Brain Imaging in Patients With Diabetes

A systematic review

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Diabetes is associated with impaired cognitive functioning and an increased risk of dementia (1,2). Patients with type 1 diabetes may show mild to moderate slowing of mental speed and diminished mental flexibility, whereas learning and memory are relatively spared (3). In patients with type 2 diabetes, cognitive impairment may be relatively more pronounced, particularly affecting verbal memory or complex information processing (4,5). The pathogenesis is still uncertain, but chronic hyperglycemia, vascular disease, repeated hypoglycemic episodes, and possibly direct effects of insulin on the brain have been implicated (6). Brain imaging studies can help to clarify the pathogenesis. An increasing number of studies report both focal vascular and more global (e.g., atrophy) cerebral changes, but the results are not always consistent.

Our aim was to systematically review brain imaging studies in patients with diabetes. Data on the relation of imaging with cognition and with relevant disease variables were also recorded.

RESEARCH DESIGN AND METHODS

— Medline and EMBASE (1966 to February 2006) were searched with the following medical subject heading terms: computed tomography (CT) and magnetic resonance imaging (MRI) studies: white matter, leukoaraiosis, lacunar infarction, subcortical, periventricular, brain, cerebral, hippocampus, atrophy, MRI, magnetic resonance imaging, CT, and tomography; magnetic resonance spectroscopy (MRS) studies: magnetic resonance spectroscopy, MRS, brain, and cerebral; positron emission tomography (PET), single-photon emission CT (SPECT), and Xenon-enhanced CT studies: cerebral blood flow, glucose metabolism, brain, cerebral, PET, SPECT, Xenon, positron emission tomography, single-photon emission tomography, and tomography; all combined with "diabetes."

The abstracts were screened and potentially relevant articles retrieved. These articles were included if they met the following four criteria: *1*) original article, written in English, on brain imaging in adult patients with diabetes in comparison with control subjects; *2*) diagnostic criteria for diabetes specified; *3*) sample size of at least 20 diabetic patients, or a total sample size >200 if the number of diabetic patients was not specified; *4*) for CT or MRI studies: specification of the rating method for white matter lesions (WMLs) or atrophy. Eligible articles were evaluated against the inclusion criteria by two independent authors (B.v.H., F.E.d.L., or G.-J.B.). In case of disagreement, a consensus meeting was held. If multiple articles reported on the same imaging outcome measure from the same study population, the article with the most detailed data on brain imaging and/or the largest study population was included.

The search strategy for MRI and CT studies yielded 271 articles. Three additional articles were identified through bibliographies of included articles (7–9). After screening of title and abstracts was completed, 117 full-text versions were retrieved, of which 46 were included. The search for MRS studies yielded 75 articles, of which 3 were included. The search strategy for PET, SPECT, and Xenon-CT yielded 84 articles, of which 6 were included.

From included studies, the source population (e.g., population or clinic based), experimental design (e.g., cross-sectional, longitudinal), sample size, and age of the participants were recorded. The procedure for diagnosing diabetes was recorded (e.g., based on history, based on oral glucose tolerance test), as well as the diabetes type of the population involved (type 1 diabetes, type 2 diabetes, mixed, or unknown). If the diabetes type was not specified and the mean age of the patients was ≥60 years, the population was classified as "predominantly type 2 diabetes." The imaging modality and the methods to rate WMLs, atrophy, lacunar infarcts, cerebral blood flow (CBF), or cerebral glucose metabolism were recorded. Effect sizes (Cohen's *d*), odds ratios (ORs), or relative risks with 95% CIs for these outcome measures were recorded or calculated based on the available data. Data on the relation between relevant comorbidity (e.g., hypertension) and diabetes-related variables (e.g., glycemic control, microvascular complications, diabetes duration, medication use) and the imaging outcome measures were also recorded.

The source of the study populations in CT or MRI studies varied considerably, from true population-based sampling to populations with vascular or cognitive pathology. To improve clarity, we therefore classified the 46 included articles into three main categories: *1*) "general cohorts" (n = 11): this category included articles on population-based studies or case-control studies, in which the cases were recruited from the general population or a diabetes clinic; *2*) "vascular cohorts" (n = 23): this category included articles on studies that primarily recruited

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Abbreviations: CBF, cerebral blood flow; CT, computed tomography; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PET, positron emission tomography; SPECT, single-photon emission CT.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Relation between diabetes and WMLs*

Study (ref.)	Study population	Subjects (total/diabetic) (*n*)	Mean age (years)	Diabetes type	Imaging
General cohorts					
Dejgaard et al. (16)	Case/control	60/20	40	1	MRI
Yousem et al. (37)	Case/ control	35/25	31	1	MRI
Longstreth et al. (7)	Population based	3,301/369	>65	2	MRI
den Heijer et al. (12)	Population based	506/41	>60	2	MRI
Schmidt et al. (13)	Population based	1,252/114	69	2	MRI
Jerekathil et al. (9)	Population based	1814/91	54	ND	MRI
Jorm et al. (15)	Population based	475/?	>60	2	MRI
Vascular cohorts					
Hijdra et al. (19)	Stroke	376/59	>65	2	CT
Schmidt et al. (17)	Stroke/vascular risk factors and control	234/38	55	ND	MRI
Manolio et al. (10)	Stroke and control	303/76	>65	2	MRI
Fukuda and Kitani (63)	Hypertension	238/52	>40	ND	MRI
Jorgensen et al. (64)	Stroke or TIA	1,084/203	>70	2	CT
Awada and Omojola (39)	Stroke	398/131	>60	2	CT
Henon et al. (65)	Stroke	610/83	64	2	CT
Padovani et al. (34)	Stroke and control	100/20	>60	2	MRI
Coskun et al. (38)	Stroke	288/57	>65	2	CT
Streifler et al. (18)	Stroke	596/110	>60	2	CT
Kario et al. (47)	Hypertension	20/20	69	2	MRI
Outpatient cohorts					
Raiha et al. (41)	Geriatric department	204/55	74	2	CT
Araki et al. (21)	MRI for any indication	2,725/159	60	2	MRI
Fukuda and Kitani (66)	Neurologically normal	253/50	66	2	MRI
Kobayashi et al. (22)	Neurologically normal	933/66	58	ND	MRI
Hogervorst et al. (24)	Alzheimer's disease and control subjects	414/29	74	2	CT
Masana and Motozaki (23)	Mild headache and vertigo	1,674/87	51	ND	MRI
Biessels et al. (11)	Memory clinic	347/29	73	2	MRI
Lazarus et al. (20)	Memory clinic	177/20	>65	2	MRI
Taylor et al. (14)	Depressive disorder and control subjects	399/34	70	2	MRI

Studies are listed in chronological order. Study populations: general cohorts, population-based or case-control studies; vascular cohorts, cohort with stroke or other cardiovascular risk factors; outpatient cohorts, neurological, or psychiatric outpatients. Diabetes type: 2 (except for the Study by Kario et al. [47]), population type classified as predominantly type 2 diabetes (see RESEARCH DESIGN AND METHODS). ND, not determined. Rating scale: Dich, dichotomous scale; Int, interval scale; Ord, ordinal scale. *Dichotomization was performed for analysis. Outcome and results (diabetic patients vs. control subjects): BG, basal ganglia; DWML, deep WMLs; GML, gray matter lesions; PVH, periventricular hyperintensities. ORs are presented with 95% CIs in parentheses. †Where possible, we calculated OR or effect sizes (*d*) if they were not provided in the original article. Mean differences (diff; with 95% CIs in parentheses), *d*, β, and *t* values >0 reflect more severe WMLs in the diabetic group relative to control subjects. Studies marked with ‡ were included in the meta-analysis presented in Table 4. *P* value: NS, not significant; ?, not specified. Adjustments/matching: apo, apolipoprotein; AF, atrial fibrillation; BP, blood pressure (including hypertension, mean arterial pressure, systolic blood pressure, use of antihypertensive drugs, left ventricular hypertrophy, and ankle-to-arm index); edu, education; HL, hyperlipidemia; ICD, ischemic cerebrovascular disease (including transient ischemic attack [TIA], stroke, leukoaraiosis, WMLs, and ultrasound examination of carotid or intracranial arteries); PVD, peripheral vascular disease (including peripheral artery disease, coronary artery disease, cardiac disease, congestive heart failure, and electrocardiogram changes).

patients with stroke or other cardiovascular risk factors and assessed the effects of diabetes within these selected populations; 3) "outpatient cohorts" ($n = 12$): this category included articles on cohorts of neurological or psychiatric outpatients (e.g., with cognitive complaints or other neurological or psychiatric conditions) and assessed the effects of diabetes within these selected populations.

Meta-analyses were performed on dichotomous outcome measures if a given outcome measure was available from at least two independent studies on the same cohort type with the same imaging modality (CT or MRI) and if the required data could be extracted from the articles. Analyses were performed with Review Manager (version 4.2; Cochrane Collaboration, Copenhagen, Denmark) on unadjusted data. For individual studies, no systematic differences were observed between these unadjusted ORs and adjusted ORs as presented in Tables 1 and 2.

RESULTS

CT and MRI studies

Diabetes and WMLs. The majority of the studies used ordinal rating scales with

Table 1—*Continued*

Rating scale	Outcome and results	*P* value	Adjustments/matching
Dich	OR 15.4 (3.8–63.2)†	<0.05	Age
Dich	No WML in either group	NS	Age, sex
Ord (0–9)	NS		Age, sex
Ord (0–9) PVH	PVH: diff +0.4 (−0.2 to 1.1), $d = 0.4$†	NS	Age, sex
Int WML	WML: diff +0.01 ml (−1.0 to 1.0), $d = 0.2$†	NS	
Int	PVH: median diff 0	0.1	Sex, age, edu, BP, smoking, BMI, HL, PVD
	WML: median diff +0.2	0.2	
Volumetry	WML: $\beta = 0.02$	0.8	Age, sex
Volumetry	WML: $r = 0.03$	NS	No
Ord (0–4)*	OR 2.0 (1.1–3.5)†‡	0.02	No
Ord (0–3)	$\beta = 0.2$ (SE 0.1)	<0.001	Age, BP, sex, ICD, PVD
Ord (0–8)	Diabetes: mean diff 0.4	0.1	No
Ord (0–5)	Diabetes: mean diff 0.1, $d = 0.2$†	0.3	No
Dich	OR 0.8 (0.5–2.3)†‡	0.3	No
Dich	OR 0.9 (0.6–1.5)†‡		No
Ord (0–3)	Estimated coefficient 1.2 (SE 0.8)	0.1	Age, sex, BP, alcohol, HL, ICD, cerebral atrophy
Ord (0–3)	$\beta = 0.02$ (SE 0.1)	0.9	Age, sex, BP, PVD, ICD, ventricular index
Ord (0–4)*	OR 0.6 (0.06–0.3)†‡	NS	No
Ord*	OR 1.6 (1.0–2.6)†‡	0.04	No
Ord*	OR 2.2 (0.5–9.0)	NS	Age, sex, BP
Dich	OR 0.9 (0.5–1.7)†	NS	No
Dich	OR 1.4 (0.7–2.8)†‡	NS	No
Ord (0-4)	$d = 0.1$†	0.6	Age, sex, BP, smoking, HL, ICD
Ord (PVH: 0–4)*	PVH: OR 2.0 (0.8–4.8)†‡	0.2	No
Dich (WML)	DWML: OR 0.8 (0.3–2.8)†‡	0.6	
Ord (0–3)*	OR 1.4 (0.5–4.3)	0.5	Age, sex, diagnosis, smoking, diabetes, BP, apoE4
Ord (0–3)	OR 1.6 (0.8–3.0)‡	0.2	Age, sex, BP, HL, family history, smoking, alcohol, ICD
Ord (0–6)	PVH: mean diff 0 (−0.5 to 0.5)	NS	Age, sex
Ord (0–24)	DWML: mean diff −0.5 (−2.0 to 1.5)	NS	
Ord (0–4)*	PVH: OR 1.6 (0.6–5.2)‡	NS	Age, BP, AF, ICD
	DWML: OR 2.9 (1.0–7.8)	?	
Volumetry	WML: $t = -1.3$	0.2	Age, sex, BP
	GML in BG: $t = -1.08$	0.3	

three to four levels, ranging from absent to severe confluent WMLs (Table 1). Other studies made a dichotomization into presence or absence of WMLs. Five studies used an ordinal scale that included nine or more grades of WML severity (7,10,11) or an interval scale (12,13). Only three studies used actual volumetric measurements (9,14,15).

From the seven studies categorized as "general cohorts," one observed a significant association between diabetes and WMLs, although the actual median total deep WML volume in the diabetic group was small (<0.1 ml) (16). From the 11 studies categorized as "vascular cohorts," 3 reported an increased severity of WMLs in patients with diabetes (17–19). From the nine studies categorized as "outpatient cohorts," only one reported a statistically significant association between diabetes and WMLs (20), although in four studies WML scores tended to be higher in the diabetic group (21–24).

Nine of the 27 WML studies could be included in the meta-analysis (Table 4). In the "vascular cohorts," there was no association between diabetes and WMLs (OR 1.1 [95% CI 0.9–1.4]). In contrast, in the "outpatient cohorts," there appeared to be a modest association between WMLs and diabetes (point estimates for ORs varied from 1.8 to 2.4 [Table 4]).

Diabetes and lacunar infarctions. Twenty articles on lacunar infarcts, which dealt with 19 study populations, were included. For one population, both cross-sectional (8) and longitudinal (25) analyses were reported. Both articles were included, but only the cross-sectional data are presented in Table 2 and included in the meta-analysis. The majority of studies used MRI. The definition of lacunar infarcts (i.e., focal hyperintensities on T2-weighted images with corresponding hypointense lesions on T1 or FLAIR imaging) was consistent across the studies.

Four studies were categorized as "general cohorts" (8,13,25,26). Two of these studies reported an association between diabetes and symptomatic infarcts but no association with silent lacunar infarcts (8,26). The only longitudinal study observed an association between diabetes and silent incident lacunar infarcts (OR 2.9 [95% CI 1.0–8.5]) without a signifi-

Table 2—*Relation between diabetes and lacunar infarcts*

Study (ref.)	Study population	Subjects (total/diabetic) (*n*)	Mean age (years)	Diabetes type	Imaging	Outcome and results	*P* value	Adjustments/ matching	Estimated power
General cohorts									
Longstreth et al. (26)	Population based	3,660/519	>65	2	MRI	Silent: OR 1.1 (0.8–1.5)	0.6	Age, sex, BP, HL, smoking, PVD, creatinine	1.0
						Symptomatic: OR 2.2 (1.1–4.5)	0.02		
Vermeer et al. (8)	Population based	1,077/75	>60	2	MRI	Silent: OR 0.7 (0.4–1.5)	NS	Age, sex, BP, smoking	0.8
						Symptomatic: OR 2.5 (1.0–5.9)	<0.05		
Schmidt et al. (13)	Population based	1,252/114	69	2	MRI	Silent: OR 1.4 (0.7–2.7)*	0.3	Sex, age, edu, BP, smoking, BMI, HL, PVD	0.6
Vascular cohorts									
Jorgensen et al. (40)	Stroke	494/79	>70	2	CT	Silent: OR 1.4 (0.9–2.4)*	0.2	No	0.8
Konemori (67)	Stroke vs. control	324/36	>50	ND	MRI	Silent: OR 0.8	NS	Age, sex, BP, HL	0.5
						Symptomatic: OR 2.5	NS		
Hsu et al. (28)	Stroke and control	132/20	>60	2	CT	Symptomatic: OR 12.5 (3.1–57.6)	<0.05	No	0.3
Adachi et al. (42)	Stroke	171/50	69	2	MRI	Silent: OR 1.9 (0.9–3.9)	0.1	No	0.5
Revilla et al. (29)	Lacunar infarcts and control	164/28	65	2	CT/MRI	Symptomatic: OR 5.4 (1.5–18.9)	0.008	Age, sex, BP, HL, smoking	0.4
Arauz et al. (27)	Lacunar infarcts	175/72	64	2	MRI	Silent: OR 3.0 (1.3–7.0)	0.03	Age, sex, BP, HL, smoking, alcohol, PVD	0.5
Selvetella et al. (43)	Hypertension	195/40	>60	2	MRI	Silent: OR 2.0 (0.9–4.1)*	0.07	No	0.5
Giele et al. (68)	Atherosclerotic vascular disease or risk factors	308/59	58	ND	MRI	Silent: OR 1.4 (0.7–2.8)*	0.4	No	0.5
Karapanayiotides et al. (30)	Stroke	4,064/611	67	2	MRI	Symptomatic: OR 1.8 (1.3–3.8)	0.009	Sex, smoking, HL	1.0
Sarkar et al. (31)	Stroke	450/171	51	ND	CT	Symptomatic: OR 2.6 (1.8–3.9)	<0.05	No	0.9
Kario et al. (47)	Hypertension	20/20	69	2	MRI	Silent and symptomatic: OR 2.3 (0.6–8.0)	NS	Age, sex, BP	0.2
Kawamoto et al. (44)	Stroke	453/40	76	2	CT	Symptomatic: OR 0.7 (0.3–1.6)	0.35	Age, sex, smoking	0.5
Outpatient cohorts									
Araki et al. (21)	MRI for any indication	2,725/159	60	2	MRI	Silent: OR 1.0 (0.7–1.4)*	NS	No	1.0
Kobayashi et al. (22)	Neurologically normal	933/66	58	ND	MRI	Silent: OR 2.4 (1.2–4.9)	0.01	Age, sex, BP, alcohol, PVD	0.5
Uehara et al. (69)	Neurologically normal	219/37	63	2	MRI	Silent LI white matter: OR 2.3 (0.98–5.6)	0.06	Age, sex, BP, HL, smoking, PVD	0.5
						Silent LI in BG: OR 0.7 (0.2–2.1)	0.6		
Biessels et al. (11)	Memory clinic	347/29	73	2	MRI	Silent: OR 2.3 (0.9–5.6)	NS	Age, sex	0.3

Studies are listed in chronological order. Study populations: general cohorts, population-based or case-control studies; vascular cohorts, cohort with stroke or other cardiovascular risk factors; outpatient cohorts, neurological outpatients. Diabetes type: 2 (except for the study by Kario et al. [47]), population type classified as predominantly type 2 diabetes (see RESEARCH DESIGN AND METHODS). ND, not determined. Outcome and results: BG, basal ganglia; LI, lacunar infarcts. ORs are presented with 95% CIs in parentheses. *Where possible, we calculated ORs if they were not provided in the original article. *P* value: NS, not significant. Adjustments/matching: AF, atrial fibrillation; BP, blood pressure (including hypertension, mean arterial pressure, systolic blood pressure, use of antihypertensive drugs, left ventricular hypertrophy, and ankle-to-arm index); edu, education; HL, hyperlipidemia; ICD, ischemic cerebrovascular disease (including transient ischemic attack, stroke, leukoaraiosis, WMLs, and ultrasound examination of carotid or intracranial arteries); PVD, peripheral vascular disease (including peripheral artery disease, coronary artery disease, cardiac disease, congestive heart failure, and electrocardiogram changes). Estimated power: For each study, the power ($1 - \beta$) to detect a statistically significant difference between the diabetic and the control group was estimated, assuming an OR for infarcts of 2.0 in the diabetic group and an α of 0.05 with two-sided testing (http://calculators.stat.ucla.edu/powercalc/).

Table 3—*Relation between diabetes and cerebral atrophy*

Study (ref.)	Study population	Subjects (total/diabetic) (*n*)	Mean age (years)	Diabetes type	Imaging	Rating scale	Outcome and results	*P* value	Adjustments/ matching
General cohorts									
Longstreth et al. (33)	Population based	3,253/?	>65	2	MRI	Ord (0–9)	Increase in cortical atrophy grade: men 0.6 (0.2–0.9); women 0.2 (0–0.4)	?	Age, race, edu, BP, PVD, alcohol
Den Heijer et al. (12)	Population based	506/41	>60	2	MRI	Int	Hippocampal volume: −4% (0–9)*	0.04	Age, sex, PVD
							Amygdalar volume: −7% (−2 to 12)*	0.004	
Schmidt et al. (13)	Population based	1,252/114	69	2	MRI	Ord (0–15), ventricle-to-brain ratio	Cortical atrophy: $d = 0.3$*	0.001	Sex, age, edu, BP, PVD, smoking, BMI, HL
							Subcortical atrophy: $d = 0.3$*	0.03	
Musen et al. (36)	Case-control	118/82	33	1	MRI	Volumetry	Cortical density loss: range 4.3–5.0%	<0.001	Age, sex, edu,
							Subcortical density loss: 5.2%	<0.001	
Vascular cohorts									
Manolio et al. (10)	Stroke and control	303/76	>65	2	MRI	Ord (0–9)	Sulcal widening: mean diff −0.3	0.3	No
							Ventricular enlargement: mean diff 0.5	<0.03	
Padovani et al. (34)	Stroke and control	100/20	>60	2	MRI	Int	Ventricular enlargement: NS	NS	No
Outpatient cohorts									
Pirttila et al. (32)	CT for any indication	416/46	>15	ND	CT	Dich	Any cerebral atrophy: OR 3.4 (1.8–6.5)*	?	No
Soininen et al. (35)	Elderly volunteers	84/25	>70	2	CT	Int	Cortical atrophy: d = range −0.2 to 0.7 (right temporal horn)*	NS	Age, head size
							Subcortical atrophy: d = range 0.2–0.4*	NS	
Araki et al. (21)	MRI for any indication	2,725/159	60	2	MRI	Dich	Any cerebral atrophy: OR 3.2 (2.3–4.4)*	<0.05	No
Biessels et al. (11)	Memory clinic	347/29	73	2	MRI	Ord	Cortical atrophy: mean diff 1.5 (0–2.5)	?	Age, sex
							Subcortical atrophy: mean diff 0 (−1.5 to 2)	NS	
							Medial temporal lobe atrophy: mean diff 0.5 (−0.5 to 0.5)	NS	

Studies are listed in chronological order. Study populations: general cohorts, population-based or case-control studies; vascular cohorts, cohort with stroke or other cardiovascular risk factors; outpatient cohorts, neurological outpatients. Diabetes type: 2 (except for the study by Soininen et al. [35]), population type classified as predominantly type 2 diabetes (see RESEARCH DESIGN AND METHODS). ND, not determined. Rating scales: Dich, dichotomous scale; Int, interval scale; Ord, ordinal scale. Outcome and results: ORs are presented with 95% CIs in parentheses. *Where possible, we calculated ORs or effect sizes (d) if they were not provided in the original article. Mean differences (diff; with 95% CIs in parentheses), d, β, and t values >0 reflect more severe atrophy in the diabetic group relative to control subjects. *P* value: NS, not significant; ?, not specified. Adjustments/matching: AF, atrial fibrillation; BP, blood pressure (including hypertension, mean arterial pressure, systolic blood pressure, use of antihypertensive drugs, left ventricular hypertrophy, and ankle-to-arm index); edu, education; HL, hyperlipidemia; ICD, ischemic cerebrovascular disease (including transient ischemic attack, stroke, leukoaraiosis, WMLs, and ultrasound examination of carotids or intracranial arteries); PVD, peripheral vascular disease (including peripheral artery disease, coronary artery disease, cardiac disease, congestive heart failure, and electrocardiogram changes).

Table 4—*Meta-analysis of WMLs and lacunar infarcts*

	Imaging measure	No. of studies	Subjects		OR (95% CI)
			Control (*n*)	Diabetic (*n*)	
WMLs					
Vascular cohorts	CT	5	2,129	604	1.1 (0.9–1.4)
Outpatient cohorts	MRI: PVH	2	1,024	86	1.8 (0.9–3.6)
	MRI: DWML	2	1,024	86	1.7 (0.9–3.5)
	MRI: any WML	2	4,071	246	2.4 (1.7–3.4)
Lacunar infarcts					
General cohorts	MRI	3	5,281	708	1.3 (1.1–1.6)
Vascular cohorts	CT	5	1,349	338	2.3 (1.8–3.0)
	MRI	7	4,389	888	2.1 (1.8–2.5)
	Total (CT + MRI)	12	5,738	1,226	2.2 (1.9–2.5)
Outpatient cohorts	MRI	4	3,934	291	1.4 (1.1–1.8)

Analyses were performed on the crude, unadjusted data. For WMLs, all studies that could be included in the meta-analysis are listed and marked with ‡ in the "Outcome and results" column in Table 1. The analysis on lacunar infarcts includes all studies listed in Table 2. any WML, studies that did not distinguish between DWML and PVH; DWML, deep WMLs; PVH, periventricular hyperintensities.

cant association between diabetes and silent infarcts at baseline (1.9 [0.4–4.8]) (25).

Of the 12 studies categorized as "vascular cohorts," 1 showed a significant association between diabetes and silent lacunar infarcts (27) and 4 between diabetes and symptomatic lacunar infarcts (28–31). Of the four studies categorized as "outpatient cohorts," one showed a significant association between diabetes and silent lacunar infarcts (22).

We calculated the power for each study to detect statistically significant differences between diabetic and nondiabetic subjects, assuming a relative risk of 2.0 for infarcts in the diabetic group. Despite the rather high contrast between the groups in this assumption, the estimated power of the majority of studies was ~0.5, although it is common to require a power between 0.8 and 0.9.

All studies on lacunar infarcts could be included in the meta-analysis (Table 4). There was a significant association between diabetes and lacunar infarcts in all cohort types (general cohorts OR 1.3 [95% CI 1.1–1.6], vascular cohorts 2.2 [1.9–2.5], and outpatient cohorts 1.4 [1.1–1.8]).

Diabetes and cerebral atrophy. Ten studies addressed the relation between diabetes and atrophy (Table 3), with marked heterogeneity in the methods for atrophy assessment. Some studies measured only cortical atrophy or hippocampal atrophy (12,21,32,33), others measured only subcortical atrophy (34), and others assessed both (10,11, 13,35,36).

All four studies categorized as "general cohorts" (12,13,33,36), one of the two studies categorized as "vascular cohorts" (10), and all four studies belonging to the "outpatient cohorts" (11,21,32,35) showed associations between diabetes and cerebral atrophy (i.e., amygdalar atrophy, cortical atrophy, or subcortical atrophy). The outcome measures on atrophy were too heterogeneous to perform a meta-analysis.

Relation of CT and MRI findings to cognition and other disease variables

Only three studies compared cognition between diabetic and nondiabetic patients (11,16,36). One study, classified as a "general cohort," showed modest impairments of cognitive performance in type 1 diabetic patients (36), whereas a study classified as a "vascular cohort" (16) and a study of patients attending a memory clinic (11) reported no difference between diabetic and nondiabetic patients. None of these studies presented analyses on the association between cognition and MRI findings in the diabetic population.

From the 46 articles, 3 study populations included only type 1 diabetic patients, 2 included only type 2 diabetes, 32 were classified as "predominantly type 2 diabetes," and 9 were classified as "diabetes of unknown type" (Tables 1–3). The diagnosis of diabetes was based on history or medication use in 20 studies (7,8,14,18,20,21,24,26,28,31–33,37–44), while in the other studies, active screening was done by fasting glucose levels, random glucose levels, or an oral glucose tolerance test. Only two studies included data on metabolic control (16,36). Two studies on type 2 diabetic patients specified which glucose-lowering therapy was used (11,27). The duration of diabetes was mentioned in two studies (16,36).

Few studies presented detailed data on relevant disease variables in relation to brain imaging. One study indicated that higher levels of HbA_{1c} (A1C), longer duration of type 1 diabetes, severe hypoglycemic events, and severity of retinopathy were associated with cortical and/or subcortical gray matter atrophy (36). Although several studies collected data on, for example, hypertension and vascular morbidity (Tables 1–3), these data were generally only entered as covariates in the analysis of the between-group difference of the population with and without diabetes. Data on the effects of these variables on lesion severity within the diabetic population were not provided.

MRS studies

Three studies examined cerebral metabolism in diabetes with ^{1}H-MRS. One study, which included 6 type 1 diabetic and 24 type 2 diabetic patients, reported increased *myo*-inositol–to–creatine ratios in the gray and white matter but did not observe significant changes in *N*-acetylaspartate ratios (45). Another study that included 17 type 1 diabetic (of which 9 were recovering from diabetic ketoacidosis) and 4 type 2 diabetic patients reported increased *myo*-inositol–to–creatine ratios and decreased *N*-acetylaspartate–to–creatine ratios (46). The third study only included type 2 diabetic patients with hypertension and hypertensive control subjects and showed decreased *N*-acetylaspartate–to–creatine

ratios (47). The latter is regarded as an indicator of reduced neuronal viability (48).

PET and SPECT studies

Four studies examined cerebral perfusion in diabetes with SPECT (49–52). Three of these studies involved patients with type 1 diabetes (mean age 30–40 years, n = 20–65) (49–51) observing both modest regional hypo- and hyperperfusion in the diabetic patients relative to control subjects, particularly in patients with long-standing diabetes and a history of severe hypoglycemic episodes. The fourth study, which predominantly involved patients with type 2 diabetes, observed 25–30% reductions in mean CBF in all cortical areas studied, as well as the cerebellum, in a group of 27 patients (mean age 64 years) relative to age-matched control subjects (52). The abnormalities were most pronounced in patients who were treated with insulin (52). A study in type 1 diabetic patients with Xenon-enhanced CT reported CBF to be in the normal range in most patients but did observe reduced flow with increased duration of diabetes (53).

One study on 21 patients with type 1 diabetes and 12 control subjects reported a 15–20% reduction in cerebral glucose metabolism in type 1 diabetes with PET, but only in a subgroup of patients with long-standing diabetes and microvascular complications (e.g., neuropathy, retinopathy) (54). No abnormalities in glucose metabolism were observed in patients with newly diagnosed diabetes (54).

CONCLUSIONS

The CT and MRI studies reviewed herein show a relation between diabetes and cerebral atrophy and lacunar infarcts but no consistent relation with WMLs. The MRS studies report elevated *myo*-inositol–to–creatine ratios and reduced *N*-acetylaspartate–to–creatine ratios in diabetic patients. The PET and SPECT studies reveal regional alterations in CBF. None of the studies assessed the relation between imaging findings and cognition, and data on the relation between imaging findings and disease variables were scarce.

Methodological limitations were observed in a considerable proportion of studies. Study design and methodology were markedly heterogeneous, involving issues such as sample selection, diabetes assessment, imaging rating methods, and data analyses. The majority of the studies based their results on relatively small populations. This leads to low statistical power, as illustrated by the power calculations in Table 2. The findings from negative studies may therefore reflect lack of power instead of lack of associations. Selective recruitment may also have confounded the results. For example, patients with more severe brain lesions are less likely to participate in imaging studies. Moreover, the results of the studies belonging to the "vascular" or "outpatient cohorts" have a low external validity and cannot readily be generalized to the diabetic population at large. The results of the meta-analysis support this point: the risk estimates for lacunar infarction, for example, clearly differ between the studies from the "vascular cohorts" and the "general and outpatient cohorts." All but one study had a cross-sectional design. A longitudinal design with repeated brain imaging could detect progression of brain abnormalities and would provide a better indication of their relation with diabetes. A high response rate on follow-up is needed to overcome selective (related to both the determinant and the outcome) participation.

The methodology for the diagnosis and classification of diabetes was suboptimal in the majority of the studies. Undiagnosed cases of diabetes will therefore have been erroneously assigned to the nondiabetic group, which can lead to an underestimation of the effect of diabetes. A distinction into diabetes type was usually not made. Based on the age of the study populations, the majority of the CT and MRI studies are likely to have predominantly included type 2 diabetic patients. PET and SPECT studies, in contrast, mainly involved type 1 diabetic patients. The relevance of the PET and SPECT findings for the CT and MRI abnormalities can therefore be questioned (and vice versa). It should be considered that type 1 and type 2 diabetes may have different effects on the brain. Type 2 diabetes, for example, is closely linked to the so-called metabolic syndrome, which refers to a cluster of vascular risk factors, including hypertension, obesity, insulin resistance, and dyslipidemia, which may each affect the brain (55). Hypoglycemic episodes, on the other hand, are more common in type 1 diabetic patients and may also have detrimental effects, albeit through entirely different pathophysiological mechanisms.

Limitations concerning the rating methods for the imaging data were also noted, in particular in studies on WMLs. The majority of the WML scales that were applied were originally developed for patients with cerebrovascular disease or vascular dementia and are relatively crude and insensitive. Although these scales adequately distinguish between patients with or without severe WMLs, they could be too insensitive to detect differences in WMLs between patients with diabetes and control subjects. True volumetric scales should be used in future studies (56). The same applies to measurement of cerebral atrophy, but apparently the association between diabetes and atrophy is more robust and has therefore been more consistently detected, even with relatively crude techniques. A possible methodological limitation of the PET and SPECT studies is failure to account for cerebral atrophy, which may have confounded the assessment of tracer uptake due to partial volume effects (57).

The included studies provide indications of pathogenesis but leave many questions unanswered. The MRI and CT studies clearly identify diabetes as a risk factor for vascular brain pathology, in particular infarctions. The mechanisms underlying cerebral atrophy, however, cannot be readily determined from cross-sectional studies. Along these lines, specific causative mechanisms cannot be derived from elevated *myo*-inositol levels and decreased *N*-acetylaspartate levels on ^{1}H-MRS studies (48). PET and SPECT studies point at disturbances of both CBF and glucose metabolism. However, blood flow changes were regional, included both hypo- and hyperperfusion, and were mostly limited to subgroups of patients. It is still uncertain whether these changes are causes or consequences of alterations in cerebral function in diabetes.

The lack of information on risk factors for brain imaging abnormalities also hampers the identification of underlying mechanisms. Only a minority of the studies included in this review took the effects of vascular risk factors, such as hypertension or atherosclerosis, into account, which should be regarded as an important omission. In the general population, hypertension, atherosclerosis, and markers of inflammation are established risk factors for WMLs and lacunar infarcts (58–60). Although cerebral atrophy is generally assumed to be due to neurodegenerative processes, it is also associated with vascular risk factors (33,61). It could therefore be argued that vascular (co)morbidity is the driving force in the

association between diabetes and brain imaging abnormalities, but this appears to be an oversimplification. A recent population-based study (proportion of diabetic patients <10%) indicated that increased A1C levels are associated with accelerated cerebral atrophy, while taking into account vascular risk factors (62). This is in line with observations from studies on cognitive functioning in diabetic patients, which also indicate that chronic hyperglycemia may have detrimental effects on the brain (3–5).

In conclusion, there is convincing evidence for an association between diabetes and cerebral atrophy and lacunar infarcts, but the risk factors for these brain imaging abnormalities have not been identified and the relation with impaired cognition has not been addressed. In addition, the issue on the association between diabetes and WMLs remains unanswered, as the methodology of available studies was not sufficiently sensitive to detect subtle alterations. Future studies should have a longitudinal design and include sufficiently large groups of well-defined diabetic patients, preferably at an early stage of the disease, in order to detect incident structural brain changes. MRI is the preferred imaging modality because the abnormalities are subtle and rating methods should be sensitive and quantitative (e.g., three-dimensional volumetry). Patients should be without cognitive impairment at study entry to assess causality with cognitive function. Standardized neuropsychological examinations should be performed at regular intervals, and data on relevant disease variables and comorbidity should be carefully recorded in order to identify the risk factors for structural brain changes. PET, SPECT, and MRS may help to identify underlying metabolic and vascular mechanisms.

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