White Matter Alteration in Metabolic Syndrome

Diffusion tensor analysis

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OBJECTIVE—We explored the regional pattern of white matter alteration in subjects with metabolic syndrome. We also investigated whether white matter alteration was correlated with BMI.

RESEARCH DESIGN AND METHODS—Seven middle-aged men with metabolic syndrome and seven without metabolic syndrome underwent diffusion tensor imaging with a 3T magnetic resonance imaging imager. We analyzed the fractional anisotropy (FA) values by using a tract-based spatial statistics technique (whole-brain analysis). We subsequently focused on measuring the mean FA values of the right inferior fronto-occipital fasciculus (IFOF) of all subjects by tract-specific analysis (regional brain analysis). We used a Pearson correlation coefficient to evaluate the relationship between BMI and mean FA values of the right IFOF.

RESULTS—In the whole-brain analysis, subjects with metabolic syndrome had significantly lower FA values than control subjects in part of the right external capsule (part of the right IFOF), the entire corpus callosum, and part of the deep white matter of the right frontal lobe. In the regional brain analysis, the mean FA value of the right IFOF was 0.41 ± 0.03 for subjects with metabolic syndrome and 0.44 ± 0.05 for control subjects. A significant negative correlation was observed between BMI and FA values in the right IFOF ($r = -0.56$, $P < 0.04$).

CONCLUSIONS—Our results show that microstructural white matter changes occur in patients with metabolic syndrome. FA values may be useful indices of white matter alterations in patients with metabolic syndrome.

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The prevalence of overweight and obesity has been increasing in most developed countries (1,2). Direct associations between obesity and several diseases, including diabetes mellitus, hypertension, and ischemic heart disease, are well recognized (3). The BMI is one of the most commonly used indices of obesity. Although increased BMI itself does not always cause symptoms, a greater-than-normal BMI in midlife is associated with increased risk of dementia (4). Recent epidemiological evidence suggests that metabolic syndrome itself may be a risk factor for cognitive decline and dementia (5,6). Several volumetric assessment studies have revealed greater-than-normal brain atrophy in middle-aged obese adults (7,8) who are potentially at greater risk than normal for future dementia and Alzheimer disease (9). Recent voxel-based approaches have shown that the whole brain volume in obese individuals is less than that in individuals of normal weight, indicating that the relationship between BMI and reduced brain volume is not limited to older adults and is found across the adult life span (10). A magnetic resonance spectroscopic imaging study has found that increased BMI in midlife is associated with neuronal or myelin abnormalities, or both, mainly in the frontal lobe (11). A recent tensor-based morphometry study has shown that higher BMI is associated with lower brain volume in cognitively normal elderly subjects (12). Orsi et al. (13) have demonstrated that the volume of the right amygdala is negatively correlated with BMI in overweight men.

As these studies indicate, associations between obesity and brain volume have been demonstrated, especially for gray matter. However, the effects of obesity on the microstructure of white matter remain less well-documented. Although recent studies have found that elderly adults with metabolic syndrome show subtle deficits in cognitive function (14) as well as microstructural changes in white matter (15), whether the microstructure of white matter is altered in middle-aged adults remains unknown.

Here, we examined whether the microstructure of white matter is altered in middle-aged individuals with metabolic syndrome. We explored the regional pattern of white matter alteration in middle-aged individuals with metabolic syndrome by using diffusion tensor imaging (DTI), which is sensitive to subtle changes in cerebral white matter (16,17) and thus is a powerful tool for analyzing such changes (16). We also investigated whether the observed white matter alterations were related to BMI.

RESEARCH DESIGN AND METHODS

Subjects

All participants were Japanese male volunteers who were right-hand-dominant,

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aged between 30 and 50 years, and recruited for the Healthy Brain Project by the Sportology Center of Juntendo University in Tokyo, Japan. A screening interview was conducted with each participant to verify the information from the participant's medical records. For all participants, we obtained measurements of triglycerides, HDL, and blood glucose from blood tests in the overnight fasting state. Measurements of blood pressure, height, body weight, and abdominal circumference were recorded for all participants during the screening sessions. Blood pressure was determined with an automatic device (Omron HEM-7020; Omron Electronics, Tokyo, Japan) in the morning after 30 min of rest. Sitting blood pressure was measured twice, and the mean was calculated. The exclusion criteria for this study were as follows: diabetes mellitus, treatment for hypertension, history of cardiovascular disease, history of central nervous system disease, serious hepatic dysfunction, hepatitis B, hepatitis C, serious renal dysfunction, or standard contraindications to magnetic resonance imaging (MRI).

After the screening sessions, seven subjects with metabolic syndrome aged 43.3 ± 4.4 years with a BMI ≥24 kg /m^2 and seven age-matched lean subjects without any risk factor of metabolic syndrome aged 42.3 ± 5.3 years with a BMI <23 kg/m^2 (Table 1) were included in the analysis. A BMI <23 kg/m^2 was considered "lean" because BMI ≥23 kg/m^2 and BMI ≥25 kg/m^2 have been defined as "overweight" and "obese," respectively, in Japan (18). The presence of metabolic syndrome was determined on the basis of the Japanese definition (19), namely that a person had central obesity (a waist circumference ≥85 cm) and any two of three additional risk factors. The risk factors in this study were defined as follows: serum triglycerides ≥150 mg/dL, serum HDL cholesterol <40 mg/dL, or both; systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or both; and fasting blood glucose levels ≥110 mg/dL. In this study, all subjects defined as having metabolic syndrome by Japanese criteria (18) also could have metabolic syndrome diagnosed by International Diabetes Federation criteria (20). The clinical characteristics of control subjects and subjects with metabolic syndrome are shown in Supplementary Table 1 and Table 2, respectively.

All procedures were approved by the Institutional Review Board for Human Subject Research at Juntendo University. Written informed consent was obtained from all subjects before participation.

MRI acquisition

MRI scans were performed with a 3.0-T unit (Achieva; Philips Medical Systems, Best, the Netherlands) and an eight-channel array head coil. For MRI screening, regular structural images such as T1-weighted spin-echo, T2-weighted turbo spin-echo, and fluid-attenuated inversion recovery images were obtained before the acquisition of diffusion tensor images.

The general scan parameters for DTI were as follows: a repetition time to echo time ratio of 5,443/70; a 128 × 128 acquisition matrix; a field of view of 224 × 224 mm^2; and a slice thickness of 3 mm with no gap. Images were obtained with (b = 1,000 s/mm^2 for each direction) and without (b = 0 s/mm^2) 32-direction diffusion encoding. A total of 50 axial-section images covering the entire cerebrum were obtained. The approximate scanning time for the acquisition of diffusion tensor images was 7 min 17 s.

Image analysis

We performed statistical analysis of the fractional anisotropy (FA) values with a tract-based spatial statistics (TBSS) technique (21) by using the diffusion toolbox implemented in the FMRIB software library 4.1 (FSL; http://www.fmrib.ox.ac.uk/fsl/). Differences of FA values between subjects with and without metabolic syndrome were evaluated with a permutation-based randomized test and inference by using the threshold-free cluster enhancement method implemented in FSL. The statistical threshold for all image analyses was set to a cluster $P < 0.05$, with family-wise errors corrected for multiple comparisons of the voxel-wise whole-brain analysis.

After the TBSS analysis, we conducted tract-specific analysis of the FA values by using dTV II and VOLUME-ONE 1.72, developed by Masutani et al. (22) (http://www.volume-one.org/). Tractography of the right inferior fronto-occipital fasciculus (IFOF) in all subjects was assessed by using the two region-of-interest (two-ROI) method (22–24). The JHU White Matter Tractography Atlas (25) provided with the FSL was used to guide the placement of the ROIs. To generate diffusion tensor tractographies of the right IFOF, the seed and target ROIs were set in the anterior and posterior parts, respectively, of the right external capsule. The mean FA values in the registered voxels within the core of the right IFOF were then measured.

Statistical analyses were performed with SPSS 20.0 for Windows (SPSS, Chicago, IL). Student *t* test was used for group differences between clinical characteristics and white matter FA values for all subjects (ROI-based analysis). Pearson correlation coefficient was used to evaluate the relationship between BMI and measured mean FA values of the right IFOF. The criterion for statistical significance was set at $P < 0.05$.

Table 1—*Clinical characteristics of participants and FA values

	Control subjects	Subjects with metabolic syndrome	
	7 males (BMI <23)	7 males (BMI ≥24)	*P*
Age (y)	42.3 ± 5.3	43.3 ± 4.4	0.71
Body height (cm)	174.6 ± 5.1	173.4 ± 7.6	0.72
Body weight (kg)	68.5 ± 4.4	77.8 ± 8.9	< 0.05†
BMI (kg/m^2)	22.5 ± 0.4	25.8 ± 1.4	< 0.05†
Abdominal circumference (cm)	81.1 ± 5.5	91.4 ± 5.0	< 0.05†
Systolic BP (mmHg)	115.9 ± 8.1	134.4 ± 9.8	< 0.05†
Diastolic BP (mmHg)	76.7 ± 4.9	91.4 ± 6.6	< 0.05†
HDL cholesterol (mg/dL)	56.4 ± 9.9	60.1 ± 18.9	0.65
Triglyceride (mg/dL)	95.1 ± 30.9	183.3 ± 45.3	< 0.05†
Blood glucose (mg/dL)	95.9 ± 7.1	101.0 ± 9.1	0.26
FA of right IFOF‡	0.44 ± 0.05	0.41 ± 0.03	< 0.05†

*Values are expressed as means ± SD. †$P < 0.05$. ‡Fractional anisotropy values of right IFOF. BP, blood pressure.

RESULTS—All 14 participants were free of any visible abnormal findings during the screening MRI scan. The TBSS analysis (whole-brain analysis) revealed that compared with the FA values in controls, those in subjects with metabolic syndrome were significantly lower in part of the right external capsule (part of the right IFOF), the entire corpus callosum, and part of the

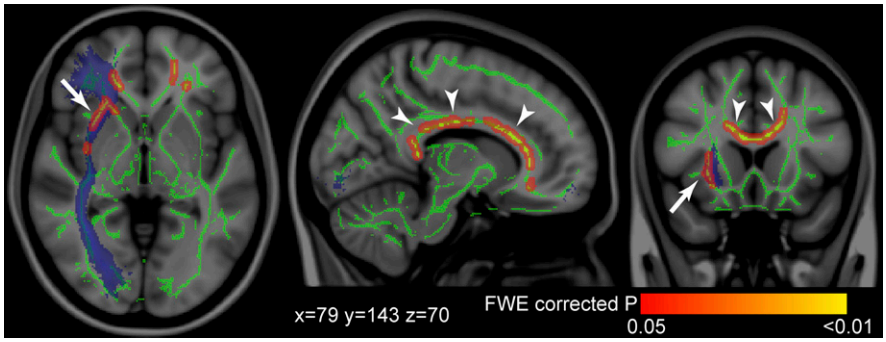

Figure 1—*Results of a tract-based spatial statistics analysis for FA. Areas with significantly reduced FA values in subjects with metabolic syndrome compared with control subjects are shown by colors ranging from red to yellow (*P *< 0.05, the family-wise error [FWE] correction for multiple comparisons). We found significant reductions in FA values in part of the right external capsule* (arrows) *and in the entire corpus callosum* (arrowheads). *Results are superimposed on the MNI152 1-mm template supplied with FSL. The mean FA skeleton is shown in green. The right IFOF, which is derived from the JHU white matter tractography atlas supplied with FSL, is shown for reference in blue. Montreal Neurologic Institute space coordinates are provided in millimeters. (A high-quality digital representation of this figure is available in the online issue.)*

deep white matter of the right frontal lobe (Fig. 1). No significant differences were found in the reverse contrasts.

In all subjects, tractographies of the right IFOF were obtained as gently curved tracts passing backward from the right frontal lobe, along the lateral border of the right caudate nucleus, and into the occipital lobe (Fig. 2). Tract-specific analysis (regional brain analysis) revealed that the mean FA of the right IFOF was 0.41 ± 0.03 for subjects with metabolic syndrome and 0.44 ± 0.05 for control subjects (Table 1); the difference between these values was significant ($P < 0.05$). A significant negative correlation was observed between BMI and the FA values of the right IFOF ($r = -0.56$, $P < 0.04$) (Fig. 3).

CONCLUSIONS—Although DTI is a powerful tool for analyzing the structure of white matter, few studies have investigated the association between BMI and alterations in white matter. Our TBSS analysis revealed white matter alteration in subjects with metabolic syndrome relative to control subjects, as measured by the significantly lower FA values in the entire corpus callosum, part of the right external capsule, and part of the deep white matter of the right frontal lobe. The results suggest that there are microstructural changes in the white matter of middle-aged individuals with metabolic syndrome. These findings add to the increasing body of neuroimaging evidence on white matter alteration in patients with hypertension, diabetes, or metabolic syndrome (15,26–28). Microstructural alterations in the white matter of younger obese individuals (11,29) may precede brain atrophy (7,30,31), cognitive impairment (11,14,32), or both in advanced metabolic syndrome.

By using both TBSS and tract-specific analysis analyses, we also observed that FA values in part of the right external capsule were significantly lower in subjects with metabolic syndrome than in controls, and that BMI was negatively correlated with FA values of the right IFOF. Several studies have shown that BMI is negatively correlated with FA values in the corpus callosum (33,34). To our knowledge, this study is the first to demonstrate a relationship between changes in the right IFOF and BMI. The IFOF is unique in that it connects all four major lobes of the brain and potentially serves an important role in linking all the components of what is commonly called the social brain (35). The social brain hypothesis could be related to human feeding behavior, because several functional MRI studies have detected a correlation between neural activity and eating behavior (36,37). However, few studies have used DTI to address microstructural changes in the white matter of subjects with metabolic syndrome (15,28). Further studies are needed to clarify the possible relationships between metabolic syndrome and brain structure. In the TBSS analysis, the left IFOF did not demonstrate a significant FA reduction, even though FA values in part of the right IFOF were significantly lower in subjects with metabolic syndrome than in controls. Our results may reflect the laterality of BMI-related alterations in the microstructure of white matter. Another possible reason why the left IFOF did not demonstrate the same result is that the sample of participants was relatively small. Hence, further studies with greater numbers of participants are needed to clarify whether BMI is associated with laterality of white matter alterations.

We found a regional pattern of significant FA reduction in middle-aged men with metabolic syndrome. The clinical

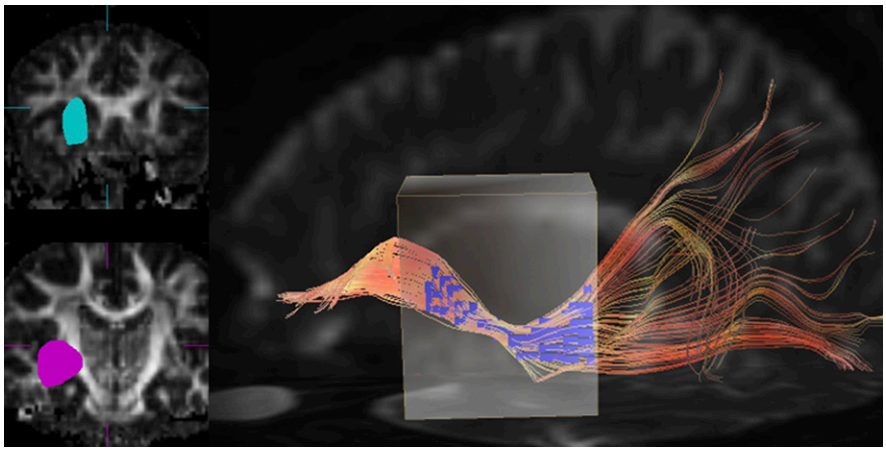

Figure 2—*Tractography of the right IFOF. The seed regions-of-interest* (blue area) *were set in the anterior parts of the right external capsule* (upper left panel). *The target regions-of-interest* (purple area) *were set in the posterior parts of the right external capsule* (lower left panel). *In all subjects, tractographies of the right IFOF were obtained as gently curved tracts passing backward from the right frontal lobe, along the lateral border of the right caudate nucleus, and into the occipital lobe* (right panel). *(A high-quality digital representation of this figure is available in the online issue.)*

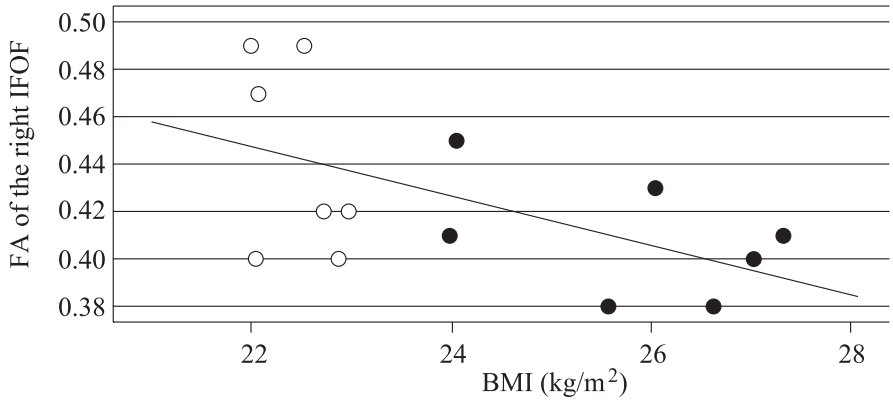

Figure 3—*The mean FA value of the right IFOF was 0.44 ± 0.05 for control subjects* (white circles) *and 0.41 ± 0.03 for subjects with metabolic syndrome* (black circles). *A significant negative correlation was observed between BMI and the FA values of the right IFOF* ($r = -0.56$; $P < 0.04$).

significance of such microstructural white matter alterations may be underreported. Most earlier studies have found FA reduction in subjects with advanced metabolic syndrome (15,27,28). Although Mueller et al. (34) have claimed a significant negative correlation between FA and BMI in women but not in men, we found a significant negative correlation between FA and BMI in middle-aged men. For the following reasons, we believe that alterations in white matter, as measured by the significantly lower FA values, occur in male subjects with metabolic syndrome. First, we observed statistically significant lower FA values in subjects with metabolic syndrome by using not only TBSS but also tract-specific analysis, whereas Mueller et al. used only the former. Second, our finding that BMI was negatively correlated with the FA values of the right IFOF was comparable with that reported by Mueller et al.

Here, we determined the presence of metabolic syndrome by using Japanese criteria for metabolic syndrome based on clinical evidence from Japanese subjects (18). The Japanese criteria have many points of similarity to International Diabetes Federation criteria (18,20), and both criteria are practical and useful in terms of clinical application. However, a diagnosis of metabolic syndrome by World Health Organization criteria requires several markers of insulin resistance (38). In the Japanese criteria, insulin resistance is not a prerequisite for diagnosis, although recent data suggest that waist circumference is linearly related to insulin resistance, and that a waist circumference of 85 cm is an optimal cut-off for predicting insulin resistance in middle-aged Japanese men (39).

Some limitations of our study are as follows. First, the sample was restricted to middle-aged men and a relatively small number of participants. The inclusion of only middle-aged men may limit the generalizability of our results, and the characteristics of our subjects with metabolic syndrome may not fully reflect those of the general population with this disease. However, our approach yielded findings similar to those of earlier reports, especially for the corpus callosum (28,34). Further studies are required to elucidate sex differences in the BMI-related microstructure of white matter. Therefore, future studies should include greater numbers of participants. Another possible limitation is that our subjects had two or more risk factors. The FA reduction may be partly explained by elevated BMI. Future multivariate analysis studies with even greater numbers of participants will be needed to detect more specific risk factors for human brain damage.

In conclusion, we found a negative correlation between BMI and FA values in middle-aged men with metabolic syndrome. Our results suggest that FA values may be useful indices of white matter alterations in patients with metabolic syndrome. Such alterations in younger overweight individuals may precede brain atrophy or cognitive impairment in advanced metabolic syndrome. A clearer understanding of these relationships is crucial to the management of patients with metabolic syndrome.

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No potential conflicts of interest relevant to this article were reported.

K.S. wrote the manuscript. K.S., O.A., T.U., H.Y., K.A., M.H., and Y.T. researched data. K.S., O.A., T.U., H.Y., K.K., M.H., A.N., Y.T., H.W., R.K., and S.A. contributed to the discussion. O.A., T.U., H.Y., K.K., K.A., M.H., A.N., Y.T., H.W., R.K., and S.A. edited the manuscript. K.S. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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