Impact of Non-Insulin Dependent Type-2 Diabetes on Carotid Wall ^{18}F-FDG-PET Uptake

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Abstract

Objective & Background—Inflammation is a pivotal process in the progression of atherosclerosis, which can be non-invasively imaged by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). In this study, the impact of non-insulin dependent type-2 diabetes on carotid wall FDG uptake in patients with documented or suspected cardiovascular disease was evaluated.

Methods—Carotid artery wall FDG uptake was quantified in 134 patients (age 60.2 ± 9.7 years; diabetic subjects: n=43). The pre-scan glucose (gluc) level corrected mean of the maximum standardized uptake value (SUV) values ($_{mean}SUV_{gluc}$), mean of the maximum target-to-background ratio ($_{mean}TBR_{gluc}$), and Single Hottest Segment (SHS_{gluc}) of FDG uptake in the artery wall were calculated. Associations between FDG uptake, the presence of risk factors for atherosclerosis, and diabetes were then assessed by multiple regression analysis with backward elimination.

Results—We demonstrated a significant association between diabetes and FDG uptake in the arterial wall (diabetes: $_{mean}SUV_{gluc}$; $\beta=0.324$, $_{mean}TBR_{gluc}$; $\beta=0.317$, and SHS_{gluc}; $\beta=0.298$; for all: $p<0.0001$, respectively). In addition, in diabetic patients, both body mass index (BMI) ≥ 30 kg/m^2 (BMI ≥ 30 kg/m^2: $_{mean}SUV_{gluc}$; $\beta=0.4$, $_{mean}TBR_{gluc}$; $\beta=0.357$, and SHS_{gluc}; $\beta=0.388$; for all: $p<0.015$) and smoking (smoking: $_{mean}TBR_{gluc}$; $\beta=0.312$, SHS_{gluc}; $\beta=0.324$; for all: $p<0.04$) were significantly associated with FDG uptake.

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Conclusions—Type-2 diabetes was significantly associated with carotid wall FDG uptake in patients with known or suspected cardiovascular disease. In diabetic patients, obesity and smoking add to the risk of increased FDG uptake values. Furthermore, the degree of carotid wall FDG uptake increases with increments of fasting glucose levels in diabetic patients.

Keywords

FDG-PET; Inflammation; Atherosclerosis; Diabetes; Carotid Arteries

Introduction

Cardiovascular disease remains one of the leading causes of death in the United States, accounting for 1 in every 2.8 deaths [1]. It is also known that diabetes is associated with a high risk of cardiovascular disease. Atherosclerotic plaque inflammation plays a central role in atherosclerotic plaque progression, vulnerability and thrombogenicity. The exact mechanisms underlying the association between diabetes and atherosclerotic disease are not well known [2]. Epidemiological studies suggest that type 2 diabetes mellitus is not merely an independent risk factor for atherosclerotic cardiovascular disease but is also associated with increased levels of inflammatory biomarkers [3]. In line with these findings, efforts have been made to use non-invasive imaging to quantify vessel wall inflammation and to provide further evidence of the impact of clinical risk factors such as diabetes on atherosclerosis.

Carotid ^{18}F-fluordeoxyglucose positron emission tomography (FDG-PET) has been shown to reflect the metabolic rate of glucose, a process known to be enhanced in inflamed tissue. FDG uptake has been shown to be significantly associated with both the degree of macrophage infiltration and the levels of inflammatory gene expression in plaques [4, 5, 6]. Several clinical cardiovascular disease (CVD) risk factors have also been shown to exhibit a significant association with carotid wall inflammation [7, 8, 9]. However, data regarding the impact of diabetic disease on vessel wall inflammation remains inconclusive. Some trials failed to show any association between diabetes and atherosclerosis as assessed by FDG-PET [8, 9], while others have observed a significant association between diabetic disease and vascular inflammation [7, 10]. Tumor PET studies have also shown that FDG accumulation is diminished during hyperglycemia [11, 12, 13]. This effect however, has not been evaluated in vascular PET imaging.

The aim of the current study was to assess the impact of non-insulin dependent type-2 diabetes on carotid wall FDG uptake whilst seeking to avoid some of the limitations of previous studies. We therefore designed a cross-sectional study in a larger sample population and performed FDG-PET imaging with protocols optimized for vessel wall visualization/analysis [7, 9, 14].

METHODS

Study Design

This was a cross-sectional study, investigating the impact of non-insulin dependent type-2 diabetes on the prevalence of carotid wall inflammation assessed by FDG-PET. This study, approved by the institutional review board, was conducted from February 2006 until October 2010 at the Mount Sinai School of Medicine, New York, U.S.A. All subjects gave written informed consent.

Inclusion criteria were as follows: Males and females with a diagnosis of CVD or individuals with multiple CVD risk factors were recruited. CVD was defined as a previous

myocardial infarction, stroke, transient ischemic attack [TIA], history of peripheral artery disease; or a history of a coronary revascularization procedure. Patients with insulin-dependent type-2 diabetes and those with type-1 diabetic disease were excluded from the study, as were subjects with fasting glucose levels   11.1 mmol/l or previous carotid surgery.

Questionnaire, Biometric and Biochemical Measurements

Presence of cardiovascular risk factors, use of medication, and family history of CVD, were assessed by a questionnaire. Presence of hypertension was defined as a history systolic blood pressure > 140 mmHg, or a diastolic blood pressure > 90 mmHg. Diabetes was defined as documented diagnosis of type-2 diabetic disease and the use of anti-diabetic treatment (diet or oral, no insulin treatment). Weight and height were measured to calculate body mass index (BMI). Smoking was defined as smoking at least one cigarette on a daily basis. Fasting glucose levels were obtained by finger stick blood glucose measurements (Accu-Chek™ Advantage™, Roche Diagnostics; Indianapolis, Indiana) prior to FDG administration.

FDG-PET/CT Imaging

FDG-PET/CT was performed after an overnight fast using a General Electric Healthcare (Milwaukee, Wisconsin) Lightspeed discovery™ ST 16-slice PET/CT scanner. FDG was administered intravenously (557.6 ± 84.0 MBq), and patients rested comfortably for 97 to 193 min (136.7 ± 21.2 min) before the scan of the neck was started. Subjects were placed into a head holder for imaging of the carotids. A low dose CT scan (140 kV, 80 mA, and 4.25 mm slice thickness) was performed for attenuation correction and co-registration. Images from one bed position (15.5 cm) with coverage extending inferior to the internal auditory meatus were acquired in 3D mode using a 128×128 pixel matrix for 15 minutes. No CT contrast agent was administered. The total radiation dose from participating into this study was approximately 12 mSv.

Image Analysis

Image analysis was performed on a dedicated commercially available workstation (Extended Brilliance™ Workspace V4.0.0.3206; Philips Medical Systems Inc.; Cleveland, Ohio). An experienced reader (J. B.) analyzed all scans. Methodology for analysis and reproducibility of the measurements have been previously reported [15].

Briefly, arterial FDG uptake was quantified by manually drawing a region of interest (ROI) around each artery (common carotid arteries) on every slice of the co-registered transaxial PET/CT images. Next, the maximum arterial standardized uptake value (SUV) (highest pixel activity within the region of interest) was determined. The SUV is the decay-corrected tissue concentration of FDG in kBq/ml, adjusted for the injected FDG dose and the body weight of the patient. By averaging the maximum SUV values of all arterial slices of the left and right carotid artery, a $_{mean}$SUV value was derived for the carotid arteries.

$_{mean}$SUV values were also corrected for patient's fasting pre-scan glucose levels to account for a competitive impact of glucose (gluc) and FDG using an established formula [16]. The measured glucose content was normalized for an overall population average of 5.0 mmol/l [16]:

$$_{mean}SUV_{gluc} = {}_{mean}SUV \times \text{patient's blood glucose (mmol/l)}/5.0 \text{ mmol/l}$$

The arterial target-to-background ratio (TBR_{gluc}) was calculated by normalizing the SUV_{gluc} for blood pool activity by dividing the SUV_{gluc} value in the artery by the average blood mean SUV estimated from both jugular veins (JV). The TBR_{gluc} is a blood-normalized arterial SUV, considered to be a reflection of arterial FDG uptake and reflective of underlying macrophage activity [14]. For evaluation of the FDG blood pool activity, at least six 3-4 mm ROIs were placed in consecutive slices of both JVs and averaged.

The arterial TBR values obtained were then averaged in order to derive a $_{mean}TBR_{gluc}$ for both carotid arteries. Additionally, we identified the glucose-corrected Single Hottest Slice (SHS_{gluc}), defined as the highest TBR_{gluc} value of the carotid arteries.

Statistical Analysis

All continuous variables are expressed as mean ± standard deviation and categorical data as absolute numbers and percentages throughout this manuscript. In order to also assess a potential relation between continuous BMI values of the patients and the different FDG uptake parameters instead of assessing the impact of increased BMI values   30 kg/m^2, Pearson or Spearman's rho correlation coefficients (r) were calculated depending on normal distribution between the BMI values between the uncorrected- and glucose corrected FDG uptake parameters in the entire study population as well as in the two subgroups of patients with and without type II diabetes. In general, normal distribution of data was tested for all of the different statistical calculations using the Kolmogorov-Smirnov-Test.

Subgroup Analysis—The study population was divided into two subgroups of patients i.e. with and without diabetes. Furthermore, in order to test for the effect of anti-diabetic medication on the degree of carotid wall inflammation, we compared the different FDG uptake parameters between patient with oral anti-diabetic drugs and those with dietary treatment only. For all comparisons of subgroups of patients, student's t-test or Mann U Whitney test was performed to compare continuous variables depending on normal distribution. Categorical variables were compared between diabetic and non-diabetic patients by using the Fisher's Exact Test.

Multiple Regression with Backward Elimination and Linear Regression with ENTER Method (significant variables of the Backward Elimination entered a consecutive Linear Regression Model in a block in a single step):

In order to look at the relationship between each of more than one independent variable on one dependent variable, multiple regression analyses were used in the present study.

In the present study, a multiple linear regression analysis with backward elimination was used to assess the association between the cardiovascular risk factors and glucose-corrected FDG uptake parameters ($_{mean}SUV_{gluc}$, $_{mean}TBR_{gluc}$, and SHS_{gluc}) in the entire study population as well as in both subgroups of patients with and without diabetes [17, 18]. FDG uptake parameters were treated as the response variables (dependent) and cardiovascular risk factors as the explanatory (independent) variables for the regression analysis. The explanatory variables included were as follows: age > 65 years, male gender, body mass index (BMI)   30 kg/m^2, statin use, type-2 diabetes, history of cardiovascular disease, smoking, alcohol use, hypertension, and family history of cardiovascular disease. In order to evaluate a potential beneficial effect of exercise on carotid wall inflammation, exercise was one of the explanatory variables in the regression analyses. Following this, the ENTER regression was used to determine independent predictors of the response variables. For this method, all of the explanatory variables of the backward elimination model that showed a significant association with the FDG uptake value were retained and entered the regression model in a block in a single step. This entry method was preferred over the forward selection

of variables since after excluding all of the explanatory variables without a significant association with the different carotid wall FDG uptake values, only few significant variables were left for a relatively low number of cases. A similar analysis approach was also followed for the FDG uptake values obtained without the applied glucose correction ($_{mean}$SUV, $_{mean}$TBR, SHS) [16]. Throughout the manuscript, all results of the multiregression models were given with the standardized regression coefficient (β), the 95% confidence interval, and the p-value for the estimate of the statistical significance.

Tertile Analysis—The patients were divided into tertiles based on their FDG-PET uptake parameters. Pearson χ^2 tests were performed to compare the prevalence of clinical variables across the groups of patients classified by tertiles of the different FDG uptake parameters ($_{mean}$SUV$_{gluc}$, $_{mean}$TBR$_{gluc}$, and SHS$_{gluc}$).

ANOVA with the appropriate adjustment for multiple comparisons was performed to compare FDG uptake values between different levels of fasting glucose in non-diabetics and patients with diabetes (according to the recommendations by The International Diabetes Federation IGF/IGT consensus statement [19]). Post hoc analyses were performed using the Tukey test.

All statistical analyses were performed using SPSS™ statistical package 16.0 (SPSS Inc.; Chicago, Illinois).

RESULTS

Population Characteristics

One hundred thirty-four patients were included in the study. In 3 of the patients, FDG-PET analysis could not be performed due to high FDG uptake in the thyroid, affecting the visualization and analysis of FDG uptake within the carotid arteries, leaving 131 eligible patients for image analysis. On average, 7.56 ± 2.49 slices for the left common carotid artery and 7.36 ± 2.5 slices for the right common carotid artery were analyzed to derive the FDG uptake parameters. Table 1a shows characteristics of the whole population, both diabetic and non-diabetic subjects. There were some differences in demographics between the diabetic and non-diabetic group (history of percutaneous coronary intervention and use of beta blockers being higher in diabetic patients, exercise, family history of cardiovascular disease, and cigarettes per day in current smokers all being higher in non-diabetics); otherwise the two groups were similar. As expected, fasting glucose was higher in the diabetic population compared to non-diabetics.

FDG-PET Imaging Results

The imaging analyses of the groups (Table 1b), however showed that glucose-corrected FDG-PET parameters ($_{mean}$SUV$_{gluc}$, $_{mean}$TBR$_{gluc}$, SHS$_{gluc}$) were significantly higher in the diabetic group compared to the non-diabetics. This difference was not observed in FDG-PET parameters that were not corrected for pre-scan glucose. Dividing patients into two groups according to their pre-scan glucose values by using the median of these values, we also found significantly higher values for all glucose-corrected FDG uptake parameters in diabetic patients in the group of higher (5.6 - 10.6 mmol/l) pre-scan glucose levels. In the group of patients with lower pre-scan glucose levels (2.8 - 5.5 mmol/l) all glucose-corrected FDG uptake parameters were also found to be higher in diabetic patients, however, these differences failed to be statistically significant (Table 1b). In diabetic patients, no significant differences were observed for all glucose-corrected FDG parameters between those patients treated with oral anti-diabetic drugs and those on dietary treatment only ($_{mean}$SUV$_{gluc}$: p = 0.313, $_{mean}$TBR$_{gluc}$: p = 0.314, SHS$_{gluc}$: p = 0.122).

FDG-PET Imaging and CVD Risk Factors

Table 2a shows the results of the multiple linear regression analysis with backward elimination to identify clinical risk factors associated with glucose-corrected FDG-PET uptake parameters (i.e. measures of plaque inflammation). Diabetes showed the strongest relationship with all FDG-PET uptake parameters ($_{mean}SUV_{gluc}$, $_{mean}TBR_{gluc}$, SHS_{gluc}) (standardized regression coefficient $\beta = 0.38$, $p < 0.0001$) followed by BMI > 30 kg/m^2 ($\beta = 0.25$, $p < 0.001$). Only risk factors that had a $p < 0.10$ were retained in the model for the ENTER regression (all significant and therefore retained variables entered this model in a block in a single step) and are shown in the Table. Following the ENTER regression, it was found that diabetes, BMI > 30 kg/m^2, and alcohol use (except of $_{mean}SUV_{gluc}$ values) were independent predictors of plaque inflammation as measured by FDG-PET imaging (Figures 1, 2, and 3).

ENTER regression also showed that $_{mean}TBR_{gluc}$ and SHS_{gluc} were inversely associated with a family history of cardiovascular disease (Figure 2 and 3).

The multiple regression analysis for non-glucose corrected FDG-PET data is presented in the Appendix (Table 2b).

Multiple Regressions in Subgroups

Multiple linear regression analyses in the subgroup of patients with and without diabetic disease is presented in Table 3a following a similar procedure as described previously. In diabetic subjects, BMI 30 kg/m^2 continued to be a significantly associated with all of the three glucose-corrected FDG-PET uptake parameters ($_{mean}SUV_{gluc}$: $\beta = 0.571$, $p = 0.009$, $_{mean}TBR_{gluc}$: $\beta = 0.443$, $p = 0.014$, SHS_{gluc}: $\beta = 0.706$, $p = 0.007$). In non-diabetic subjects, hypertension showed the strongest association with the FDG-PET uptake parameters ($_{mean}SUV_{gluc}$: $\beta = 0.371$, $p = 0.002$, $_{mean}TBR_{gluc}$: $\beta = 0.361$, $p < 0.0001$, SHS_{gluc}: $\beta = 0.434$, $p = 0.001$). These and other associations are shown in Table 3a.

Again, results for the regression analysis for non-glucose corrected FDG-PET data is presented in the Appendix (Table 3b).

Tertile Analysis

Table 4 (Appendix) shows clinical characteristics stratified by tertiles of $_{mean}SUV_{gluc}$, $_{mean}TBR_{gluc}$, and SHS_{gluc}. The prevalence of type 2 diabetes and BMI 30 kg/m^2 were both significantly higher at higher tertiles of the three glucose-corrected FDG-PET uptake parameters.

Correlation between Continuous BMI Values and the FDG Uptake Parameters in the Entire Study Population and the Subgroups

Positive significant correlations were found between the continuous BMI values and all of the uncorrected- and glucose-corrected FDG uptake parameters in the entire study population and the two subgroups ($r > 0.25$, $p < 0.02$ for all) except of TBR_{max} values in the total study population and in non-diabetic patients, SUV_{max} values in diabetic patients as well as $TBR_{maxgluc}$ and SHS_{gluc} values in non-diabetic patients.

Distribution of the FDG-PET Uptake Parameters According to the Pre-Scan Glucose Levels

Figures 4 (Appendix) depict significantly increasing FDG uptake parameters ($_{mean}SUV_{gluc}$, $_{mean}TBR_{gluc}$, and SHS_{gluc}) by increments of fasting glucose levels in patients with type 2 diabetes. Remarkably, FDG uptake values in non-diabetic subjects were similar (SHS_{gluc}) or even slightly, but not significantly, higher ($_{mean}SUV_{gluc}$, $_{mean}TBR_{gluc}$)

compared to diabetic patients with fasting glucose levels within the normal range (< 6.1 mmol/l, Figures 4; Appendix).

DISCUSSION

The aim of our study was to determine if the presence of type 2 diabetes was related to carotid wall FDG uptake. This relation might therefore represent a link between diabetic disease and carotid wall inflammation in a population of patients with known cardiovascular disease or multiple risk factors for it. We used a cross sectional study design in a larger sample population than previous studies [7, 8, 9, 10] and performed FDG-PET imaging with protocols optimized for vessel wall FDG uptake [9, 14]. Our results demonstrate that diabetes was significantly associated with the FDG uptake in the carotid wall. Additionally, we showed that obesity was also related to carotid wall inflammation as depicted by FDG-PET. In the non-diabetic group, hypertension was the leading variable associated with inflammation measured by FDG-PET uptake. We also identified increasing fasting glucose levels in diabetic patients to be significantly associated with increments of the FDG uptake, which might be indicative of a higher propensity for carotid wall inflammation with increasing degrees of hyperglycemia.

FDG-PET/CT Methodology

The rationale for choosing to perform glucose correction of the FDG uptake is based on several oncology studies, which suggest that elevated pre-scan glucose levels can influence significantly the tumor's uptake of FDG during PET imaging [12, 20, 21]. One potential pitfall to using a glucose correction however is a resultant increase in the variability of the SUV measurements [22]. The role of glucose correction of FDG uptake in non-cancer lesions is not well understood. However, we felt that since the mechanism of uptake of FDG into inflammatory cells is the same as for tumor cells, that the same correction should be applied. In accordance to the European Association of Nuclear Medicine procedure guidelines for tumor PET imaging, we have also presented the results without glucose correction (Appendix) [16].

Multivariate regression analyses revealed an unexpected negative association between diabetes and the uncorrected $_{mean}$SUV values of the carotids in our study. This finding is in contrast to the well-known clinical impact of diabetes on cardiovascular disease. However, future studies still need to be performed to investigate whether the corrected- or uncorrected FDG uptake values are more sensitive surrogate markers for carotid wall inflammation by correlating both FDG uptake parameters with the histological assessment of vascular inflammation.

Impact of Circulation Time on FDG-Uptake

The optimal circulation time before imaging plaque inflammation has still not been definitively established. Typically, a circulation time between one and three hours is used by most groups [4, 5, 23, 24]. In order to exclude an impact of the FDG circulation time on the FDG uptake in patients with and without diabetes, we compared the FDG circulation time between both groups of patients. As we did not find a statistically significant difference, the differences of the FDG uptake between diabetic and non-diabetic patients cannot be explained by different FDG circulation times in both groups.

Type-2 Diabetes and Carotid Wall Inflammation

We observed that type-2 diabetes and obesity (BMI) were independently associated with increased FDG-PET uptake values. In patients with type-2 diabetes, obesity and smoking added additional risk for increased FDG uptake in the carotid wall. In non-diabetics

however, only hypertension was found to be significantly associated with carotid wall inflammation as depicted by all FDG uptake parameters.

Our results are in agreement with some of the previously published studies evaluating the association between cardiovascular risk factors and vessel wall inflammation. In a case-control study of patients with type-2 diabetes, impaired glucose tolerance, and controls, Kim et al. reported higher TBR_{max} values in both study groups compared to controls [10]. As in the current study, they also observed increasing prevalence of diabetes with increments of maximum TBR values as depicted by tertiles. However, glucose correction was not used in their study, and this may have resulted in an underestimation of FDG-PET uptake values.

Previous studies have demonstrated the link between circulating insulin levels and its effect on the over expression of GLUT transporter types [10, 11]. Tahara et al. have also shown that carotid inflammation was associated with several cardiovascular risk factors including a homeostasis model assessment of insulin resistance [7]. They found obesity, as assessed by waist circumference and use of hypertensive medication to be significantly associated with carotid wall inflammation. However, fewer subjects in their population had cardiovascular disease and the cardiovascular risk profile for their population was much lower primarily because their retrospective analysis was done in cancer patients. In our study, we found a relationship between hypertension and carotid wall inflammation measured by FDG-PET in the non-diabetic group and a relationship between BMI and carotid wall FDG uptake both diabetics and non-diabetics.

Relationship between Fasting Glucose Levels and Carotid Wall FDG-Uptake

Studies have shown that hyperglycemia leads to increased oxidative stress producing endothelial dysfunction [25]. Several observational studies have shown an association between levels of glycemia and macrovascular events in patients with diabetes [26, 27]. Early data from the UKPDS suggested a protective effect of improved glucose control on cardiovascular disease incidence and mortality [26 29]. Results from our study seem to support these findings, as we found similar $_{mean}TBR_{gluc}$ values in patients with diabetes and fasting glucose levels < 6.1 mmol/l compared to non-diabetic patients (p = 0.985). We also observed higher FDG uptake parameters with increasingly poorer glycemic control.

Relationship between Hypertension and Carotid Wall FDG-Uptake

Two recently published trials prospectively investigated the impact of hypertension on cardiovascular risk in patients with and without diabetic disease [28, 29]. Both trials found hypertension to be associated with a higher risk of cardiovascular disease in diabetic patients but failed to show a significant interaction between diabetes and increased blood pressure. We found that hypertension showed a significant association with carotid wall FDG uptake only in the non-diabetic subgroup.

Limitations

There are several limitations to our study that need to be addressed. Firstly, we did not obtain serum lipid levels, markers of glucose metabolism or serum inflammatory markers. Secondly, this is a cross-sectional study. Therefore we could not address whether there was a causal relationship between the presence of diabetic disease and vessel wall inflammation. Thirdly, it is unknown if vessel wall FDG uptake is predictive of progression of disease or future cardiovascular events in diabetic patients. Longitudinal studies are currently underway to establish such a relation. Finally, in the present study image analyses was performed by only one reader. This might reduce statistical noise related to inter-observer variation but might raise concerns regarding intra-observer bias. However, previous reports demonstrated that this method has good inter- and intra-observer reproducibility [15].

CONCLUSION

In the current study, we show that type-2 diabetes has a significant impact on the FDG uptake in the wall of the carotid arteries. Obesity (BMI   30 kg/m^2) and smoking are also significantly associated with FDG-PET uptake parameters in diabetic patients. In non-diabetics, hypertension was significantly associated with carotid wall inflammation. Furthermore, the degree of the carotid wall FDG uptake increases with increments of fasting glucose levels in diabetic patients. Whether the glucose-corrected FDG uptake parameters are indicative of vessel wall inflammation has to be determined by future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

FDG-PET	^{18}F-Fluordeoxyglucose Positron Emission Tomography
SUV	Standardized Uptake Value
TBR	Target-to-Background Ratio
SHS	Single Hottest Segment
JV	Jugular Vein
CVD	Cardiovascular Disease
TIA	Transient Ischemic Attack
BMI	Body Mass Index
GLUT	Glucose Transporter Protein

Figure 1. Clinical Risk Factors of Carotid Vessel Wall Inflammation

This figure shows differences in $_{mean}SUV_{gluc}$ values in patients with and without diabetes and with and without BMI values ≥ 30 kg/m². Both variables were identified as significant ($p < 0.05$) independent predictors for carotid wall inflammation as depicted by $_{mean}SUV_{gluc}$ values. Data is presented as median (bolded line), 25th - 75th percentile (box), 5th - 95th percentile (whiskers). Circles represent outliers. The p-value for each of the given independent predictors for carotid wall inflammation as depicted by $_{mean}SUV_{gluc}$ values is adjusted for the other significant variable given in Table 2a (diabetes, BMI ≥ 30 kg/m², and alcohol). Alcohol failed to show a statistical significant association ($p < 0.05$) with the $_{mean}SUV_{gluc}$ values in the ENTER regression model and is therefore not shown as an independent predictor in this figure.
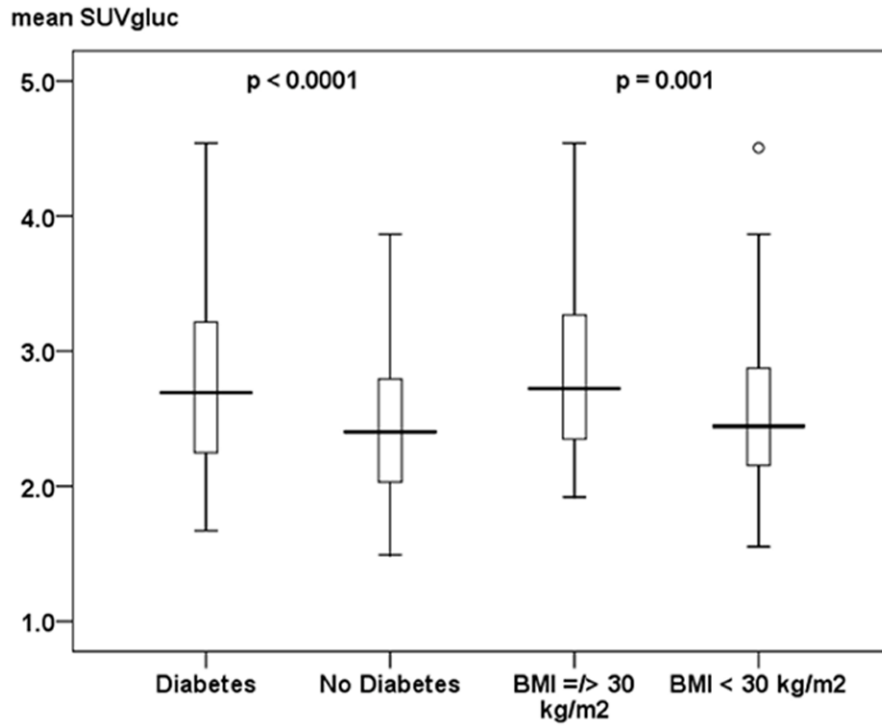
Figure 2. Clinical Risk Factors of Carotid Vessel Wall Inflammation

This figure shows differences in $_{mean}TBR_{gluc}$ values in patients with and without diabetes, BMI 30 kg/m^2, and alcohol. All variables were identified as significant ($p < 0.05$) independent predictors for carotid wall inflammation as depicted by the mean Target-to-Background-Ratio ($_{mean}TBR_{gluc}$). Family history is independently associated with a decreased risk of carotid wall inflammation as revealed by significantly lower $_{mean}TBR_{gluc}$ values in patients with a family history of cardiovascular disease. Data is presented as median (bolded line), 25th - 75th percentile (box), 5th - 95th percentile (whiskers). Circles represent outliers. The p-value for each of the given independent predictors for carotid wall inflammation as depicted by $_{mean}TBR_{gluc}$ values is adjusted for the other significant variables given in Table 2a (diabetes, BMI 30 kg/m^2, alcohol, and family history of cardiovascular disease).
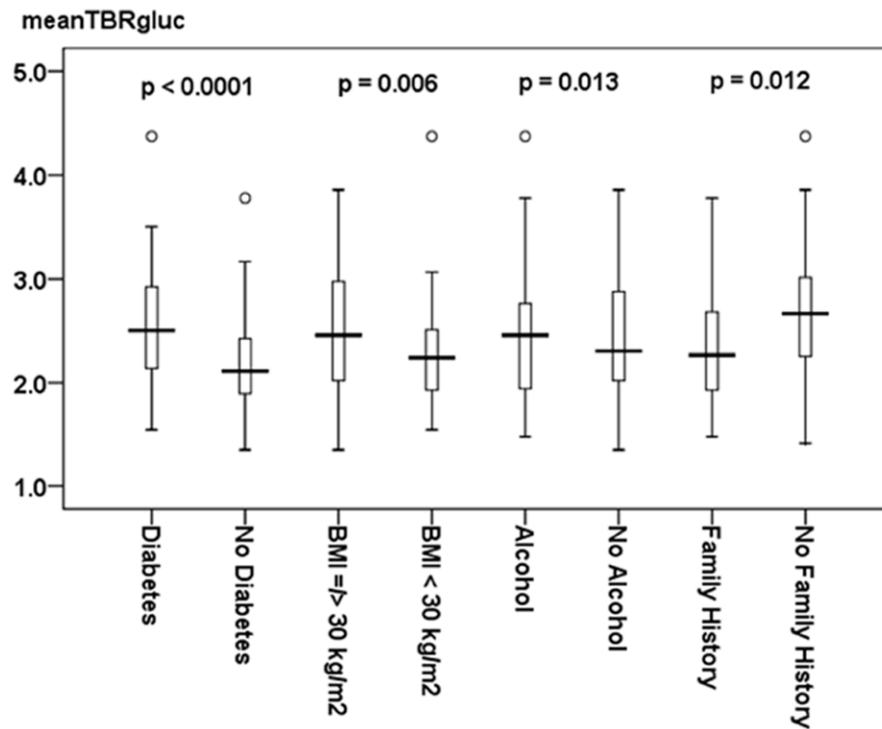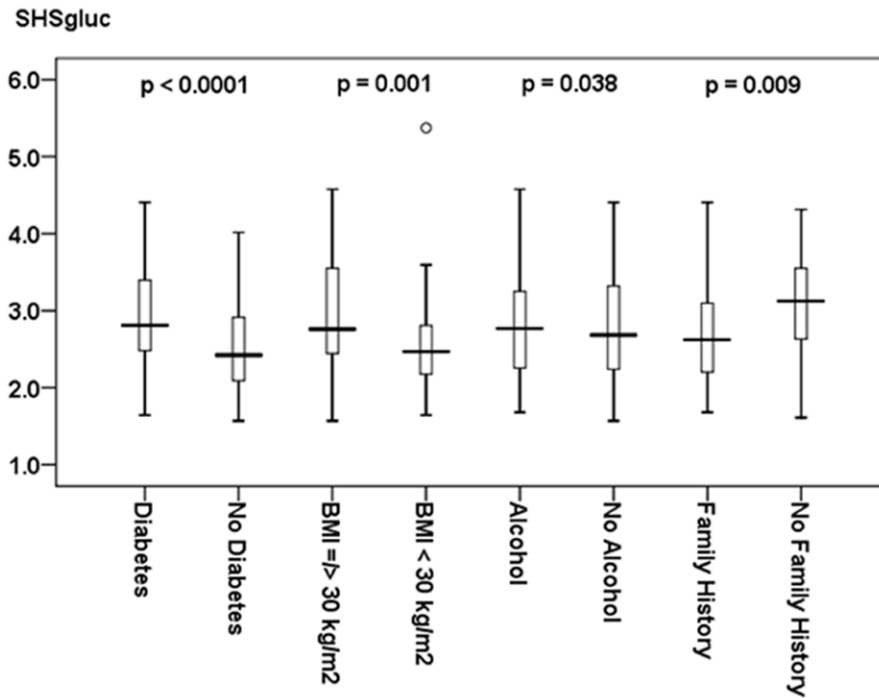
Figure 3. Clinical Risk Factors of Carotid Vessel Wall Inflammation
This figure shows differences in SHS_{gluc} values in patients with and without diabetes, BMI 30 kg/m^2, and alcohol. All variables were identified as significant ($p < 0.05$) independent predictors for carotid wall inflammation as depicted by the Single Hottest Segment (SHS_{gluc}). Family history is independently associated with a decreased risk of carotid wall inflammation as revealed by significantly lower SHS_{gluc} values in patients with a family history of cardiovascular disease. Data is presented as median (bolded line), 25th - 75th percentile (box), 5th - 95th percentile (whiskers). Circles represent outliers. The p-value for each of the given independent predictors for carotid wall inflammation as depicted by SHS_{gluc} values is adjusted for the other significant variables given in Table 2a (diabetes, BMI 30 kg/m^2, alcohol, and family history of cardiovascular disease).

Table 1

a. Characteristics of Study Population.

	Total	Diabetic Subjects	Non-Diabetic Subjects	
n (%)	134	43 (32)	91 (68)	
Characteristics				*p-value*
Age (years)	60.2 ± 10.1	61.3 ± 10.0	59.6 ± 10.2	0.37
• Age > 65 years (n, %)	46 (34)	16 (37)	30 (33)	0.7
Gender				
• Male (n, %)	96 (72)	33 (77)	63 (69)	
• Female (n, %)	38 (28)	10 (23)	28 (31)	0.42
Body Mass Index (BMI; kg/m^2)	28.9 ± 5.7	29.6 ± 4.8	28.6 ± 6.1	0.34
• BMI < 25 (n, %)	32 (24)	8 (19)	24 (26)	0.39
• BMI 25 < 30 (n, %)	54 (40)	17 (40)	37 (41)	1.0
• BMI 30 (n, %)	48 (36)	18 (42)	30 (33)	0.34
Lifestyle				
Smoking				
• Never (n, %)	58 (43)	19 (44)	40 (44)	1.0
• Former (n, %)	57 (43)	21 (49)	35 (39)	0.35
• Cigarettes per day (Range)	24.7 ± 14.6 (2 - 80)	24.4 ± 15.8 (2 - 60)	24.8 ± 14.3 (3 - 80)	0.82
• Current (n, %)	19 (14)	3 (7)	16 (18)	0.12
• Cigarettes per day (Range)	12.6 ± 11.9 (2 - 40)	3.0 ± 1.0 (2 - 4)	14.6 ± 12.2 (3 - 40)	**0.004**
Alcohol Users (n, %)	50 (37)	12 (28)	38 (42)	0.13
Exercisers (n, %)	72 (54)	16 (37)	56 (62)	**0.010**
• Times per week	4.46 ± 2.08	5.0 ± 2.4	4.31 ± 2.0	0.34
• Time per session (min)	46.7 ± 30.0	41.2 ± 22.2	48.1 ± 31.7	0.65
Medical history				
Cardiovascular Disease				
• Myocardial Infarction (n, %)	27 (21)	8 (19)	19 (21)	1.0
• Percutaneous Coronary Intervention (n, %)	60 (46)	25 (58)	35 (39)	**0.041**
• Coronary Artery Bypass Surgery (n, %)	22 (17)	11 (26)	11 (12)	0.078
• Stroke/Transient Ischemic Attack (TIA)	11 (8)	2 (5)	9 (10)	0.5
• Peripheral Artery Disease	5 (4)	0 (0)	5 (6)	0.18
Family History of Cardiovascular Disease (n, %)	80 (60)	19 (44)	61 (67)	**0.015**
Hypertension (n, %)	90 (67)	32 (74)	58 (64)	0.24
• Duration of Hypertension (months)	129.9±119.7	110.5 ± 96.9	142.8 ± 132.4	0.3
Diabetes Type II	43 (32)	43 (100)	Ø	
• Duration of Diabetes (years) (Range)	7.25 ± 7.35	7.25 ± 7.35	Ø Ø	
Fasting Glucose (mmol/l)	(0.5 - 34.0)	(0.5 - 34.0)	5.4 ± 0.8	**<0.000 1**
• < 6.1 mmol/l (n, %)	5.9 ± 1.3	6.8 ± 1.7	73 (80)	**<0.000 1**
• 6.1 - < 7.0 mmol/l (n, %)	89 (66)	16 (37)	15 (17)	0.81
• 7.0 mmol/l (n, %)	23 (17)	8 (19)	3 (3)	**0.030**
• 7.8 mmol/l (n, %)	9 (7)	6 (14)	0 (0)	**<0.000 1**

	Total	Diabetic Subjects	Non-Diabetic Subjects	
	13 (10)	13 (30)		
Medication				
Statin (n, %)	**104 (78)**	37 (86)	67 (74)	0.13
• Duration (months)	**51.6 ± 64.4**	44.3 ± 56.3	54.5 ± 67.7	0.49
Beta-blockers (n, %)	**63 (48)**	26 (61)	37 (41)	**0.041**
Calcium Channel Blockers (n, %)	**21 (16)**	8 (19)	13 (14)	0.61
ACE Inhibitors (n, %)	**43 (33)**	17 (40)	26 (29)	0.24
AT II Blockers (n, %)	**20 (16)**	6 (14)	14 (15)	1.0
Nitrates (n, %)	**7 (5)**	2 (5)	5 (6)	1.0
Diuretics (n, %)	**20 (15)**	6 (14)	14 (15)	1.0
Aspirin (n, %)	**91 (70)**	30 (70)	61 (67)	0.84
Clopidrogrel (n, %)	**61 (47)**	23 (54)	38 (42)	0.27
Oral Anti-Diabetics (n, %)	**36 (27)**	36 (84)	Ø	Ø

b. FDG-PET Imaging Results.

	Total	Diabetic Subjects	Non-Diabetic Subjects	
n (%)	**131**	**42 (32)**	**89 (68)**	
FDG-PET / CT				*p-value*
FDG uptake time (time difference between FDG injection and starting time of data acquisition; min)	**136.7 ± 21.2**	136.2 ± 21.6	137.5 ± 20.5	0.71
$_{mean}SUV$	**2.17 ± 0.35**	2.12 ± 0.29	2.20 ± 0.37	0.21
$_{mean}SUV_{gluc}$	**2.53 ± 0.64**	2.84 ± 0.71	2.01 ± 0.33	**<0.0001**
$_{mean}TBR$	**1.99 ± 0.32**	1.95 ± 0.3	2.17 ± 0.48	0.34
$_{mean}TBR_{gluc}$	**2.31 ± 0.56**	2.6 ± 0.62	2.31 ± 0.43	**< 0.0001**
SHS	**2.30 ± 0.44**	2.29 ± 0.48	2.50 ± 0.61	0.42
SHS_{gluc}	**2.68 ± 0.76**	3.06 ± 0.9		**< 0.0001**
Blood Pool Activity (left and right jugular vein; meanSUV of the mean)	**1.11 ± 0.2**	1.09 ± 0.11	1.11 ± 0.2	0.59
Glucose-corrected FDG uptake parameters depending on patient's fasting glucose levels (median 5.5 mmol / l)				
Group 1 (2.8 - 5.5 mmol / l): n (%)	**65**	12 (18.5)	53 (81.5)	
$_{mean}SUV_{gluc}$	**2.17 ± 0.46**	2.21 ± 0.38	2.16 ± 0.48	0.77
$_{mean}TBR_{gluc}$	**2.01 ±0.41**	2.13 ± 0.45	1.98 ± 0.4	0.26
SHS_{gluc}	**2.32 ± 0.51**	2.55 ± 0.71	2.27 ± 0.44	0.09
Group 2 (5.6 - 10.6 mmol / l): n (%)	**66**	30 (45.5)	36 (54.5)	
$_{mean}SUV_{gluc}$	**2.89 ± 0.59**	3.09 ± 0.65	2.72 ± 0.48	**0.011**
$_{mean}TBR_{gluc}$	**2.61 ± 0.54**	2.78 ± 0.58	2.46 ± 0.46	**0.013**
SHS_{gluc}	**3.03 ± 0.8**	3.26 ± 0.9	2.84 ± 0.66	**0.032**

Values are indicated as mean ± SD and categorical data is indicated as absolute numbers and percentages. Significant differences were found with regard to exercise and family history of cardiovascular disease being higher in non-diabetic patients as well as for percutaneous coronary intervention and medication with beta-blockers being higher for subjects with diabetes. As expected, mean fasting glucose levels as well as increased levels of the classified glucose values were significantly higher in diabetic patients whereas glucose values within the normal range were significantly more often found in non-diabetic subjects. No significant differences between both groups were observed for slightly increased glucose values 6.1 - < 7.0 mmol/l.

Values are indicated as mean ± SD and categorical data is indicated as absolute numbers and percentages. By averaging the maximum SUV values of all arterial slices of the left and right carotid artery, a $_{mean}$SUV value was derived for the carotid arteries. By averaging the mean SUV values of all analyzed slices of the left and right jugular vein the $_{mean}$SUV for the FDG bloodpool activity was calculated. TBR is the Target-to-Background-ratio, SHS is the Single Hottest Segment. No statistically significant differences were found between patients with and without diabetic disease with regard to the FDG uptake time. Whereas all of the glucose-corrected FDG uptake parameters were significantly higher in diabetic patients no significant differences between the groups were found for the uncorrected parameters. Dividing the patients into two groups of different pre-scan glucose levels by using the median of all glucose values revealed statistically significant differences between patients with type II diabetes and patients without diabetes for all glucose-corrected FDG uptake values in the group of patients with higher pre-scan glucose levels.

Table 2

a: Multiple Linear Regression Analyses with Backward Elimination to Identify Clinical Risk Factors of Carotid Vessel Wall Inflammation as Depicted by Glucose- Corrected FDG Uptake Parameters in the Whole Study Population.

	Standardized Coefficient β	95 % Confidence Interval	Adjusted R²	Significance	p - value
Glucose-Corrected FDG Uptake Parameters					
mean**SUV**gluc			0.201	<0.0001	
Diabetes	**0.324**	**0.227 - 0.656**			**<0.0001**
BMI 30 kg/m²	0.282	0.168 - 0.587			0.001
Alcohol	0.157	-0.001 - 0.411			0.051
mean**TBR**gluc			0.229	<0.0001	
Diabetes	**0.317**	**0.191 - 0.570**			**<0.0001**
BMI 30 kg/m²	0.219	0.077 - 0.440			0.006
Family History of Cardiovascular Disease	-0.2	-0.408 - -0.051			0.012
Alcohol	0.197	0.049 - 0.406			0.013
SHSgluc			0.234	<0.0001	
Diabetes	**0.298**	**0.228 - 0.737**			**<0.0001**
BMI 30 kg/m²	0.259	0.168 - 0.656			0.001
Family History Cardiovascular Disease	-0.21	-0.564 - -0.084			0.009
Alcohol	0.163	0.014 - 0.494			0.038

meanSUVgluc, mean Target-to-Background Ratio (meanTBRgluc), and Single Hottest Segment (SHSgluc) respectively, were the response variables and the cardiovascular risk factors age > 65 years, male gender, body mass index (BMI) 30 kg/m², statin medication, history of cardiovascular disease, smoking, alcohol use, exercise, hypertension, diabetes, and family history of cardiovascular disease were the explanatory variables. Variables were retained in the model when p < 0.10. β is the standardized regression coefficient. Diabetes was the most significant predictor for carotid wall inflammation as depicted by all of the FDG uptake parameters followed by obesity as depicted by BMI values 30 kg/m². Notably, the results were highly consistent among the different FDG uptake values.

Table 3

a: Multiple Linear Regression Analyses with Backward Elimination to Identify Clinical Risk Factors of Carotid Vessel Wall Inflammation as Depicted by Glucose-Corrected FDG Uptake Parameters in Diabetic- and Non-Diabetic Subjects.

	Standardized Coefficient β	95 % Confidence Interval	Adjusted R^2	Significance	p-value
Glucose-Corrected FDG Uptake Parameters					
meanSUV$_{gluc}$					
Diabetic Subjects			**0.139**	**0.009**	
BMI 30 kg/m²	0.4	0.153 - 0.989			0.009
Non-Diabetic Subjects			**0.153**	**<0.0001**	
Hypertension	0.325	0.146 - 0.597			0.002
BMI 30 kg/m²	0.212	0.017 - 0.483			0.036
meanTBR$_{gluc}$					
Diabetic Subjects			**0.22**	**0.003**	
BMI 30 kg/m²	0.357	0.093 - 0.793			0.014
Smoking	0.312	0.072 - 1.405			0.031
Non-Diabetic Subjects			**0.185**	**<0.0001**	
Hypertension	0.361	0.167 - 0.555			<0.0001
SHS$_{gluc}$					
Diabetic Subjects			**0.256**	**0.001**	
BMI 30 kg/m²	0.388	0.205 - 1.208			0.007
Smoking	0.324	0.169 - 2.081			0.022
Non-Diabetic Subjects			**0.109**	**0.001**	
Hypertension	0.345	0.182 - 0.685			0.001

meanSUV$_{gluc}$: mean Target-to-background ratio (meanTBR$_{gluc}$) and Single Hottest Segment (SHS$_{gluc}$), were the response variables and the cardiovascular risk factors age > 65 years, male gender, body mass index (BMI) 30 kg/m², statin medication, history of cardiovascular disease, smoking, alcohol use, exercise, hypertension, and family history of cardiovascular disease were the explanatory variables. Variables were retained in the model when p < 0.05. The best model is shown. β is the standardized regression coefficient. Same models were calculated in diabetic- and non-diabetic patients.

BMI 30 kg/m² and smoking were significantly associated with all FDG uptake parameters (except of smoking with regard to meanSUV$_{gluc}$) in diabetic subjects. In non-diabetic subjects, hypertension was consistently associated with all FDG uptake parameters.