gression analysis showed that OR for death of the high-risk group was 6.2 (95% CI 1.7–21.6, p = 0.005) after adjustment for age.

Discussion

In this study, we demonstrated for the first time that, although age was significantly associated with death in patients with MPO-ANCA-associated vasculitis with renal involvement, JVAS was an independent predictor for poor prognosis within 2 years of initial diagnosis in these subjects. BVAS is a more precise measurement of the dissemination of vasculitis than JVAS, but its clinical use has potential limitations because (1) to evaluate the 68-item lists in 9 separate organ systems is complex in a clinical setting, and (2) weights of 1–3 were determined empirically [23]. Therefore, the present results suggest that compared with BVAS, assessment by JVAS [19] may be more feasible for evaluating disease severity and death in MPO-ANCA-associated microscopic vasculitis with renal involvement in Japan.

The mortality rate was reported to be significantly associated with the BVAS value in systemic vasculitis patients, including polyarteritis nodosa, microscopic polyangiitis and Churg-Strauss syndrome [16]. Further, in the multivariate Cox regression, the BVAS value on admission was one of the significant predictors of mortality in AAV [18]. However, BVAS was not associated with death in our subjects. The differences in subject population (systemic vasculitis vs. MPO-ANCA-associated vasculitis with renal involvement) and ethnicity could account for the discrepant results. Itabashi et al. [17] reported that age but not BVAS value at the onset of the disease was associated with death in Japanese subjects with AAV, thus supporting our speculation. In addition, renal injury is more severe in MPO-ANCA-positive microscopic polyangiitis patients [12]. Microscopic polyangiitis patients are also reported to have a tendency toward increased mortality compared with other types of AAV [16, 18]. Therefore, BVAS may not be a suitable tool for predicting the mortality in the severe form of AAV with rapidly progressive glomerulonephritis. Harper and Savage [24] previously reported that the 5-year survival rate of ANCA-positive glomerulonephritis patients was 60–80%, and age and renal dysfunction were associated with poor prognosis; their results are consistent with our present findings. Intensive therapy with steroids and cyclophosphamide resulted in complete remission rates of greater than 90% [24], but it is unlikely that immunosuppressive drugs could confound the present results because among our patients there were no significant differences in immunosuppressive treatments between the survivors and non-survivors.

Components of items evaluated by JAVS and BVAS differ [15, 19]. JVAS is composed of items such as age and CRP, whereas BVAS includes symptoms and signs of extrapulmonary-renal organ vasculitis. The present study showed that JVAS, but not CRP is associated with death and is independent of age. These observations suggest the clinical utility of assessment using JVAS, especially in the evaluation of both age and CRP for predicting mortality in MPO-ANCA-positive glomerulonephritis patients. Further, symptoms and signs of extrapulmonary-renal organ vasculitis may not necessarily reflect fetal organ damage. To evaluate them could not increase the sensitivity and specificity of BVAS for the prediction of death in MPO-ANCA-associated vasculitis patients with renal involvement. Little et al. [25] reported that the greatest threat to patients with AAV in the first year of therapy is from adverse events rather than active vasculitis. At disease onset before therapy, JVAS was able to predict poor prognosis in our subjects; therefore, it may be a useful tool to determine which patients should be intensively treated with immunosuppressants. In other words, patients with MPO-ANCA-associated renal involvement whose JVAS value is ≥ 5 points may have to be treated more intensively.

The potential limitations of our study were that it was retrospective and had a small sample size. Further, we could not totally exclude the possibility that immunosuppressive treatments could affect the relationship between the JVAS value at disease onset and poor prognosis in our subjects. In addition, whether JVAS could be a good predictor of poor prognosis for other ethnic patients remains unclear. Further large-scale prospective studies will be required to address this issue.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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Serum immunoglobulin G4 associated with number and distribution of extrapancreatic lesions in type 1 autoimmune pancreatitis patients

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autoimmune pancreatitis, extrapancreatic lesions, immunoglobulin G4.

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Abstract

Background and Aim: Type 1 autoimmune pancreatitis (AIP) is characterized by the increase of serum immunoglobulin (Ig)G4 and abundant IgG4 plasma cell infiltration in the pancreas and various extrapancreatic lesions (EPL), which are proposed as IgG4-related disease. We assessed the correlation between serum IgG4 and the number of EPL, and the association between serum IgG4 and the distribution of EPL in type 1 AIP patients.

Methods: Serum IgG4 was measured in 35 type 1 AIP patients and 71 non-AIP patients. The clinical characteristics and distribution of eight EPL were determined in 35 type 1 AIP patients.

Results: Serum IgG4 in type 1 AIP was significantly higher than in non-AIP ($P < 0.001$). A total of 33 patients had EPL among 35 patients with type 1 AIP (94.3%). There was a significant correlation between serum IgG4 and the number of EPL ($\rho = 0.75$, $P < 0.001$). Further, to assess the association between serum IgG4 and the distribution of EPL, type 1 AIP patients were divided into two groups: as abdominal localized EPL and systemic EPL. Both serum IgG4 and total numbers of EPL in systemic EPL were remarkably higher than those in abdominal localized EPL. Serum IgG4 cut-off value was 346 mg/dL to distinguish between abdominal localized EPL and systemic EPL according to the receiver–operator characteristic curve data.

Conclusions: Our findings indicated that serum IgG4 was useful in both the diagnosis of type 1 AIP and the detection of systemic EPL. Our finding may help the concept and diagnostic criteria of IgG4-related disease with type 1 AIP.

Introduction

Autoimmune pancreatitis (AIP) is a particular type of pancreatitis that is thought to have an autoimmune cause. However, its precise pathogenesis or pathophysiology remains unclear.[1,2] In 2001, Hamano *et al.* showed that serum immunoglobulin (Ig) G4 was frequently and significantly increased in AIP patients.[3] In 2006, the Japanese criteria were modified and IgG4 was newly added to the serological criteria, including elevated titers of γ-globulin and IgG, and autoantibodies.[4] In 2008, serum IgG4 elevation in addition to IgG and autoimmune antibodies is an important criteria to diagnose AIP in the Asian diagnostic criteria proposed by a consensus of Japanese and Korean pancreatologists.[5] Further, the HISORt criteria suggested by the Mayo Clinic allow serum IgG4 alone as a serological criterion.[6] Thus, serum IgG4 is a useful marker for diagnosing AIP from other pancreatic diseases.

Recent studies have suggested the existence of two subtypes of AIP: type 1 AIP, related to IgG4 (lymphoplasmacytic sclerosing pancreatitis); and type 2 AIP, related to a granulocytic epithelial lesion (idiopathic duct-centric chronic pancreatitis). Compared with type 2 AIP, the clinicopathological features of type 1 AIP were characterized as increasing serum IgG4 levels, and abundant infiltration of IgG4 + plasmacytes and lymphocytes. Based on these findings, international consensus diagnostic criteria (ICDC) for AIP were proposed in 2010.[7]

Type 1 AIP showed the inflammation of extrapancreatic lesions (EPL), such as sclerosing cholangitis,[8,9] sclerosing sialadenitis,[10] retroperitoneal fibrosis,[11] and lymphadenopathy.[12] They share several characteristic features of AIP, such as dense lymphoplasmacytic infiltration with abundant IgG4 + plasma cells and fibroplasias. Considering these clinical features of type 1 AIP and EPL, the concept of IgG4-related disease has been proposed by several groups.[13–15] Although several studies showed that serum IgG4 concentration was higher in AIP with EPL than it in AIP alone,[16] it has been unclear whether serum IgG4 was associated with the clinical features of EPL, such as the number and distribution in type 1 AIP.

Therefore, the aim of this study was to determine whether serum IgG4 was associated with type 1 AIP and the numbers of EPL. Further, another aim was to assess the association between serum IgG4 concentration and the distribution of EPL in type 1 AIP patients.

Methods

This study was approved by the Kurume University Hospital. Between April 2000 and February 2011, 35 patients with type 1 AIP were identified from a prospectively collected database. All the patients with AIP fulfilled the Asian diagnostic criteria for AIP,[5] and the ICDC for AIP.[7] Three patients with normal IgG4 concentration underwent pancreatoduodenectomy, in order to rule out pancreatic cancer. Lymphoplasmacytic sclerosing pancreatitis was diagnosed in surgical specimens by histological examination. As a comparison group, 71 patients with non-AIP, including 17 pancreatic cancer patients, 24 chronic pancreatitis patients, seven primary sclerosing cholangitis (PSC) patients and 23 biliary system cancer patients enrolled between January 2004 and February 2011, were randomly selected, and serum IgG4 were measured by using collected blood samples from these patients.

We estimated the sensitivity and specificity of serum IgG4 concentration in the diagnosis and differentiation of AIP from non-AIP at the concentration being used as a cut-off value by the Japan Pancreas Society (IgG4 ≥ 135 mg/dL).[6] Serum IgG4 were measured by using automated nephelometry (BN-II nephelometer, Dade Behring, Germany).

To detect the extrapancreatic lesions, we performed physical examination, computed tomography (CT), magnetic resonance imaging (MRI), endoscopic retrograde cholangiopancreatography (ERCP) and ^{18}F-fluorodeoxy glucose–positron emission tomography (FDG-PET) or gallium-67 citrate (Ga-67) scintigraphy in all AIP patients. The extrapancreatic lesions included sclerosing cholangitis, sclerosing cholecystitis, sclerosing sialadenitis, dacryoadenitis, retroperitoneal fibrosis, interstitial change of the lung, hilar lymphadenopathy and cervical lymphadenopathy (the maximum number of EPL was eight). We evaluated the correlation between serum IgG4 concentration and the numbers of EPL.

We divided type 1 AIP patients into two groups as follows: (i) patients who had EPL localized on the abdomen were defined as abdominal localized EPL; and (ii) patients who had extra-abdominal EPL, either sclerosing sialadenitis, dacryoadenitis, interstitial change of the lung, hilar lymphadenopathy or cervical lymphadenopathy with or without abdominal EPL, were defined as systemic EPL. Then, we assessed the association between the distribution of EPL (abdominal localized EPL and systemic EPL) and serum IgG4 concentration in type 1 AIP patients.

Statistical analyses were performed using the Wilcoxon rank sum test for quantitative variables and Fisher's exact test for qualitative variables. Correlations were established using Spearman's rank correlation coefficients. Serum IgG4 concentration to distinguish between abdominal localized EPL and systemic EPL was evaluated by receiver–operator characteristic (ROC) curve analysis. All statistical analyses were performed with SAS software Ver. 9.2 (SAS Institute Inc., Cornelius, NC, USA). Two-sided *P*-values less than 0.05 were considered statistically significant.

Results

Sensitivity and specificity of serum IgG4 in type 1 AIP

The enrolled individuals consisted of 35 patients (27 men and eight women) with type 1 AIP and 71 non-AIP patients, including pancreatic cancer, chronic pancreatitis patients, primary sclerosing cholangitis (PSC), and biliary system cancer (47 men and 24 women). There was no type 2 AIP patient in our hospital. The median (range) for age was 66.0 (38–82) years in type 1 AIP groups and 63.0 (24–85) years in non-AIP groups. The median (range) for serum IgG4 in type 1 AIP and non-AIP were 336.0 (63.6–2740) mg/dL and 29.8 (3–243) mg/dL, respectively. IgG4 in type 1 AIP was significantly higher than those of IgG4 in non-AIP ($P < 0.001$) as previously described (Table 1). The sensitivity of serum IgG4 (≥ 135 mg/dL) in type 1 AIP patients was 91.4% (32/35). The specificity was 97.2% (69/71) in differentiating type 1 AIP from non-AIP.

Association between serum IgG4 concentration and the number of extrapancreatic lesions in type 1 AIP patients

After diagnosing type 1 AIP, we examined CT, FDG-PET and Ga scintigraphy to detect EPL in AIP patients. The EPL, including (i) sclerosing cholangitis; (ii) sclerosing cholecystitis; (iii) sclerosing sialadenitis; (iv) dacryoadenitis; (v) retroperitoneal fibrosis; (vi) interstitial change of the lung; (vii) hilar lymphadenopathy; and (viii) cervical lymphadenopathy were found in our study. A total of 33 patients had EPL among 35 type 1 AIP patients (94.3%). Figure 1 shows a scattergram of the numbers of EPL according to serum IgG4 concentration. By Spearman's rank correlations, there

Table 1 Serum IgG4 concentration in various patients groups

	Type 1 AIP	Pancreatic cancer	Chronic pancreatitis	PSC	Bile system cancer
n	35	17	24	7	23
Age	66 (38–82)	64 (42–83)	59 (31–81)	60 (24–77)	69 (32–85)
Male : female ratio	27:8	12:5	14:10	4:3	17:6
IgG4 level	336 (63.6–2740)	25.9 (3–104)	38.1 (3–174)	34.6 (15.5–71.8)	39.9 (3–243)
IgG4(≥ 135 mg/dL)	91.4% (32/35)	0% (0/17)	4.2% (1/24)	0% (0/6)	4.3% (1/23)

Median (range) is shown for continuous variables.
AIP, autoimmune pancreatitis; Ig, immunoglobulin; PSC, primary sclerosing cholangitis.

was a significant correlation between serum IgG4 concentration and the numbers of EPL ($\rho = 0.75$, $P < 0.001$).

Distinguishing between abdominal and systemic extrapancreatic lesions by serum IgG4 concentration

Sclerosing cholangitis, sclerosing cholecystitis, and retroperitoneal fibrosis were the peripancreatic inflammations in the abdomen. These inflammations were frequently observed among all AIP patients (71.4%). We supposed that the increased numbers of EPL were dependent on the extension of EPL outside the abdomen. To assess our hypothesis, we divided type 1 AIP patients into two groups as abdominal localized EPL and systemic EPL. Table 2 shows the characteristic features of EPL in the patients of systemic EPL and abdominal localized EPL. Interestingly, Table 2 shows that both serum IgG4 and total numbers of EPL in systemic EPL were remarkably higher than those in abdominal localized EPL (627 *vs* 219.5 in IgG4, $P < 0.001$, 3 *vs* 1 in total numbers of EPL, $P < 0.001$).

Next, we assessed whether serum IgG4 concentration could distinguish between abdominal localized EPL and systemic EPL. The ROC curve data suggested that the serum IgG4 cut-off value was 346 mg/dL. Using this cut-off value, sensitivity was 78.9% and specificity was 87.5% in diagnosing systemic EPL. The area under the ROC curve was 0.89 (Fig. 2). Thus, IgG4 concentration

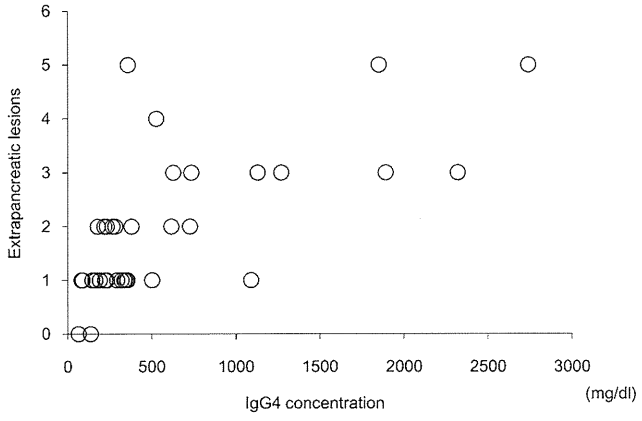

Figure 1 Scattergram of the numbers of extrapancreatic lesion according to serum immunoglobulin (Ig) G4 concentration in type 1 autoimmune pancreatitis patients.

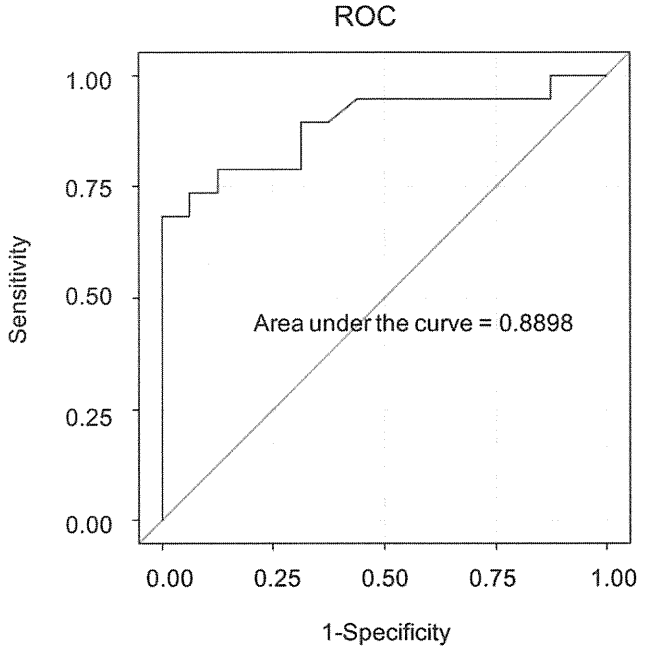

Figure 2 Receiver–operator characteristic (ROC) curve data for distinguishing between abdominal localized extrapancreatic lesion and systemic extrapancreatic lesion.

Table 2 Characteristics of patients and EPL in systemic EPL and abdominal localized EPL

	Systemic EPL	Abdominal localized EPL	*P*
n	19	16	
Male : female ratio	13:6	14:2	0.24
Age	70 (53–82)	66 (38–75)	0.28
The total number of EPL	3 (1–5)	1 (0–2)	< 0.001
Serum IgG4 concentration (mg/dL)	627 (87.7–2740)	219.5 (63.6–379)	< 0.001
Extrapancreatic lesions			
Sclerosing cholangitis	10 (52.6%)	12 (75.0%)	
Sclerosing cholecystitis	2 (10.5%)	1 (6.3%)	
Retroperitoneal fibrosis	4 (21.1%)	5 (31.3%)	
Sclerosing sialadenitis	8 (42.1%)	—	
Dacryoadenitis	3 (15.8%)	—	
Interstitial change of the lung	4 (15.8%)	—	
Hilar lymphadenopathy	13 (68.4%)	—	
Cervical lymphadenopathy	6 (31.6%)	—	

Median (range) is shown for male : female ratio, age, total number of EPL, and serum IgG4 concentration.
The number of each EPL (percentage) is shown.
EPL, extrapancreatic lesions; Ig, immunoglobulin.

was significantly associated with the number and the distribution of EPL in type 1 AIP patients.

Discussion

The IgG4 is the rarest IgG subclass and it accounts for only 3–6% of total IgG in humans. The IgG4 subclass is unique among IgG subclasses in its inability to bind the C1q complement protein and it activates the complement pathway.[17] The diagnostic value of serum IgG4 as a serologic marker for AIP was first established by Hamano *et al.*, and the authors reported that the sensitivity of IgG4 for AIP was 95.0%.[3] The subsequent studies on serum IgG4 in AIP have reported the sensitivity of IgG4 for AIP as around 80%.[18] In our 35 cases, IgG4 was significantly increased in AIP patients and its sensitivity was 91.4%. This is consistent with previous reports.

In 2005, Ohara *et al.* investigated EPL in case reports of AIP.[19] They showed that seven of 31 AIP patients had EPL and this frequency of EPL was low (22.6%). In addition, serum IgG4 concentration was significantly higher in AIP patients with EPL than those without.[19] Subsequent studies showed that the frequency of EPL in AIP patients was around 80–90%, 24 of 28 (85.7%)[20] and 61 of 64 (95.0%) in AIP patients.[21] Our study also showed high frequency (94.3%) of EPL in type 1 AIP patients. As the high IgG4 concentration in AIP was associated with the presence of EPL,[16] we assessed the association between IgG4 concentration and the clinical features of EPL in type 1 AIP.

A previous study could not find a significant correlation between IgG4 concentration and the numbers of EPL.[22] This was because the database of EPL was not sufficient and lacking data in many cases. However, they showed that patients with multiple EPL tended to have higher IgG4 concentration than those with few EPL. Our study is the first report showing serum IgG4 is significantly correlated with the number of EPL. This correlation may suggest that patients with many EPL have a more active disease state than those with few EPL. Furthermore, Hamano *et al.* showed that AIP patients with hilar lymphadenopathy or lachrymal and salivary gland lesions had a significantly higher IgG4 concentration than those without.[22] They also showed that patients with extrapancreatic bile duct lesions and retroperitoneal fibrosis had lower serum IgG4 concentration than those with lachrymal and salivary gland lesions. Therefore, it raised one hypothesis that serum IgG4 concentration was increased in the extent of inflammation outside the abdomen. To assess the association between serum IgG4 concentration and distribution of EPL, we divided type 1 AIP patients into two groups as abdominal localized EPL and systemic EPL. Indeed, both serum IgG4 and total numbers of EPL in systemic EPL were remarkably higher than those in abdominal localized EPL. This result suggested that IgG4 concentration was significantly associated with the numbers and distribution of EPL in type 1 AIP patients. As several groups have proposed that type 1 AIP was one character of the IgG-related diseases,[15] systemic EPL may be considered as systemic IgG4-related disease that differs from abdominal localized EPL as AIP localized around the pancreas. The ROC curve data demonstrated that the serum IgG4 cut-off value to distinguish between abdominal localized EPL and systemic EPL in type 1 AIP was 346 mg/dL. Our data suggest that the serum IgG4 concentration is a marker to indicate the activity and distribution of EPL in type 1 AIP. We did not find any significant difference of clinical outcomes between AIP with abdominal localized EPL and AIP with systemic EPL, because the number of patients was small. In a future large-scale study, we need to clarify the difference of clinical significance between them.

In conclusion, our findings indicate that serum IgG4 is useful in diagnosing disease activity as well as detecting systemic EPL in type 1 AIP. We suppose that our findings may contribute to the understanding and diagnostic criteria of IgG4-related diseases with type 1 AIP.

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肥満と脳梗塞

Body mass index and stroke incidence in a Japanese community : the Hisayama study.
Yonemoto K *et al* : *Hypertens Res* **34** : 274-279, 2011

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はじめに

わが国では，生活習慣の欧米化に伴い肥満が増えつづけている．肥満は虚血性心疾患と強く関連することが知られているが，脳卒中との関連については結果が一致しておらず，結論は得られていない．そこでわが国の一般住民を対象にした前向きコホート研究において，肥満と脳卒中発症との関連を検討した．

対象と方法

1988年に，福岡県久山町の循環器健診において75 g経口ブドウ糖負荷試験を受けた40～79歳の住民のうち，脳卒中・虚血性心疾患の既往歴のない2,421名を対象とし，12年間前向きに追跡した．対象者をbody mass index (BMI) レベル (kg/m^2) 別に21.0未満，21.0～22.9，23.0～24.9，25.0以上の4群に分類し，BMIと脳梗塞 (ischemic stroke : IS) および出血性脳卒中発症（脳出血＋くも膜下出血）との関連を検討した．解析は男女別にCox比例ハザードモデルを用いておこない，調整因子として年齢，収縮期血圧，心電図異常（左室肥大，ST低下，心房細動），糖尿病，総コレステロール，高密度リポ蛋白（HDL）コレステロール，中性脂肪，喫煙，飲酒，余暇時の運動を用いた．さらにBMI 25.0 kg/m^2以上を肥満と定義し，肥満の有無とおもな危険因子の合併がISのリスクに与える影響を検証した．

結 果

図1に，BMIレベル別にみた年齢調整後の病型別脳卒中発症率を示す．男性ではBMIレベルの上昇に伴い，IS発症率が有意に増加した．上記の危険因子を調整した多変量解析でも，この関係に変りはなかった．一方，BMIレベルは女性のIS発症および男女の出血性脳卒中発症と有意な関連を示さなかった．

男性において，ISのおもな危険因子である高血圧・糖尿病・喫煙と肥満が合併した場合のISのリスクを他の危険因子を調整した多変量解析で検証した．その結果，肥満に糖尿病あるいは喫煙が合併するとISのリスクが相乗的に上昇した（**表1**）．高血圧にはそのような相乗効果は認められなかったが，高血圧の有無に関係なく肥満はISの有意な危険因子であった．

考 察

これまでのコホート研究では，われわれの男性のようにBMIレベルと全脳卒中あるいはISとのあいだに有意な正の関連を見出した研究もあるが，なかには両者のあいだに明らかな関連を認めなかった研究，あるいは負の関連やU字型の関連を認めた研究もある．この違いの理由として，両者のあいだに有意な正の関連を認めなかった研究のすべてが脳卒中を病型に分けずに解析していることや，その多くが脳卒中死亡をエンドポイントとしていることが可能性としてあげられる．肥満の影響は脳卒中の病型により異なると考えられる．また，肥満と脳卒中死亡との関連を検討した研究では，体重減少をもたらす喫煙や潜在疾患の影響を制御できないなどの問題があり，その解釈には注意が必要である．

他の多くの研究と異なり，また一部の研究と同様に，本研究では高血圧・糖尿病・脂質異常症のような介在因子を調整してもBMIとIS発症との関係は弱まらなかった．つまり，既知の危険因子と独立して，過体重や肥満がIS発症に影響を及ぼすことが示唆される．その機序として，過体重や肥満を有する者では，血液凝固因子や炎症マーカーが上昇し，インスリン抵抗性およびメタボリックシンドロームが亢進していることが指摘されている．

われわれの層別解析では，肥満に糖尿病および喫煙が合併すると，ISのリスクが相乗的に上昇した．これらの危険因子を有する者では，すでに全身の動脈硬化が進んでおり，それに肥満が合併すると，肥満に特異的な上記

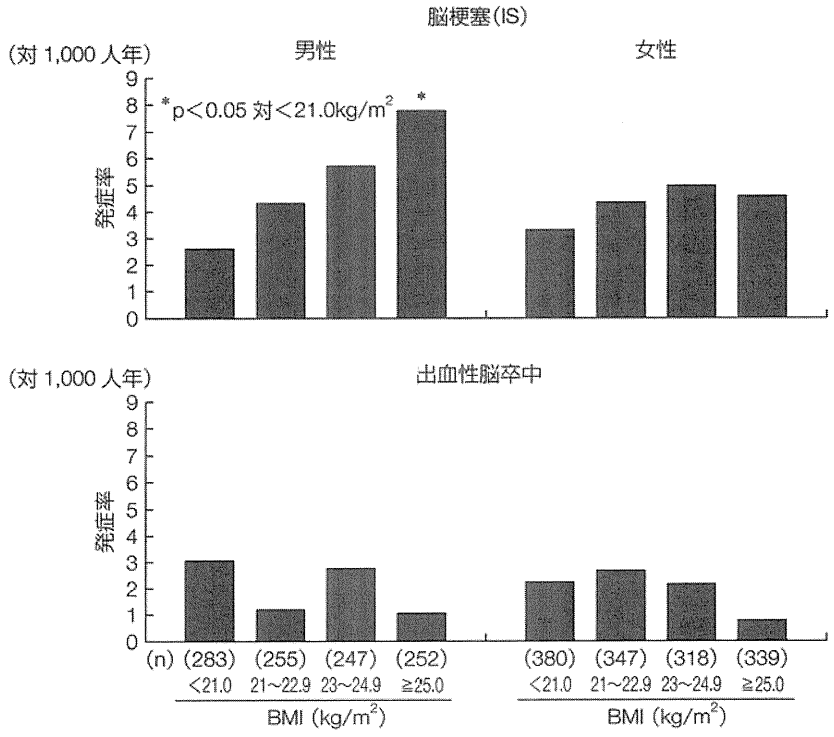

図 1. BMI レベル別にみた脳卒中発症率，年齢調整

表 1. 肥満と他の危険因子の有無別にみた IS 発症の多変量調整ハザード比，男性

		対象集団	イベント数	ハザード比	95%信頼区間	p 値
肥満	高血圧					
なし	なし	477	14	1.00	基準	
なし	あり	308	17	1.59	0.76~3.34	0.22
あり	なし	111	7	3.79	1.44~10.00	0.007
あり	あり	141	9	2.95	1.19~7.30	0.02
肥満	糖尿病					
なし	なし	678	25	1.00	基準	
なし	あり	107	6	1.60	0.65~3.97	0.31
あり	なし	200	8	1.83	0.77~4.38	0.17
あり	あり	52	8	7.91	3.08~20.28	<0.001
肥満	喫煙					
なし	なし	369	17	1.00	基準	
なし	あり	416	14	1.18	0.56~2.48	0.67
あり	なし	148	8	2.13	0.83~5.46	0.11
あり	あり	104	8	3.62	1.39~9.43	0.008

調整因子：年齢，収縮期血圧，心電図異常，糖尿病，総コレステロール，HDLコレステロール，中性脂肪，喫煙，飲酒，余暇時の運動（層別に使った因子は除外）
肥満：BMI≧25.0 kg/m²

の病態が血管傷害をさらに進展させて IS のリスクを高める可能性がある．一方，高血圧にはそのような相乗効果は認められなかった．この対象集団では高血圧治療が普及しており，それが影響している可能性がある．

おわりに

現代の日本人男性では，過体重や肥満は IS の有意な危険因子と考えられる．IS 予防には，他の危険因子とともに体重の管理が重要である．

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