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# Brain Lesions on MRI in Elderly Patients with Type 2 Diabetes Mellitus

Barbera van Harten[a] Joukje M. Oosterman[c] Bert-Jan Potter van Loon[b]
Philip Scheltens[d] Henry C. Weinstein[a, d]

Departments of [a]Neurology and [b]Internal Medicine, Sint Lucas Andreas Hospital, [c]Department of Clinical Neuropsychology, Vrije Universiteit, and [d]Alzheimer Centre of the Department of Neurology, Vrije Universiteit University Medical Centre, Amsterdam, The Netherlands

**Key Words**
Diabetes mellitus, type 2 · Brain imaging abnormalities · Cognitive dysfunction

**Abstract**
***Background and Purpose:*** Diabetes mellitus (DM) type 2 has been associated with poor cognitive performance and dementia, particularly in elderly patients. The exact mechanisms underlying the cognitive dysfunction in DM remain unclear. Imaging studies of the brain could be helpful to give more insight into possible structural brain lesions underlying these cognitive dysfunctions. Therefore, we performed a study in independently living patients with DM type 2 in order to investigate the association between DM and brain imaging abnormalities. ***Methods:*** The study population consisted of 45 patients with DM type 2 without hypertension (mean age 73.4 ± 5.1 years, mean duration 16.5 ± 11.5 years), 45 patients with DM type 2 and hypertension (mean age 73.5 ± 6.1 years, mean duration 11.9 ± 9.2 years) and 44 control subjects (mean age 73.1 ± 5.4 years). All patients and control subjects underwent an MRI of the brain. White matter lesions (WML), cerebral atrophy and medial temporal lobe atrophy were rated by a standardized visual rating scale. Lacunar infarcts were defined as focal hypo-intensities on fluid-attenuated inversion recovery sequences with a hyperintense rim around it. ***Results:*** WML occurred more frequently in diabetic patients with hypertension as well as without hypertension. Significantly more deep WML were found in DM patients with and without hypertension when compared to control subjects, whereas no difference was found in the occurrence of periventricular hyperintensities. In all 3 groups, lacunar infarcts occurred sporadically. A trend towards higher atrophy scores was seen in patients with DM compared to control subjects. ***Conclusions:*** The data of this cross-sectional study suggest that type 2 DM is an independent risk factor for deep WML in the independently living elderly patients.


The results were published at a poster session during the 2nd congress of the VASCOG Society, Florence, 2005. The data have not been published or submitted to a journal in this form.

## Introduction

Diabetes mellitus (DM) has been associated with cognitive impairment and dementia, particularly in the elderly [1]. The exact cerebral mechanisms underlying these cognitive deficits remain unclear but brain atrophy and vascular changes have both been assumed. Although a significant relation between DM and cortical or subcor-

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B. van Harten
Department of Neurology
Medisch Centrum Leeuwarden, Postbus 888
NL–8901 BR Leeuwarden (The Netherlands)
Tel. +31 58 286 3046, Fax +31 58 286 6218, E-Mail bvanharten@hotmail.com

tical atrophy has been found in several studies, the results with regard to the relation of DM and white matter lesions (WML) or lacunar infarcts are conflicting [2–10]. Reasons for these inconsistencies are methodological problems, like the number of patients studied, the use of insensitive rating scales to assess WML and patient selection. Moreover, most studies were not specifically designed to assess the effects of DM on structural brain lesions but were performed in a group of selected patients who already suffered from a stroke [2, 5, 7, 9]. In addition, a distinction into type 1 or type 2 DM was usually not made in most studies, while they may have different effects on the brain. Often type 2 DM typically develops in the context of a cluster of vascular and metabolic risk factors, like hypertension, dyslipidaemia and obesity, also called the 'metabolic syndrome', which each could lead to brain damage itself. Indeed, hypertension is the most consistent risk factor associated with WML and has been reported to increase the risk for WML approximately twofold [11–13]. More detailed insight into structural brain abnormalities that may underlie changes in cognition in diabetic patients could provide important clues into the pathogenesis.

Therefore, we performed a study in a well-defined group of independently living elderly patients with type 2 DM to investigate the association between type 2 DM, WML, lacunar infarcts and brain atrophy. Furthermore we compared diabetic patients with and without hypertension to assess if concomitant hypertension could be defined as a relevant disease variable in DM patients or if DM is an independent risk factor.

## Methods

The study population consisted of 45 type 2 DM patients with hypertension, 45 type 2 DM patients without hypertension and 44 control subjects without DM and without hypertension. DM patients were recruited from the department of internal medicine in the Sint Lucas Andreas Hospital during a time period from 2001 to 2004. The diagnosis of DM was made according to the WHO criteria [14].

Control subjects were age-matched healthy partners or neurological out-patients, visiting the hospital for low back pain or a peripheral nerve problem. Control subjects were without any cardiovascular or metabolic disorder. All were recruited by the same neurologist (B.v.H.). Exclusion criteria for patients as well as control subjects were cerebrovascular accidents, intracranial tumours, neurodegenerative diseases and alcohol intake of >3 units/day.

Information on current health status, medical history, drug prescriptions, smoking behaviour and level of education was obtained by means of an interview. Educational attainment was rated on an ordinal scale ranging from 1 (incomplete primary) to 7 (university). Total serum cholesterol, high-density lipoprotein, glucose and glycosylated haemoglobin (glyco-Hb) were determined. Blood pressure was measured in the upright sitting position using an aneroid sphygmomanometer. Measurements were done on 2 different occasions with a minimal interval of 4 weeks. The diagnosis of hypertension was based on history or if the mean of at least 2 measurements was systolic ≥160 mm Hg or diastolic ≥95 mm Hg.

Brain MRI were obtained with a 1.5-tesla scan (General Electric, Milwaukee, Wisc., USA). Whole-brain axial and coronal fluid-attenuated inversion recovery (FLAIR) and axial $T_2$-weighted images were acquired to allow detailed visualization of WML and lacunar infarcts. Coronal FLAIR images and sagittal $T_1$-weighted images were acquired to allow measurement of medial temporal lobe atrophy (MTA) and whole-brain volume. The MRI scans were analysed by an experienced rater (P.S.) who was blinded to all clinical information. The Scheltens scale was used to assess periventricular hyperintensities (PVH), white matter hyperintensities (WMH), basal ganglia hyperintensities and infratentorial foci of hyperintensities [15]. The PVH were examined in 3 regions, frontal and occipital gaps and periventricular bands, which were rated as follows: none (score 0); 5 mm or less (score 1); 6 mm or greater (score 2). The WMH were examined in 4 regions of the brain, the temporal, frontal, parietal and occipital lobes, which were rated as follows: none (score 0); 3 mm or less and 5 or fewer lesions (score 1); 3 mm or less and 6 or more lesions (score 2); 4–10 mm and 5 or fewer lesions (score 3); 4–10 mm and 6 or more lesions (score 4); 11 mm or greater and 1 or more lesions (score 5); and large confluent lesions (score 6). The basal ganglia hyperintensities were examined in 5 regions of the basal ganglia, the head of the caudate, putamen, globus pallidus, thalamus, and internal and external capsule (scores similar to the WMH). The infratentorial foci of hyperintensities were examined in 4 regions of the infratentorial structures, the cerebellum, mesencephalon, pons and medulla with scores similar to the WMH. Total scores and subscores were used for analysis, whereby a total of deep WML (DWML) was derived by summing WMH and basal ganglia hyperintensity scores. The presence of PVH and DWML is illustrated in figure 1.

Cerebral atrophy and MTA were measured by a 5-point visual rating scale [16, 17]. Mean scores of left and right MTA were used for analysis. Lacunar infarcts were defined as focal hypo-intensities corresponding on FLAIR sequences with a hyperintense rim around it (fig. 1d). Distinction from dilated perivascular spaces was made on the basis of location, size and shape of the hypo-intense abnormalities. The number of patients with lacunar infarcts ($n \geq 1$) was used for analysis.

*Statistical Analysis*

Data were analysed with the statistical package SPSS for Windows (release 12.0, SPSS, Chicago, Ill., USA). Baseline differences between groups were assessed using analysis of variance (ANOVA), Kruskal-Wallis test and $\chi^2$ tests as appropriate. Nonparametric tests were used for comparison of WML, lacunar infarcts, MTA and cerebral atrophy. Correlations were computed with Spearman's correlation coefficient. All statistical tests were two-tailed, and significance was accepted at a level of $p < 0.05$.

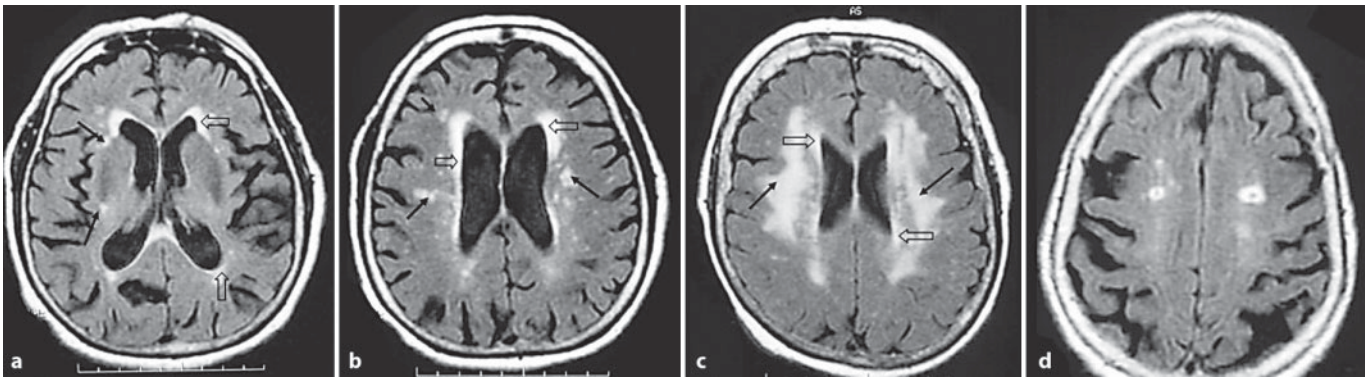


**Fig. 1.** Examples of PVH (open arrows), DWML (black arrows; **a–c**) and lacunar infarcts (**d**) on axial FLAIR sequences.

**Table 1.** Characteristics of the study population

| | DM with hypertension | DM without hypertension | Control subjects |
|---|---|---|---|
| n | 45 | 45 | 44 |
| Age, years | 73.5 (6.1) | 73.4 (5.1) | 73.1 (5.4) |
| Sex (M/F) | 19/26 | 21/24 | 21/23 |
| Duration of DM, years | 11.9 (9.2)[b] | 16.5 (11.5) | – |
| Median education, years | 4.0 | 4.0 | 4.5 |
| Smoking behaviour (yes/no) | 3/42 | 7/38 | 6/38 |
| Atrial fibrillation | 4 | 4 | 0 |
| RR systolic | 155 (19)[a, b] | 136 (12) | 144 (14.9) |
| RR diastolic | 80 (10)[b] | 75 (7)[a] | 83 (8) |
| Cholesterol/HDL | 4.8 (1.3) | 4.2 (1.4) | 4.5 (1.4) |
| Glyco-Hb | 7.7 (1.0)[a] | 7.8 (1.0)[a] | 5.8 (1.1) |
| OAD/insulin | 9/36 | 14/31 | – |

Data are expressed as means, with SD in parentheses; analyses were done with ANOVA with post hoc Bonferroni tests, $\chi^2$ tests or Kruskal-Wallis tests when appropriate.

HDL = High-density lipoprotein; OAD = oral antidiabetics.

[a] $p < 0.05$ compared to the control group

[b] $p < 0.05$ compared to the other patient group.

## Results

The groups were comparable with regard to sociodemographic factors and lipoprotein levels (table 1). The mean systolic pressure was significantly higher in the DM group with hypertension. The mean duration of DM was significantly longer in patients without hypertension. MRI data were inconclusive in 2 patients due to claustrophobia. The total WML score was statistically significantly higher in DM patients compared to control subjects ($p = 0.02$; table 2). DWML occurred more frequently in patients with DM ($p = 0.007$), whereas the occurrence of PVH did not ($p = 0.3$). The total amount of WML and DWML showed higher scores in DM patients with hypertension compared to those without, but significance was not reached ($p = 0.74$ and $p = 0.91$, respectively). The prevalence of lacunar infarcts in all 3 groups was low without significant differences ($p = 0.68$; table 2). Although atrophy scores tended to be higher in the DM group, a statistically significant association was not found for MTA ($p = 0.48$) or global atrophy ($p = 0.25$; table 2). A significant positive correlation was found between the value of glyco-Hb and total WML score ($r = 0.25$, $p = 0.02$) as well as DWML score ($r = 0.25$, $p = 0.02$). The correlation of glyco-Hb with PVH was not significant. The duration of DM correlated significantly with PVH ($r = 0.24$, $p = 0.03$), DWML ($r = 0.28$, $p = 0.01$) and total WML score ($r = 0.29$, $p = 0.008$).

## Discussion

We found more DWML in a group of independently living elderly patients with type 2 DM compared to healthy control subjects. A relation between DM and lacunar infarcts and DM and atrophy was not found. No significant differences were found between the DM groups with and without hypertension. The significantly positive correlation between the duration of DM and WML may explain the non-significant differences in findings between diabetic patients with and without hypertension. To strengthen the association between type 2 DM and DWML, we found significantly positive correla-

**Table 2.** Prevalence of WML, lacunar infarcts and atrophy between the different groups

| | DM | | Control subjects (n = 44) |
|---|---|---|---|
| | with hypertension (n = 44) | without hypertension (n = 44) | |
| Total WML score | 5.9 (5.6)* | 5.4 (3.7)* | 3.3 (2.4) |
| PVH | 2.5 (1.5) | 2.8 (1.6) | 2.2 (1.4) |
| DWML | 3.3 (4.4)* | 2.6 (2.5)* | 1.2 (1.4) |
| IFH | 0.1 (0.4) | 0.0 (0.1) | 0 (0) |
| Lacunar infarcts (patients) | 5 | 3 | 3 |
| MTA | 0.38 (0.56) | 0.44 (0.70) | 0.28 (0.55) |
| Global atrophy | 1.0 (0.5) | 1.2 (0.7) | 0.9 (0.6) |

IFH = Infratentorial foci of hyperintensities.

Values of the WML total score, subscores, medial temporal lobe atrophy and global atrophy scores are expressed as means, with SD in parentheses. The lacunar infarcts are expressed as the number of patients with lacunar infarcts; Kruskal-Wallis tests were performed for the analysis of WML and atrophy, $\chi^2$ tests for the differences of lacunar infarcts.

* $p < 0.05$ compared to the control group.

tions between the severity of DWML and the value of glyco-Hb and the duration of DM, respectively.

A number of studies addressing the association between DM and WML have been published previously with inconsistent results. We have chosen a case-control study design consisting of independently living elderly out-patients with type 2 DM, which may have implications for these specific patients. Our results with regard to DWML are in line with a recently published study in a group of patients with type 2 DM recruited from general practitioners, but in contrast to our study differences in atrophy scores were also significant [18]. Two other relatively small case-control studies have shown conflicting results with regard to DM and WML, but only patients with type 1 DM were included [19, 20]. Two population-based studies demonstrated a relation of DM with cerebral atrophy, whereas an association with WML was not found [3, 6]. Most other studies used dichotomous or ordinal rating scales, which may be not sensitive enough in the discrimination between various degrees of WML [2, 7–10]. This might be important, because the consistently reported modest cognitive deficits in DM patients do not suggest severe lesions and the used scales may therefore underestimate WML in DM patients [1]. In contrast, the Scheltens scale, which was used in the present study, is able to detect small amounts of WML [15]. Furthermore, other studies were not designed to specifically assess the effects of DM on neuro-imaging modalities but assessed the effect of DM in selected patients with stroke or other cardiovascular risk factors [2, 5, 7, 9]. The results of these studies have low external validity and do not allow to generalize to the DM population visiting an out-patient clinic.

The difference between the association of DM with DWML versus PVH supports the hypothesis that DWML and PVH are pathologically different. It has already been suggested that PVH is more associated with atrophic processes involving ventricular enlargement whereas DWML is associated with cerebrovascular risk factors [21, 22].

The results of the present study may be important to provide clues for the pathogenesis of cognitive impairment in DM patients. To our knowledge only one study analysed cognitive function and brain imaging within a type 2 DM population and found some associations between cognitive function and brain MRI abnormalities [18].

Among the limitations of the present study is firstly the use of a visual rating scale for assessing atrophy. Although visual rating of MTA is a clinically useful method for differentiating Alzheimer's disease from controls and is quicker and more accurate than volumetry [23], volumetric scales may be more sensitive in our study population without clinically diagnosed dementia. This may explain the non-significant trend towards higher atrophy scores in DM patients compared to controls. Secondly, actual volumetric assessments may be more sensitive to assess WML, but in fact a significant agreement of the Scheltens scale with quantitative volumetric measurements has been shown, so results are not expected to differ much when volumetry had been used [24]. Finally, the

prevalence of lacunar infarcts was low and may therefore explain the non-significant differences in the DM patients with hypertension compared to those without as well as the control subjects due to lack of statistical power.

In conclusion, the data of this cross-sectional study show that type 2 DM is an independent risk factor for DWML in the independently living elderly patients. The significantly positive correlation between the value of glyco-Hb and the severity of WML may have important therapeutic implications suggesting that better metabolic control in the elderly patients with type 2 DM could prevent worsening of WML. Further studies are needed to investigate the relations between MRI measures and cognitive decline in DM patients.


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