vitamin D levels below the median (23.1 ng/ml; OR = 1.82, 95% CI 1.05–3.15, P = 0.02). On the other hand, vitamins A or E did not significantly modify the association between diabetes and the physical functions, confusion or memory problems.

Diabetes was associated with falls in the past year (OR: 2.00, 95% CI: 1.20, 3.35, P = 0.008, Table 3). Participants with diabetes or prediabetes were more likely to fall if they had difficulties in stooping, crouching, or kneeling (OR: 2.28, 95% CI: 1.23, 4.22), house chores (OR: 1.78, 95% CI: 1.08, 2.94), getting in and out bed (OR:2.18, 1.27, 3.75), standing for long periods (OR: 3.00, 95% CI: 1.67, 5.37), grasping/holding objects (OR: 2.00, 95% CI: 1.22, 3.28), or confusion/memory problems (OR: 1.74, 95% CI: 1.10, 2.76). The levels of vitamins A, D, and E did not affect these associations.

5. Discussion

After extensive literature search and to the best of our knowledge, this is the first study to examine physical function and confusion or memory problems in people who were unaware of their diabetes, the first to compare physical function and confusion or memory problems in people who were diagnosed before and after age 40, and the first to evaluate the effects of serum vitamins A, D, and E on falls, physical function and confusion or memory problems in people with diabetes. Falls, physical limitations, and confusion or memory problems were common in people with diabetes. Participants diagnosed before age 40 had higher odds of having physical difficulties and confusion or memory problems than those diagnosed at age 40 or older. This suggests that early onset diabetes results in people losing muscle and memory earlier, aging faster, and having a greater degree of limitation.
We found diabetes to be associated with confusion or memory problems only in participants with lower serum vitamin D levels. Recently, the association between serum vitamin D levels and cognitive impairment was assessed in patients with type II diabetes, and a significant negative association was also found (Chen et al., 2014). Adequate serum vitamin D levels may protect against cognitive impairment by stimulating Abeta phagocytosis, preventing Ab42 accumulation, increasing glutathione levels, and reducing atherosclerosis (Chen et al., 2014). An animal study found that vitamin D could prevent diabetes-associated memory impairment by affecting acetylcholinesterase and Na + K+ -ATPase activity, avoiding lipid peroxidation in the cerebral cortex (Calgaroto et al., 2014). Given the association between diabetes-related cognitive impairment and low vitamin D levels, longitudinal studies are needed, and preventive measures should be investigated.

Vitamin D is also involved in calcium and bone metabolism, as well as in numerous other metabolic processes that are important for maintaining physical health. However, in this study, vitamin D levels were not associated with falls, and the role of low vitamin D levels on falls is controversial, and some recent studies have found that vitamin D supplementation does not reduce the risk of falls (Bolland, Grey, Gamble, & Reid, 2014; LeBlanc & Chou, 2015; Wise, 2015). Vitamin D3 is produced in the human skin with the influence of sunlight (ultraviolet B: 290–315 nm) from 7-dehydrocholesterol (7-DHC) (Holick, 2007). Given the cross-sectional nature of our and previous studies, cause–effect statements cannot be made, and it is possible that the preclinical and/or physical impairments lead to decreased vitamin D levels because people with impairments may go out less often and be less frequently exposed to sun light. Therefore, longitudinal studies that allow for the assessment of temporality (what comes first?) are necessary.

In this study, vitamins A and E levels were not associated with falls, physical limitations, confusion or memory problems, and previous studies found no benefit of vitamin E supplementation on physical or cognitive performance (Beaton, Allan, Tarnopolsky, Tiidus, & Phillips, 2002; Sano et al., 1997; Theodorou et al., 2011). Less is known in regards to the potential benefits of vitamin A, but the large vitamin A and E storing capabilities of the body may explain the lack of associations observed (Lukaski, 2004).

The association between diabetes and falls, physical limitations, confusion or memory problems (in those with low Vit D levels) is consistent with the findings of previous studies conducted in the US (Giovannini et al., 2007; Taylor, Dunstan, & Prescott, 2007; West, Hammarström, & Hernell, 2009; Wickens et al., 2008; Yesilova, Čalıka, Akdeniz, & Berktas, 2012) and in other parts of the world (Prescott et al., 2008; Rautava, Kainnen, Salminen, & Isolauri, 2012; Roman, Cambier, Calders, Van, & Delbaere, 2013). Using NHANES III data from 1988 to 1994, an association between diabetes and difficulties in walking for a quarter mile, and housework was identified in people ≥60 years old (Yesilova et al., 2012). An association between diabetes and falls in the past year has also been identified in people ≥60 years old, and the participants with diabetes also had problems walking (higher timed up and go times) (Chiba et al.). People with diabetes have been found to have vestibular dysfunction, falls, fear of falls and mobility problems more often than people without diabetes (Agrawal, Carey, Della Santina, Schubert, & Minor, 2010; Bruce, Hunter, Peters, Davis, & Davis, 2015). A study analyzed data from 30,000 Americans and found diabetes to be associated with difficulty walking 12 city blocks, sitting for 2 h, stooping, bending or kneeling, reaching over head, grasping objects, visiting friends, and even watching television or listening to music (Taylor et al., 2007). Yet another study found higher prevalence of physical limitations in people with prediabetes, but similarly to our findings there was no significant association after adjusting for socio-economic factors and chronic diseases (Chen, Lin, Jan, Chen, & Wang, 2010). To the best of our knowledge, our study may be first to examine and identify a
The higher odds of people with diabetes of having physical limitations may be due to accelerated muscle loss, decreased cardiopulmonary reserve, restricted movement, high concentrations of glucose, and chronic systemic inflammation (Anton, Karabetian, Naugle, & Buford, 2013; Wong et al., 2013). Diabetes-associated physiological changes lead to loss of muscle mass, strength and quality, creating a vicious cycle of impairments leading to less mobility, less stimuli, and progressive deconditioning. Older adults with diabetes have been found to have two to three times the odds of disability than older adults without diabetes (Kalyani, Saudek, Brancati, & Selvin, 2010). Consistent with our findings, diabetes has also been reported to be associated with cognitive impairment (Gore et al., 2012; Yesilova et al., 2012). Midlife onset of diabetes may affect late-life cognition through loss of brain volume, while late-life onset could have fewer effects on brain pathology and cognition (Roberts et al., 2014). The effects of diabetes on the brain may take decades to take place and show up as brain damage and memory/cognition symptoms. This may help explain why we also found an association between duration of diabetes and confusion or memory problems. The impact of vascular disease on cognition may not be restricted to localized cerebral small vessel disease or to altered blood flow and ischemic damage, but cognitive decline could also reflect systemic atherosclerotic changes (Feinkohl et al., 2013).

The accelerated physical decline of people with diabetes adds a layer of complexity to understanding muscle loss during aging and its effects on mobility, disability and quality of life of people with diabetes. Age 40 is a diagnostic criteria for type 2 diabetes, but using age of diabetes diagnosis as a way of differentiating type 1 from type 2 diabetes is controversial (Largay, 2012). We observed that diabetes diagnosed before the age of 40 was more strongly associated with memory problems than diabetes diagnosed at or after age 40 even after adjusting for diabetes duration; we hypothesize that the greater the length of exposure to the catabolic environment promoted by diabetes, the greater or more accelerated muscle mass loss.

One of the limitations of this study is that there was a single question on memory complaints and/or history of confusion. In addition, this was a cross-sectional study and therefore, no cause-effect statements can be made. Our and other studies have found that falls, physical and cognitive impairment were associated with diabetes (Bell, Talbot-Stern, & Hennessy, 2000; Scheffer, Schuurmans, van Dijk, van der Hoof, & de Rooij, 2008). However, further longitudinal studies are required before cause-effect conclusions can be made. Another limitation of this study was that falls, physical limitations, confusion and memory problems were self-reported. Self-reported measures are susceptible to under/over reporting and memory issues. Therefore, future studies should try to use more direct measures of falls (for example: use of accelerometers), physical limitations (for example: use of physical testing of activities of daily living), confusion and memory problems (for example: use of questionnaires and validated tools).

With regard to the 17% of the diabetic participants who were unaware of their condition (participants with undiagnosed diabetes), we cannot emphasize enough the importance of regular medical checkups and screenings for early diabetes detection. According to the World Health Organization, early detection benefits include: 1) improved length and/or quality of life by reducing the severity and frequency of immediate effects and by delaying long-term diabetes--related complications, and 2) health care savings and resource redistributions by reducing the levels of care required due to diabetes-related complications.

### Table 3

<table>
<thead>
<tr>
<th>Issues reported (comparison group = reporting no difficulties or issues)</th>
<th>OR (95% CI) of having fallen during the previous 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty walking a ¼ mile</td>
<td>0.71 (0.46, 1.11)</td>
</tr>
<tr>
<td>Difficulty stooping, crouching, kneeling</td>
<td>2.28 (1.23, 4.22)**</td>
</tr>
<tr>
<td>Difficulty with house chores</td>
<td>1.78 (1.08, 2.94)*</td>
</tr>
<tr>
<td>Difficulty getting in and out bed</td>
<td>2.18 (1.27, 3.75)**</td>
</tr>
<tr>
<td>Difficulty in standing for long periods</td>
<td>3.00 (1.67, 5.37)**</td>
</tr>
<tr>
<td>Difficulty in sitting for long periods</td>
<td>0.77 (0.47, 1.27)</td>
</tr>
<tr>
<td>Difficulty reaching over head</td>
<td>0.92 (0.56, 1.51)</td>
</tr>
<tr>
<td>Difficulty grasping/holding objects</td>
<td>2.00 (1.32, 3.28)**</td>
</tr>
<tr>
<td>Difficulty attending social events</td>
<td>1.09 (0.63, 1.89)</td>
</tr>
<tr>
<td>Confusion or memory problems</td>
<td>1.74 (1.10, 2.76)*</td>
</tr>
</tbody>
</table>

Odds ratios calculated using logistic regression. Models adjusted for age, gender, race/ethnicity, family income to poverty ratio, education level, smoking, BMI, hypertension, arthritis, cardiomyopathies, stroke, comorbidities, glycemic hemoglobin and total cholesterol.  
* P < 0.05.  
** P < 0.01.  
*** P < 0.001.

6. Conclusions

Falls, physical function limitations, and confusion or memory problems were common in people with diabetes. Diabetes was significantly associated with falls, difficulties in stooping, crouching, kneeling, house chores, getting in and out bed, standing for long periods, sitting for long periods, reaching up over head, grasping, holding objects, attending social events, and confusion or memory problems. The association between diabetes and confusion or memory problems was stronger in patients diagnosed before age 40, even after adjusting for diabetes duration. Memory problems were reported only by people with diabetes with lower vitamin D levels. On the other hand, vitamins A or E did not significantly modify the association between diabetes and falls or any of the physical functions, confusion or memory problems. Prediabetes was associated with difficulty standing for long periods, and those who were unaware of their diabetes status (undiagnosed diabetes) were more likely to have difficulties in stooping, crouching, or kneeling, standing and sitting for long periods, and attending social events than those without diabetes.

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