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Diabetes Mellitus–Related Fractional Glucose Uptake in Men and Women Imaged With ^{18}F-FDG PET-CT

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Context: Cohort studies show that cognitive dysfunction and both vascular and Alzheimer's dementia are more common in patients with type 2 diabetes mellitus (T2DM).

Objective: To review and compare brain volume and ^{18}F-fluorodeoxyglucose (FDG) uptake in brain of individuals age 60 to 70 years with or without type 2 diabetes.

Design: We searched 620 medical records for negative ^{18}FDG PET-CT scans obtained during 33 months. Records showing history of cognitive impairment, Alzheimer's disease, neurologic disorders, any history of brain atrophy, or documented cerebral infarction on neuroimaging were excluded from the study.

Results: A total of 119 medical records met the inclusion criteria. Data from 63 women and 56 men (without T2DM, 86; with T2DM, 33) were analyzed. Brain volume was larger in men than women (mean ± SD, 1411 ± 225 cm^3 vs 1325 ± 147 cm^3, respectively; $P = 0.02$), but men had a significantly lower fractional glucose uptake (SUV_{gluc}), calculated as fasting blood glucose × $SUV_{max.}$ [median (minimum, maximum), 63.6 (34.6, 126.6) vs 70.0 (36.4, 134.3); $P = 0.02$]. Brain volume was also larger in persons without T2DM than in those with T2DM (1392 ± 172 cm^3 vs 1269 ± 183 cm^3; $P < 0.001$), but SUV_{gluc} was similar between these groups. Brain volume correlated with SUV_{gluc} in both men and women overall ($P < 0.001$) but not in men and women with T2DM ($P = 0.20$ and 0.36, respectively).

Conclusion: In men without T2DM, median brain volume was larger and fractional glucose uptake was less than in women without T2DM. In men and women with T2DM, brain volume and fractional glucose uptake were similar. The findings support the hypothesis that fractional glucose uptake becomes impaired in men with T2DM.

Freeform/Key Words: brain, type 2 diabetes, 18-FDG PET-CT, fractional glucose uptake

The global prevalence of type 2 diabetes mellitus (T2DM) among adults > 18 years of age has increased from 4.7% in 1980 to 8.5% in 2014 (380 million people). This number is expected to rise to 592 million people by 2035 [1, 2]. Complications related to long-lasting diabetes affect multiple organ systems, such as the kidneys, heart, eyes, and peripheral and autonomic

Abbreviations: BMI, body mass index; FBG, fasting blood glucose; FDG, fluorodeoxyglucose; PET, positron emission tomography; SUV_{gluc}, fractional glucose uptake; SUV_{max}, maximum standardized uptake value; T2DM, type 2 diabetes mellitus.

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nervous system. Studies in large cohorts show that cognitive dysfunction and both vascular and Alzheimer's dementia are more common in patients with T2DM [3–5].

Factors such as hypoglycemia, insulin resistance, and hyperglycemia play an important role in the pathophysiology of cognitive dysfunction [6–8]. However, exact pathophysiological mechanisms of diabetes-related brain changes are not yet fully understood. Through brain imaging technology, we have some relevant clues about the underlying processes. In a Japanese study among elderly people with T2DM, cognitive dysfunction was associated with MRI visualization of white matter hyperintensities and subcortical atrophy [9]. A study using positron emission tomography (PET)–CT technology in patients with microangiopathy with or without existing T2DM found that impairment of blood flow rather than microangiopathy caused diabetes-related cortical atrophic changes [10]. However, other studies have shown that diabetes accelerates cognitive impairment through microvascular disease as main cause of cerebral atrophy [11–14]. A population study showed that having both conditions was associated with a more than additive risk for dementia [15].

Hyperglycemia and diabetes clearly affect the quality of PET-CT images because of interference with ^{18}F-fluorodeoxyglucose (FDG) uptake in both pathological and non-pathological tissues [16, 17]. Moreover, poor glycemic control in T2DM is believed to be associated with a lower maximum standardized uptake value (SUV_{max}) in brain tissue as imaged by ^{18}F-FDG PET-CT [18, 19]. However, it is uncertain whether it is only poor diabetes control or other mechanisms that are responsible for low brain metabolism and cognitive impairment leading to Alzheimer's disease. In the 1980s, research showed that cerebral glucose utilization and energy metabolism represent very early abnormalities that precede or accompany the initial stages of cognitive impairment [20, 21]. This scientific concept was further developed, leading to the concept of impaired insulin signaling in the pathogenesis of brain changes related to Alzheimer's disease [22]. Moreover, alteration of phosphorylation and tau gene expression are regulated by insulin and insulin-like growth factor signaling cascades [22, 23].

The aim of this retrospective study was to analyze brain volume and relationships with glucose metabolism in T2DM after correction for possible confounding factors, such as age, sex, differences in diabetes duration and diabetes control, smoking, consumption of alcohol-containing beverages, and body mass index (BMI) and BMI-based calculated FDG dose. To answer this research question, we compared all available medical records of individuals who underwent PET-CT from the time PET-CT scanning became available until its replacement by digital PET-CT.

1. Materials and Methods

A. Patient Selection

The Regional Medical Ethical Committee (METC ZWH) waived the need for informed consent considering the retrospective chart review study in line with regional guidelines. We retrospectively analyzed data from 620 patients who were consecutively imaged from January 2015 through September 2017 with ^{18}F-FDG PET-CT for various malignant and nonmalignant conditions. Patient files were reviewed for the following data: age, sex, FBG (in millimoles per liter), height, weight, BMI, hemoglobin A1c (in millimoles per moles), type and duration of diabetes, reported history of cognitive impairment, Alzheimer's disease, neurologic disorders, any history of brain atrophy, or documented cerebral infarction on neuroimaging.

Final analysis was performed on patients selected according to the following inclusion criteria: age between 60 and 70 years, no abnormalities found on PET-CT, and FBG $<$ 10 mmol/L. We excluded patients with (i) reported history of cognitive impairment or Alzheimer's disease, (ii) any other neurologic disorder, (iii) known or reported brain atrophy/cerebral infarction, and (iv) receipt of chemotherapy in the past 6 months. Data were also collected on the use of antidiabetic medications, smoking, and alcohol consumption. To compare the effect of existing T2DM, groups were defined according to the

American Diabetes Association's criterion for the diagnosis of diabetes: FBG ≥ 7.0 mmol/L (≥126 mg/dL) [24].

B. FDG PET-CT Protocol

All patients had undergone ^{18}F-FDG PET-CT from skull vertex to midthigh or feet with a Philips Gemini GXL Scanner (Philips Medical Systems International, Eindhoven, Netherlands). We used a line-of-response reconstruction for PET with normal filter. For CT, as a reconstruction we used filtered back projection. The PET and CT images were reconstructed in coronal, sagittal, and axial slices. Each patient had fasted for 6 hours before ^{18}F-FDG administration, and FBG was measured before imaging. Images were obtained an average of 60 minutes after ^{18}F-FDG injection. The dose of ^{18}FDG was calculated on the basis of body weight (3.5 MBq/kg). Image acquisition time per bed position was 2 minutes.

C. Image Analysis

^{18}FDG PET and CT images were evaluated at a workstation equipped with an OsiriX DICOM viewer (Pixmeo SARL, Bernex, Switzerland). The brain SUV_{max} and brain volume were calculated by using an automatic three-dimensional region-of-interest method based on the PET images (Fig. 1a and 1b). The liver SUV_{max} was calculated manually by drawing regions of interest on the right hepatic lobe with a diameter of almost 2 to 3 cm. Because fractional glucose uptake (SUV_{gluc}) is most conveniently reproducible and is least affected by the regional variation of glucose metabolism in different areas of brain, we used brain SUV_{gluc} calculated from $SUV_{max} \times$ FBG in the analysis. This correction is also mentioned in the European Association of Nuclear Medicine procedure guidelines for PET brain imaging [25].

D. Statistical Analyses

Statistical analyses were performed by using Statgraphics Centurion XVII software, version 17.2.05 for MS Windows (StatPoint Inc.,Warrenton, VA). Baseline characteristics were compared by using the independent-samples Welch *t* test or Wilcoxon-Mann-Whitney rank-sum test depending on the distribution of numeric data. Associations (counts) were analyzed by using Pearson χ^2 test or Fisher exact test and adjusted standardized residuals scores.

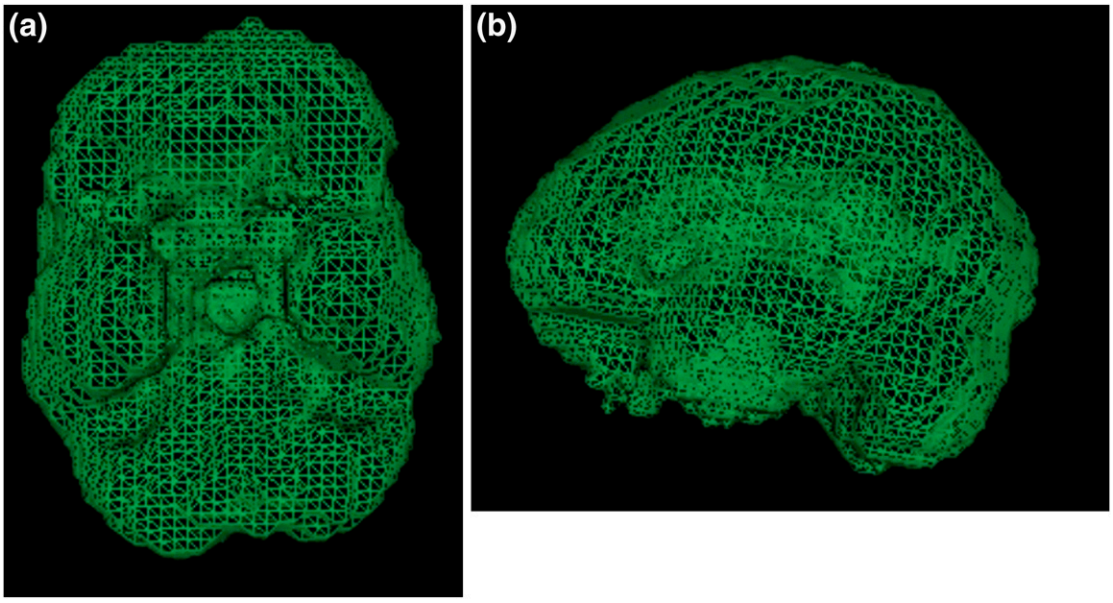

Figure 1. Three-dimensional PET images of brain. (a) Inferior view. (b) Lateral view.

Pearson or Spearman correlation coefficients were used as appropriate to analyze the relationship between numeric variables. Autocorrelation was tested by using variation inflation factor (criterion < 2.5) and condition indexes (criterium < 30; $P < 0.5$). Multiple (linear) regression was applied by using brain volume as the outcome variable and, accounting for sample sizes, clinically relevant numeric variables as predictors. Where applicable, a P value < 0.05 was considered to indicate a statistically significant difference at the 95% confidence level.

2. Results

On the basis of inclusion and exclusion criteria, data from 119 of 620 patients—63 women (53%) and 56 men (47%)—were used in the final analysis (Table 1). Through use of the appropriate statistical test for comparisons, men and women were found to differ in terms of brain volume and FDG dose but not age, BMI, FBG, brain SUV_{max}, and liver SUV_{max}. The median brain volume was 8.5% lower in women than in men. However, men had a lower FBG × brain SUV_{max} (Ki) compared with women ($P = 0.02$). Men received a 14% higher median FDG dose than women (Wilcoxon-Mann-Whitney test, $P = 0.02$).

The next step in the analysis was the comparison of the non-T2DM group (n = 86; 72%) vs the T2DM group (n= 33; 28%). These two groups were balanced for age, sex, and percentages of patients with and without tobacco use (Table 2). The daily use of alcohol was significantly

Table 1. Demographic Characteristics and Indications for PET-CT in Patients With a Normal Scan

Characteristic	All Patients (n = 119)	Men (n = 56)	Women (n = 63)	*P* Value
Age, y	66 ± 3.3	66 ± 6	66 ± 7	
Patients, n (%)		56 (47)	63 (53)	
BMI, kg/m^2	27 ± 5.3	27 ± 4.5	26 ± 6.4	
FDG dose, MBq	228 ± 50	234 ± 42	201 ± 53	0.01
FBG, mmol/L	5.7 ± 1.2	5.7 ± 1.0	5.6 ± 1.3	
Daily alcohol use, n/n (%)	46/119 (39)	27/56 (48)	19/63 (30)	
Smoking, n/n (%)	40/119 (34)	21/56 (37.5)	19/63 (30)	
Brain volume, cm^3	1366 ± 192	1411 ± 225	1325 ± 147	0.02
Brain SUV_{max}	11.2 ± 3.7	11.2 ± 3.7	11.2 ± 3.8	
Liver SUV_{max}	3.2 ± 0.8	3.1 ± 0.6	3.2 ± 0.9	
FBG × brain SUV_{max}	67.3 (34.6, 134.3)	63.6 (34.6, 126.6)	70.0 (36.4, 134.3)	0.02
Indications for PET-CT, n				
Analysis lung nodule	21	12	9	
Analysis B symptoms	25	8	17	
Suspicion of unknown malignancy	14	8	6	
Analysis pleural thickening	3	3	0	
TNM staging/ restaging colorectal carcinoma	7	4	3	
Staging/restaging breast cancer	10	0	10	
TNM staging/restaging melanoma	3	2	1	
Restaging/recurrent lung cancer	7	6	1	
TNM staging/restaging bladder cancer	6	3	3	
Recurrent lymphoma	4	3	1	
Recurrent ovarian carcinoma	1	0	1	
Analysis eye swelling	1	1	0	
Analysis high ESR and arthritis	1	1	0	
Staging/restaging prostate cancer	1	1	0	
Recurrent leiomyosarcoma	1	0	1	
Polyneuropathy of unknown origin	1	1	0	
Suspicion thyroid malignancy	1	1	0	

Data are presented as mean ± SD, median (minimum, maximum), or number/total (%). P values < 0.05 refer to statistically significant differences between men and women.
Abbreviations: ESR, erythrocyte sedimentation rate; NA, not applicable.

Table 2. Data Comparisons between Non-T2DM and T2DM Groups

Variable	Non-T2DM Group (FBG < 7 mmol/L; n = 86)	T2DM Group (FBG ≥ 7 mmol/L; n = 33)	*P* Value
Age, y	66 (3.2)	67 (3.5)	
Sex, n			
Men	44	14	
Women	42	19	
BMI, kg/m^2	25.5 ± 4.7	31 ± 5.8	<0.001
FBG, mmol/L	5.5 ± 0.6	7.3 ± 1.3	<0.001
Daily use of alcohol, n/n (%)[a]	40/86 (46.5)	6/33 (18)	0.02
Smoking , n/n (%)	31/86 (36)	9/33 (27)	
FDG dose, MBq[b]	219 ± 46	251 ± 53	0.002
Duration of diabetes, y	NA	8	NA
Hemoglobin A1c, mmol/mol	NA	54	NA
Brain volume, cm^3	1392 ± 172	1269 ± 183	<0.001
Brain SUV_{max}	12.3 ± 2.5	8.0 ± 2.7	<0.001
Liver SUV_{max}	3.1 ± 0.6	3.3 ± 0.5	
FBG × brain SUV_{max}	68.1 (34.6, 134.3)	62.5 (38.1, 90.3)	

Data are presented as mean ± SD, median (minimum, maximum) or number (%). *P* values < 0.05 refer to statistically significant differences between the two groups.
Abbreviation: NA, not applicable.
[a]Daily alcohol use in non-T2DM group is more frequent than in T2DM group.
[b]Average FDG dose is higher in T2DM group than in non-T2DM group.

more frequent in the non-T2DM group ($P = 0.01$). Therefore, alcohol use as a factor for low brain volume was excluded from the analyses. This was also the case for FDG dose because the received FDG dose (in megabecquerels) in the T2DM group was higher than in the non-T2DM group ($P = 0.002$). Comparing the T2DM with the non-T2DM group showed a significantly lower median brain volume of 28% and lower median brain SUV_{max} of 42%, and a nonsignificant median decrease in Ki of 8.2% to 62.5 in the T2DM group. Liver SUV_{max} was similar in the non-T2DM and T2DM groups.

We also compared men without (n = 44) and with (n = 14) T2DM and women without (n = 45) and with (n = 19) T2DM (Tables 3 and 4). All groups were balanced for age, sex, and percentage of patients with or without tobacco use or daily use of alcohol. In men with T2DM, brain volume and brain SUV_{max} were significantly lower, but SUV_{gluc} was similar. In women

Table 3. Data Comparisons in Men Between Non-T2DM and T2DM Groups

Variable	Non-T2DM Group (FBG < 7 mmol/L; n = 44)	T2DM Group (FBG ≥ 7 mmol/L; n = 14)	*P* Value
Age, y	65 ± 3	65 ± 3	
BMI, kg/m^2	26.5 ± 4.0	29.1 ± 5.8	
FBG, mmol/L	5.4 ± 0.6	7.2 ± 1.2	<0.001
Daily use of alcohol, n/n (%)	24/58 (45.3)	4/58 (7.6)	
Smoking , n/n (%)	16/58 (27.6)	5/58 (8.6)	
FDG dose, MBq	226 (170, 381)	250 (165, 331)	
Duration of diabetes, y	NA	8 (0,33)	
Hemoglobin A1c, mmol/mol	NA	52 (40,105)	
Brain volume, cm^3	1469 ± 196	1229 ± 218	<0.001
Brain SUV_{max}	12.2 (5.9, 23.4)	6.7 (4.6, 12.4)	<0.001
Liver SUV_{max}	3.1 (2.3, 6.1)	3.1 (2.7, 3.4)	
FBG × brain SUV_{max}	65.1 (34.6, 126.6)	52.4 (38.1, 74.8)	

Data are presented as mean ± SD, median (minimum, maximum) or number/total (%). *P* values < 0.05 refer to statistically significant differences between the two groups.
Abbreviation: NA, not applicable.

Table 4. Data Comparisons in Women Between Non-T2DM and T2DM Groups

Variable	Non-T2DM Group (FBG < 7 mmol/L; n = 45)	T2DM Group (FBG ≥ 7 mmol/L; n = 19)	*P* Value
Age, y	65 ± 3	66 ± 4	
BMI, kg/m^2	25.4 ± 5.3	31.7 ± 6.7	<0.001
FBG, mmol/L	5.5 ± 0.6	7.6 ± 1.6	<0.001
Daily use of alcohol, n/n (%)	18/64 (31.6)	2/64 (3.5)	
Smoking , n/n (%)	15/64 (25)	4/64 (6.7)	
FDG dose, MBq	204 (45)	253 (57)	<0.001
Duration of diabetes, y	NA	8 (1, 18)	
Hemoglobin A1c, mmol/mol	NA	54 (11.4)	
Brain volume, cm^3	1344 ± 139	1271 ± 149	
Brain SUV_{max}	12.7 (7.4, 23.2)	9.3 (4.6, 13.9)	<0.001
Liver SUV_{max}	3.1 (0, 6.2)	3.5 (0, 4.5)	
FBG × brain SUV_{max}	70.5 (36.4, 134.3)	68.3 (46.3, 90.3)	

Data are presented as mean ± SD, median (minimum, maximum) or number/total (%). *P* values < 0.05 refer to statistically significant differences between the two groups.
Abbreviation: NA, not available.

with T2DM, brain volume and SUV_{max} were similar. Brain volumes (mean ± SD) in men without T2DM and women without T2DM were 1469 ± 60 vs 1344 ± 42, respectively ($P < 0.001$), whereas in patients with T2DM brain volume did not differ between the sexes: 1271 ± 72 vs 1229 ± 126, respectively ($P = 0.51$).

Correlations were analyzed between age, BMI, diabetes duration, FBG, hemoglobin A1c, brain volume, brain SUV_{gluc}, liver SUV_{max}, and FDG dose, stratified by sex and by T2DM status; no significant correlations were noted between diabetes control (hemoglobin A1c)/diabetes duration and the other variables mentioned.

In men (groups pooled), a relatively strong correlation was found between brain volume and FBG × brain SUV_{max} (Spearman rho = −0.69; $P < 0.001$). There was a relatively weak correlation in women (groups pooled), which was weaker compared with men (Spearman rho = −0.50; $P < 0.001$). This difference can be explained by a smaller brain volume in women than men ($P = 0.02$) (Table 1).

In the non-T2DM group (consisting of both men and women) a significant but rather weak correlation was found between brain volume and FBG × brain SUV_{max} (Spearman rho = 0.50; $P < 0.001$). In the T2DM group, a weak and not significant correlation was found between brain volume and FBG × brain SUV_{max} (Spearman rho = 0.44; $P = 0.051$).

Brain volume in men was larger, and the range wider, than in women (Table 1). In a linear fitted model, it appeared that in men the FBG × brain SUV_{max} (brain SUV_{gluc}) explained 45.4% (R^2 adjusted, %) of the variance in brain volume about its mean, whereas it explained only 30.1% in women. In addition, brain SUV_{gluc} explained 35.0% of this variance in patients without T2DM and even less (7.1%) in patients (both men and women) with T2DM (Fig. 2a–2d).

Multiple regression analysis between brain volume and age, BMI, brain SUV_{max}, brain SUV_{gluc}, and liver SUV_{max} for men or women with or without T2DM confirmed a positive relationship between brain volume and brain SUV_{gluc}. However, this was seen only in patients without T2DM. In both men and women with T2DM, there were no significant associations (Table 5).

3. Discussion

This study focused on a well-established previously reported finding of lower brain glucose uptake along with higher fasting glucose blood levels in T2DM. This issue has been previously studied and debated in several reports [16, 17–19]. The phenomenon pertains only to brain

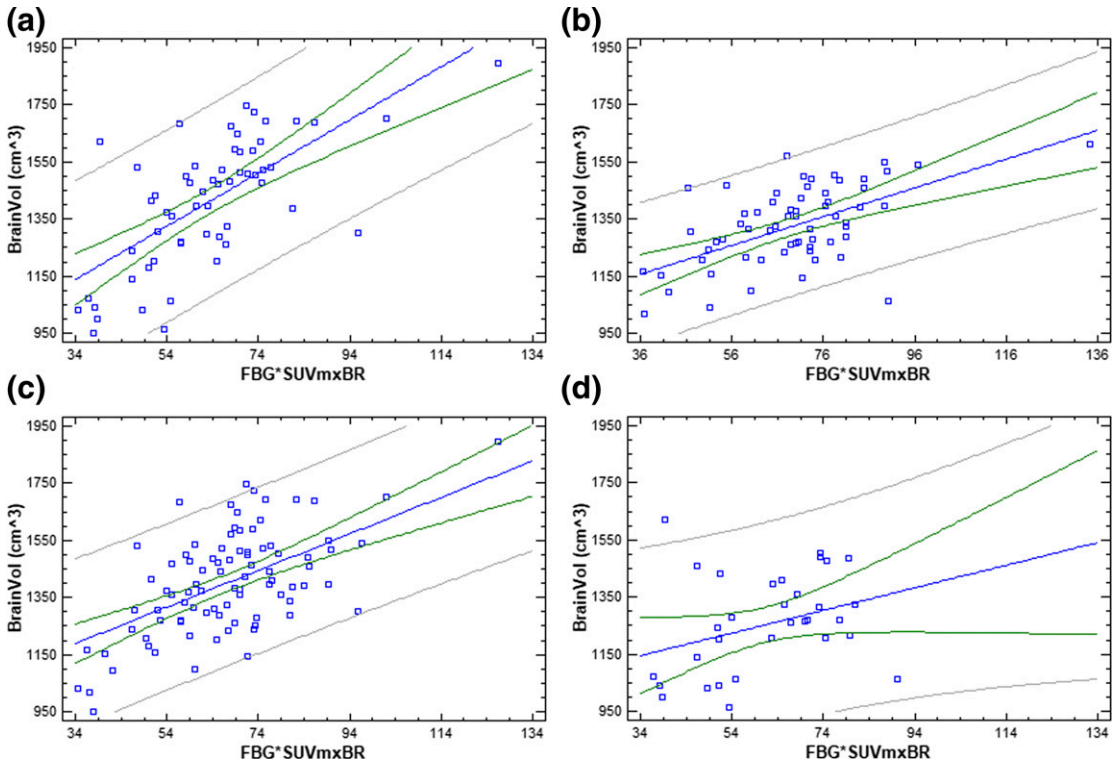

Figure 2. Linear models depicting prediction limits (outer lines), 95% confidence limits (inner lines), regression line, and adjusted R^2 to describe the relationship and percentage of variance explained between the variables brain (BR) volume and FBG × brain SUV_{max}. (a) Fitted linear regression model for men. Brain volume = 823.175 + 9.29662 × FBG × brain SUV_{max}; R^2 (adjusted for degrees of freedom) = 45.4%. Relationships were statistically significant. (b) Fitted linear regression model for women. Brain volume (Vol) = 975.543 + 5.03206 × FBG × SUV_{max}BR; R^2 (adjusted for degrees of freedom) = 30.1%. Relationship was statistically significant. (c) Fitted linear regression model for patients without T2DM. BrainVol = 971.316 + 6.38852 × FBG × SUV_{max}BR; R^2 (adjusted for degrees of freedom) = 35.0%. Relationship was statistically significant. (d) Fitted linear regression model for T2DM. BrainVol = 1010.67 + 3.95181 × FBG × SUV_{max}BR; R^2 (adjusted for degrees of freedom) = 7.1%. Relationship was not statistically significant.

uptake and not liver uptake [26]. Lower brain volume and lower brain glucose uptake were not affected by duration of T2DM or tightness of diabetes control (this study).

In patients without T2DM, we found a positive relationship between brain volume and brain glucose uptake for men and women, but we also showed that the variance in brain volume about the mean is related to its fractional glucose uptake by 45.4% (for men) and 30.1% (for women). This picture changed in the case of T2DM. In that scenario, male brain volume became smaller and was similar to that of women, whereas any association between brain volume and fractional glucose uptake had disappeared. This outcome raises two questions: (i) Is abnormal glucose handling in brain cells part of early diabetic brain changes [27]? (ii) Do brain insulin resistance and neuronal glucose deprivation cause lower cerebral metabolism leading to neuronal tissue damage [28]?

Brain glucose levels range from ~0.7 to 2.5 mmol/L during plasma euglycemia, can reach ~5 mmol/L under severe plasma hyperglycemia, and can decrease to 0.2 to 0.5 mmol/L under hypoglycemia [29]. Moreover, rapid changes in extracellular glucose concentrations cause rapid changes in brain glucose concentrations [30]. Adequate brain activity is ensured by the tightly regulated interaction between systemic glucose resulting from energy supply, storage, and glucose release. Glucose-sensing cells are found outside the brain, in tissues such as the endocrine pancreas (glucose-excited β cells and glucose-inhibited α cells [31, 32]) and the gut (glucose-excited L cells [33]), but also in the brain itself. Subgroups of glucose-sensing

Table 5. Multiple Regression Analyses

Independent Variable Predictor	*P* Value
Men without T2DM	
Age (y)	0.88
FBG × brain SUV_{max}	<0.001
Liver SUV_{max}	0.11
Men with T2DM	
Age (y)	0.32
FBG × brain SUV_{max}	0.91
Liver SUV_{max}	0.19
Women without T2DM	
Age (y)	0.23
FBG × brain SUV_{max}	<0.001
Liver SUV_{max}	0.77
Women with T2DM	
Age (y)	0.29
FBG × brain SUV_{max}	0.39
Liver SUV_{max}	0.18

Results of fitting a multiple linear regression model to describe a relationship between the dependent variable brain volume (in cubic centimeters) and three possible predictors in men and women with or without T2DM: age (y), FBG × brain SUV_{max}, and liver SUV_{max}. *P* values < 0.05 refer to statistically significant relationships. BMI (kilograms per meters squared) and brain SUV_{max} were excluded from each of the four models.

astrocytes act as a thermostat to monitor body energy status [34–36]. These cells behave as glucose excited or glucose inhibited and are mainly located in specific brain areas, mainly the hypothalamus and brain stem, but not in the thalamus or cortex. Glucose-sensing adaptive responses of orexin/hypocretin-containing neurons have been postulated to be involved in stimulating the sympathetic outflow to the liver and pancreas to increase blood glucose and in feeding and reward seeking activated by hunger and stress (and thus are cortical activities) and autonomic adjustments in blood glucose levels [37]. The hypothalamus plays a critical role for energy maintenance of the brain via its glucose-sensing neuronal cells dictating the amount of glucose needed to keep up with brain homeostasis. In the case of insulin resistance, too much insulin crosses the blood-brain barrier to the hypothalamus; this causes perturbed energy sensing because neurons are insulin-responsive, not dependent [38]. This leads initially to neuronal GLUT3 glucose uptake independent of peripheral hormone status. The moment the hypothalamic insulin concentration becomes too high, glucose transport slows down (hypothalamic GLUT4 transporters), which finally impairs the energy status in the brain and promotes upregulation in protein synthesis, including amyloid precursor protein [7, 38, 39]. This led to the proposition of a neuro-energetic model of gradual cognitive decline, which occurs on a spectrum linear to cerebral metabolic changes [39].

Research is assessing the use of PET with several FDG compounds to quantify early degenerative changes of the brain during aging and early detection of Alzheimer's disease. Apart from age, having a first-degree family history of Alzheimer's disease is a major risk factor for development of the disease in healthy individuals [40, 41]. Furthermore, evidence also shows that T2DM is connected to mild cognitive impairment and late-onset AD [42–45]. The presented data elaborate on previous studies showing that patients with T2DM and preclinical cognitive impairment may have the combination of lower brain volume and lower brain metabolism than individuals of the same age without T2DM [11, 46, 4947 The additional information presents a different picture in men and women according to static low-dose CT and dynamic uptake of glucose by the brain. Perhaps men with T2DM are more vulnerable to brain insulin resistance than women and that a similar situation occurs in women when they get older. An interesting hypothesis is the onset of slow deterioration of glucose-sensing relay in the brains of diabetic patients. Whether this process primarily pertains to glucose-sensing cells and the exact role of sex, T2DM duration, and T2DM control remain

unclear and require further study. Clinical research strongly suggests reversibility of the process, at least to some extent [6, 48].

This study was limited by its cross-sectional design and the small number of included patients with T2DM. Prospective research is needed to clarify many unresolved issues, such as the role of the metabolic syndrome in younger and elderly patients with T2DM, the role of diabetes control, and the role of antidiabetic drugs (particularly in elderly patients with mild cognitive impairment or even Alzheimer's disease). Finally, more studies using high-resolution digital PET-CT scanners should be done to refine early detection of brain PET-CT changes, particularly in younger groups.

In summary, this study provides additional evidence for previously described harmful effects caused by diabetes in the human brain. We performed analyses in middle-age men and women. in the men studied, the brain seemed to be more vulnerable than in women. In men with T2DM, brain volume was lower than in men withoutT2DM, whereas brain volume was similar between women with those without T2DM. However, FDG uptake corrected for FBG (SUV_{gluc}), used as a dynamic index for glucose metabolism in the brain, did not significantly differ between men and women with T2DM.

The study findings, albeit based on retrospective data, indicate that brain volume in men but not women with T2DM decreases with a genuine decrease in glucose uptake. In women with T2DM, a decrease in glucose uptake could well be an artifact because brain volume did not change and SUV_{gluc} is still regarded as a proxy for brain glucose uptake [25]. The role of metabolic disease and insulin resistance is obviously critical, and early detection of dynamic changes of brain glucose dynamics provides an opportunity to intervene with lifestyle intervention programs and medical treatments. Early detection and follow-up of aging of the brain may become essential in future prospective intervention studies of patients with T2DM and individuals with metabolic syndrome, particularly men.

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