Improved diabetes control in the elderly delays global cognitive decline

Jose A. Luchsinger, MD, MPH[1,2], **Walter Palmas, MD, MS**[1], **Jeanne A. Teresi, EdD, PhD.**[3,4], **Stephanie Silver, MPH**[3], **Jian Kong, MS**[3], **Joseph P. Eimicke, MS**[3], **Ruth S. Weinstock, MD, PhD.**[5,6], and **Steven Shea, M.D.**[1,2,7] **For the IDEATel Consortium**

[1]Department of Medicine, Columbia University, New York, NY

[2]Department of Epidemiology, Joseph Mailman School of Public Health, Columbia University, New York, NY

[3]Research Division, Hebrew Home at Riverdale, Bronx, NY

[4]Stroud Center, Columbia University, and New York State Psychiatric Institute, New York, NY

[5]Joslin Diabetes Center and Division of Endocrinology, Diabetes and Metabolism, SUNY Upstate Medical University, Syracuse, NY

[6]Department of Veterans Affairs, VA Medical Center, Syracuse, NY

[7]Department of Biomedical Informatics, Columbia University, New York, NY

Abstract

OBJECTIVES—to examine whether improved diabetes control is related to better cognitive outcomes.

DESIGN—randomized control trial

SETTING—a randomized trial of telemedicine vs. usual care in elderly persons with type 2 diabetes.

PARTICIPANTS—Participants were 2169 persons 55 years and older with type 2 diabetes from New York City and Upstate New York.

INTERVENTION—The diabetes case management intervention was implemented by a diabetes nurse, via a telemedicine unit in the participant's home, and in coordination with the primary care physician.

MEASUREMENTS—Hemoglobin A1c (HbA1c), systolic blood pressure (SBP), and low density lipoprotein cholesterol (LDL), were measured at a baseline visit and at up to 5 annual follow-up visits. Global cognition was measured at those visits with the Comprehensive Assessment and Referral Evaluation (CARE).

Corresponding author: José A. Luchsinger, MD, Division of General Medicine, PH9East-105, 630 West 168th street, New York, NY 10032, Tel: 212-3054730, Fax: 212-3059349, jal94@columbia.edu. Alternative corresponding author: Walter Palmas, MD, wp56@columbia.edu.

RESULTS—In mixed models the intervention was related to slower global cognitive decline in the intervention group (p = 0.01). Improvements in HbA1c (p = 0.03), but not SBP or LDL, mediated the effect of the intervention on cognitive decline.

CONCLUSION—Improved diabetes control in the elderly following existing guidelines through a telemedicine intervention was associated with less global cognitive decline. The main mediator of this effect seemed to be improvements in HbA1c.

Keywords

Diabetes treatment; cognitive impairment; clinical trials

INTRODUCTION

Type 2 diabetes (T2D) is related to higher cognitive impairment and dementia risk [1, 2]. This is important given that T2D affects 25% of the elderly in the United States (US)[3]. Whether T2D control affects cognitive outcomes is unclear. We explored this in the Informatics in Diabetes Education and Telemedicine Study (IDEATel), a randomized trial of telemedicine vs. usual care in 2169 persons. IDEATel showed improved diabetes control in hemoglobin A1C (HbA1c), blood pressure (BP), and low density lipoprotein (LDL) after 5 years of intervention[4]. We sought to assess whether the intervention was related to better global cognitive outcomes. We also tested which T2D control parameter mediated the effect of the intervention on global cognition.

METHODS

IDEATel was a randomized controlled trial with blinded outcomes assessment. Detailed descriptions were published[4]. Subjects were enrolled through primary care providers (PCP) in New York City (Columbia University Medical Center), and Upstate New York (State University of New York Upstate Medical University at Syracuse). The Institutional Review Boards at participating institutions approved the study. Participants provided informed consent. An independent Data and Safety Monitoring Board monitored the study.

Setting and Participants

The sample consisted of 2169 subjects recruited and randomized between December, 2000 and October, 2005. Inclusion criteria were: age 55 years, Medicare beneficiary, diabetes defined by physician's diagnosis and being on treatment with diet or diabetes medications, residence in a federally designated medically underserved area, and fluency in English or Spanish. Exclusion criteria were: moderate or severe cognitive impairment, severe visual, mobility, or motor coordination impairment, severe co-morbid condition, severe expressive or receptive communication impairment, lack of electrical outlet for telemedicine unit, and spending more than 3 months a year at a location different from their residence. A flow diagram of the study is shown in Appendix Figure 1.

Randomization and Interventions

Participants were randomized by PCP clusters. The telemedicine intervention has been described elsewhere.[4] The target HgbA1c was 7%, except for participants with reduced life expectancy and/or severe hypoglycemic unawareness, for whom that target was 8%. At study onset the BP goal was < 130/85 mmHg, or < 125/75 mmHg in the presence of proteinuria (> 1g/24h) or renal insufficiency. In 2003 the BP goal changed to < 130/80 mmHg, except for proteinuria or renal insufficiency. The LDL goals were < 130 mg/dl for primary prevention, and < 100 mg/dl for those with cardiovascular disease. In 2001, the

LDL goal changed to < 100 mg/dl.[5] In 2004 the LDL goal for participants with high cardiovascular risk changed to < 70 mg/dl. [6]

Usual Care—Participating PCPs cared for patients in both trial arms. PCPs were mailed diabetes care guidelines. Usual care group participants received clinical care from PCPs, without guidance from study personnel.

Diabetes control parameters

Diabetes control parameters were HbgA1c, BP, and LDL. Follow-up examinations were conducted at one-year-intervals. Data from baseline and five follow-up visits through February 28, 2007 were used in the analyses.

Subjects came to the baseline and follow-up visits fasting, having held their glycemic control medications, but taking their BP medications. Detailed description of parameter measurements can be found elsewhere.[4]

Outcomes

The Comprehensive Assessment and Referral Evaluation (CARE)-Diagnostic Scale developed by Gurland and colleagues[7] was used for cognitive screening. The CARE-Diagnostic has 14 items, including age recall, year of birth, address, telephone number, date, and if memory problems affect remembering "things like names of people in your family or close friends?", "to shop", "to get chores done around the house", and "keep track of your personal business, like paying bills or handling money." Higher scores represent worse cognitive impairment. A moderate cut score of six was used to exclude subjects with moderate to severe cognitive impairment. This measure has been used with community samples of diverse race/ethnic backgrounds. The scale was used for cognitive screening in two large epidemiological studies of dementia among Latinos, African-Americans and non-Latino Whites in North Manhattan. Cronbach's alphas were .83, .84, and .83, for the Latino, African-American and White subgroups, respectively[8]. The Cronbach's alpha estimates for the current sample were lower (ranging from 0.56 to 0.75) because of lower item base rates resulting from baseline exclusion of individuals with moderate to severe cognitive impairment. The sensitivity of the scale with clinical diagnosis was .87, the specificity was .79. The scale is relatively unbiased across education and race/ethnic groups[8].

Statistical analyses

First, variable distribution was examined. We compared baseline characteristics between the trial arms using chi-squared for categorical outcomes and t-test for continuous outcomes. For variables not normally distributed we used the Wilcoxon rank-sum test.

We examined the longitudinal relationship between cognitive decline and treatment group. First examined was a model treating cognition as a continuous variable using SAS PROC MIXED. We conducted sensitivity analyses modeling the outcome as a Poisson distribution using SAS PROC GLIMMIX. Analyses used an intent-to-treat approach. We used several approaches to model missing data and results were similar.

We examined which diabetes control parameter mediated the effect of the intervention on cognitive decline. Only the three primary outcomes in IDEATel were examined; the pre-specified alpha level for each outcome was set at 0.05. Methods for examination of mediation effects have received recent attention in terms of statistical power [9, 10] and performance. Although evidence from Monte Carlo studies support simple joint significance tests of the mediating path coefficients[11, 12], also examined were two other formal tests of mediation effects[13, 14]. The mediating paths examined were between the intervention and

the diabetes control parameter (e.g. HbA1C), and between the diabetes control parameter and cognition. If both paths were statistically significant, we considered the diabetes control parameter to be mediating the effect of the intervention on cognition. These formulas are appropriate for multilevel analyses with random effects such as those used to provide estimates of the path coefficients[15]. For these analyses, Aroian Z, MacKinnon & Lockwood asymmetric distribution of products[11], and joint significance of the coefficient relating the intervention with the mediator (a), and the mediator with the outcomes (b) [11] were used. Confidence intervals for the product of a and b were determined using the method of MacKinnon, Lockwood, and Williams[16].

RESULTS

The maximum follow-up was 5 years. The analyses included 2169 persons. The majority (87%) had one or more follow-ups, and about half (43%) had four or five years of follow-up.

Table 1 shows a comparison of characteristics between the trial arms. There were no significant differences in any baseline characteristic.

As expected, both trial arms experienced cognitive decline during the study, evidenced by increasing CARE scores. However, the treatment group experienced significantly less decline (Figure 1), indicated by a statistically significant interaction term of randomization group and time with a negative coefficient (Table 2). Sensitivity analyses using a Poisson distribution for the CARE-Diagnostic yielded similar results.

Mediation analyses

The primary endpoints of IDEATel were HbA1c, BP, and LDL[4]. The intervention arm resulted in improvements in these parameters compared to usual treatment. HbA1c (p = 0.02), systolic BP (SBP) (p =0.008), and LDL (p=0.0004) showed more beneficial changes in the intervention compared with the usual care group (8). We explored whether a particular parameter mediated the association between the treatment arm and cognitive outcome. When cognition was modeled linearly, only HbA1c was demonstrated to be a significant mediator (p=0.03) (Figure 2). (The 95% confidence limits for the product of the coefficient relating the intervention with HbA1c, and the coefficient relating HbA1c with cognition, were 0.0005 and 0.0278.)

Systolic BP and LDL were also examined, but were found not to have a mediating effect on cognition. Sensitivity analyses modeling the CARE-diagnostic in a Poisson distribution yielded similar results.

DISCUSSION

We found that improved HbA1c, SBP, and LDL in the elderly was related to slower global cognitive decline in a 5-year clinical trial. This association was mediated by HbA1c, but not SBP, or LDL.

T2D is associated with higher risk of cognitive decline [17, 18], cognitive impairment without dementia[2, 19], mild cognitive impairment (MCI)[1], and dementia[2] in epidemiologic studies. Furthermore, T2D is associated with both amnestic cognitive impairment, including amnestic MCI[1] and dementia due to Alzheimer's disease (AD) [20], and non-amnestic cognitive impairment, including non-amnestic MCI[1] and vascular dementia (VD)[2]. The association between T2D and VD is stronger than the association with AD[21].

While there is ample epidemiologic data relating T2D to an increased risk of cognitive impairment[22, 23], it is not clear how treatment affects cognitive impairment risk among persons with T2D. The diabetes control and complications trial (DCCT) in type 1 diabetes demonstrated that improved HbA1c was related to improved cognition in non-amnestic domains[24]. To the best of our knowledge, there are no published data from clinical trials in the elderly exploring the effect of improved diabetes control on cognition. Our study, like the DCCT, demonstrated that improved HbA1C is related with better global cognition.

Better HbA1c mediated the association between the intervention and better global cognition. HbA1c is an advanced product of glycosilation (AGE). AGEs are produced as elevated glucose promotes the Maillard reaction. In a hyperglycemic environment, diabetic animal and human tissues contain increased AGE and upregulation of its receptor (RAGE).[25] AGE in vascular basement membranes promote vascular leakage [26] and contribute to diabetic nephropathy[27, 28] retinal neovascularization [29, 30] and diabetic neuropathy.[31] Increased RAGE is also observed in AD [32–34]. Vasculature with deposited Aβ from patients with AD display increased RAGE antigen compared to age-matched controls [32, 35]. Expression of RAGE is enhanced in blood vessels near Aβ deposits in the AD brain [32, 35]. Along with increased RAGE in the AD brain, there is a shift of RAGE distribution from neuron to microvasculature[36]. We cannot make direct inferences about the role of AD pathology in our results. However, the strongest correlate of the CARE-Diagnostic in a subsample of 594 individuals with domain specific neuropsychological data was total recall (Pearson correlation coefficient (r)= −0.42; p <0.0001) and delayed recognition (r=0.39; p <0.0001) of the Buschke Selective Reminding Test[37], neuropsychological markers and predictors of AD [38]. Non-amnestic tests, better markers of vascular cognitive impairment[39], were less strongly correlated with the CARE. For example the color trails 1 and 2, measures of frontal and executive functions, more commonly affected by cerebrovascular disease[40], had weaker correlations with the CARE-Diagnostic (r and p = 0.27 and <0.0001 for color trails 1, and 0.23 and <0.0001 for color trails 2). Thus, our findings indirectly support a role for AGE in cognitive impairment in T2D. This has potentially important therapeutic implications, because AGE-specific therapeutic agents can be used to decrease brain deposition of amyloid beta, the culprit of AD[41], and decrease the risk of AD[32] in persons with T2D.

Another potential mechanism relating T2D to cognitive impairment is cerebrovascular disease (CVD)[42]. CVD could cause cognitive impairment through white matter hyperintensities, a correlate of microvascular disease, or infarcts [21, 43]. CVD could also interact with amyloid pathology to precipitate cognitive impairment[44]. LDL and SBP, the major predictors of macrovascular disease and infarcts[45], did not mediate the effect of the intervention arm on global cognitive decline, suggesting that the difference in these parameters between the treatment groups was not large enough to affect cognition. Although we attempted to identify the individual role of diabetes control parameters as mediators of the intervention on cognitive decline, it is possible that the sum of the improvements of HbA1c, SBP, and LDL caused by the intervention was stronger than the effect of each parameter alone.

Our study has limitations. Cognition was not a primary outcome of the IDEATel trial. The CARE-Diagnostic was primarily used as a cognitive impairment screen but was measured at each visit. Post-hoc analyses of outcomes in clinical trials may result in chance findings. This is a major concern when results for the primary outcomes are negative[46]. IDEATel showed a significant effect of telemedicine on its primary outcomes[4], and we demonstrated that improvement in one of those primary outcomes, HbA1c, explained cognitive outcomes. Another limitation is the use of a global measure of cognition. The Action to Control Cardiovascular Risk in Diabetes Memory Study (ACCORD-MIND)[47] will report whether intensive glycemic, lipid, and blood pressure control improved domain-specific cognitive

outcomes. Another limitation is the lack of data on hypoglycemia. The DCCT showed that hypoglycemia was not related to cognitive impairment[24], but a observational study showed that lower HbA1c and hypoglycemia in persons with T2D was related to a higher risk of dementia[48]. However, IDEATel glycemic control goals were less strict compared with ACCORD[49], which demonstrated increased mortality in its intensive glycemic control arm.

Our findings show that improving T2D control in the elderly following current guidelines may slow global cognitive decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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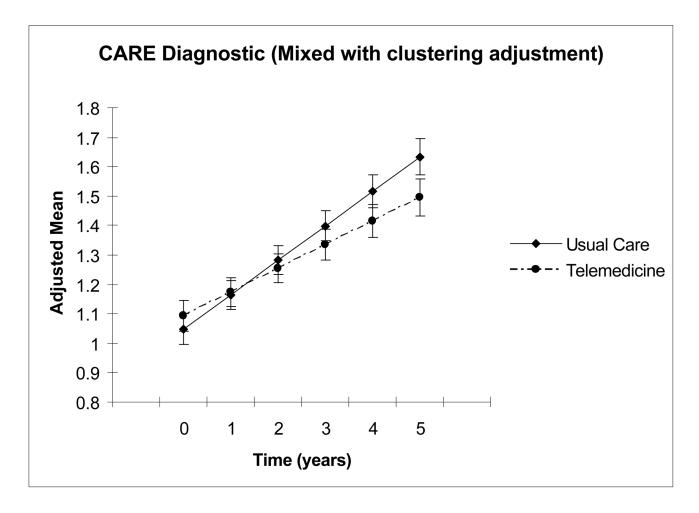
Figure 1.
Comparison of changes in adjusted means in the Comprehensive Assessment and Referral
Evaluation (CARE)-Diagnostic Scale between the intervention and control from mixed
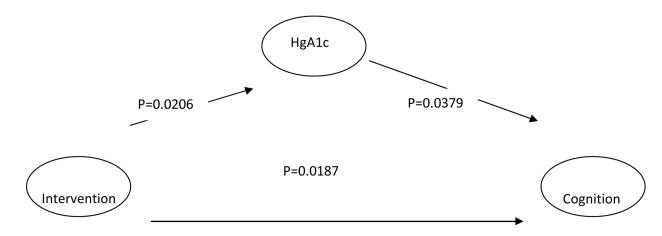models (adjusted for clustering) during a maximum follow-up of 5 years.

Figure 2.
Path diagram depicting the direct and indirect effects of the telemedicine intervention through Hemoglobin A1c on cognition (n = 2169)[a].

[a] SAS PROC Mixed with a compound symmetry covariance structure was used in the cognition analyses with an adjustment for clustering within PCP. HgA1c was treated as a time-varying covariate in the cognition analyses. SAS PROC Mixed was used to predict HgA1c and included adjustments for clustering and heterogeneity of variances in group and residual variances and exponential terms to model the nonlinear distribution of HgA1c over time. A first order auto-regressive covariance structure was used for the HgA1c analyses. Up to six waves of data (baseline plus five follow-up) were included in the analyses.

Table 1

Comparison of baseline demographic and clinical characteristics between the intervention and usual care group.

Characteristic	Intervention N = 1093	Usual Care N = 1076
Age at randomization, years	70.6 (6.6)	70.4 (6.8)
Women, (%)	676 (61.8)	648 (60.2)
Race/Ethnicity, (%)		
African-American (non-Hispanic)	147 (13.4)	136 (12.6)
Hispanic	379 (34.7)	365 (33.9)
White (non-Hispanic)	558 (51.1)	568 (52.8)
Other	9 (0.8)	7 (0.7)
Upstate New York	610 (55.8)	610 (56.7)
Education		
Elementary	574 (52.6)	565 (52.6)
High school	329 (30.2)	306 (28.5)
College	168 (15.4)	186 (17.3)
Duration of diabetes, years	10.9 (9.4)	10.7 (9.0)
Body mass index	32.4 (7.0)	32.2 (7.0)
Systolic blood pressure	142.5 (23.6)	141.4 (23.2)
HbA1c	7.4 (1.5)	7.4 (1.6)
LDL	103.9 (35.1)	104.2 (36.4)
Microalbumin creatinine ratio	1.5 (0.6)	1.5 (0.6)
Duration of follow-up (years)	3.5(1.4)	3.6 (1.4)
CARE score	0.92 (1.25)	0.91 (1.24)

Table 2

Longitudinal analyses of the CARE Diagnostic Cognitive Impairment Screening scale based on intent-to-treat analyses using SAS Proc mixed with an adjustment for clustering within PCP (n = 2169). The group variable compares baseline scores between the intervention and usual care arms. The time variable estimates the change in CARE Diagnostic scores over time. The interaction term of group by time tests differences in changes in the CARE Diagnostic scores between the intervention and usual care arms. The negative coefficient and the significant p value for the interaction term indicate that cognitive decline, indicated by higher scores in the CARE-Diagnostic, was slower in the intervention group.

	Estimate	Std. Err.	p-value
Intercept	1.28	0.04	<0.0001
Group (Intervention vs. usual care)	−0.02	0.05	0.59
Time (years)	0.11	0.01	<0.0001
Group by Time	−0.03	0.01	0.01