than the TG+TT genotypes ($P=.031$). In addition, eNOS Glu298Asp genotype has an effect on triglyceride levels dichotomized by its demarcation line, according to the chi-square test ($P=.021$). It is possible that the high frequency of the GG genotype (86%) has masked the results of statistical analyses presented in past reports (Metzger et al. 2007). Because of the small sample study, ours has no power to analyze the differences in cardiovascular events between GG and TG+TT genotypes.

Whether eNOS Glu298Asp is a functional SNP or not continues to be widely discussed. There has been report on eNOS Glu298Asp and cardiac disease, including hypertension, showing that T allele may be involved in a higher risk (Srivastava et al. 2008). Importantly, this SNP resulting non-functional has also been reported in the yeast *Pichia pastoris* and in human endothelial cells (Golser et al. 2003; McDonald et al. 2004). Based upon the inconsistently reported functionality of this polymorphism, we suggest that further research is required to clarify the cell types in which the eNOS Glu298Asp polymorphism is functional.

In this report, the most novel finding obtained by focusing the analysis on elderly women is the relationship between the ERα IVS1-401 polymorphism and plasma BNP concentration. BNP is composed of 32 amino acids. It is synthesized in the heart ventricles, and is a well-known biomarker for heart failure (Tsutamoto et al. 1999). Neither its transcriptional regulation nor its biochemical importance is well understood (Daniels and Maisel 2007). For the ERα IVS1-401 polymorphism, the C allele, but not the T allele, is thought to result in elevated ERα expression (Herrington et al. 2002a; Schuit et al. 2004). This C allele, results either positive or negative against protective effect on cardiovascular disease (Hirschberg et al. 2009). Although estrogen up-regulates BNP mRNA and protein levels in rat neonatal cardiomyocytes (Pedram et al. 2005) and ERα and BNP proteins are both produced in adult rat cardiomyocytes (Nuedling et al. 1999; Pedram et al. 2005), there are no reports on the relation of polymorphism of ERα and BNP. Further, a previous study of ER knockout mice showed that ERβ encoded by the ESR2 gene, and not ERα, might be important for protection against heart failure (Pelzer et al. 2005; Babiker et al. 2006; Pedram et al. 2008). ERβ is known to distribute in atherosclerotic area not normal artery nor ubiquitously and the study of SNP on ERβ in human is rare. The relation of the contribution to heart failure between ERα and ERβ, especially the relation to gene polymorphism needs to be clarified.

Overall, the present results suggest that ERα IVS1-401 influences the estrogen/BNP cascade. It is remarkable that no such finding has been reported in the past, since both ERα and BNP are major factors, and produced in the same cells as discussed above. Therefore, it is possible that this study's population focus and sample collection is a key that may lead to other undiscovered SNPs that are specific to older people.

There are several guidelines for relating BNP concentration to the severity of heart failure. Interestingly, according to our results, 12 of 13 samples from ERα IVS1-401 CC genotype carriers contained under 80 pg/mL BNP (as shown in Fig. 2), which is below the limit of 100 pg/mL and outside of the gray zone of 100–500 pg/mL (Maisel et al. 2002; Brenden et al. 2006). The implication that the ERα IVS1-401 polymorphism has clinical importance on BNP levels, it needs to be further studied in larger case-control studies and in other countries, since our study size is limited and ethnic difference is untouched. We suggest that, when profiling elderly persons' clinical marker levels in order to judge their predisposition to specific diseases, SNP genotypes may play a role as prognostic factors in elderly.

Limitation of the study

This is a relatively small sample size, and a spurious association cannot be fully ruled out.

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Appendix A. Supplementary data

Supplementary data associated with this data can be found in the online version at 10.1016/j.lfs.2009.06.009.

References

Babiker FA, Lips D, Meyer R, Delvaux E, Zandberg P, Janssen B, van Eys G, Grohé C, Doevendans PA. Estrogen receptor β protects the murine heart against left ventricular hypertrophy. Arteriosclerosis, Thrombosis, and Vascular Biology 26 (7), 1524–1530, 2006.

Bertina RM, Koeleman BPC, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden PA, Reitsma PH. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature 369 (6475), 64–67, 1994.

Brenden CK, Hollander JE, Guss D, McCullough PA, Nowak R, Green G, Saltzberg M, Ellison SR, Bhalla MA, Bhalla V, Clopton P, Jesse R, Maisel AS, for the REDHOT Investigators. Gray zone BNP levels in heart failure patients in the emergency department: results from the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT) multicenter study. American Heart Journal 151 (5), 1006–1011, 2006.

Casco VH, Veinot JP, Kuroski de Bold ML, Masters RG, Stevenson MM, de Bold AJ, Veinot JP. Natriuretic peptide system gene expression in human coronary arteries. The Journal of Histochemistry and Cytochemistry: Official Journal of the Histochemistry Society 50 (6), 799–809, 2002.

Chinkers M, Garbers DL, Chang MS, Lowe DG, Chin HM, Goeddel DV, Schulz S. A membrane form of guanylate cyclase is an atrial natriuretic peptide receptor. Nature 338 (6210), 78–83, 1989.

Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, Sidney S, Rosendaal FR, for the Women's Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis. JAMA: The Journal of the American Medical Association 292 (13), 1573–1580, 2004.

Daniels LB, Maisel AS. Natriuretic peptides. Journal of the American College of Cardiology 50 (25), 2357–2368, 2007.

Dawson S, Hamsten A, Wiman B, Henney A, Humphries S. Genetic variation at the plasminogen activator inhibitor-1 locus is associated with altered levels of plasma plasminogen activator inhibitor-1 activity. Arteriosclerosis and Thrombosis 11 (1), 183–190, 1991.

Eriksson P, Kallin B, van' t Hooft FM, Bavenholm P, Hamsten A. Allele-specific increase in basal transcription of the plasminogen-activator inhibitor 1 gene is associated with myocardial infarction. Proceedings of the National Academy of Sciences of the United States of America 92 (6), 1851–1855, 1995.

Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, Christiansen C, Delmas PD, Zanchetta JR, Stakkestad J, Glüer CC, Krueger K, Cohen FJ, Eckert S, Ensrud KE, Avioli LV, Lips P, Cummings SR. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) investigators. JAMA: The Journal of the American Medical Association 282 (7), 637–645, 1999.

Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, Vogel V, Robidoux A, Dimitrov N, Atkins J, Daly M, Wieand S, Tan-Chiu E, Ford L, Wolmark N. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. Journal of the National Cancer Institute 90 (18), 1371–1388, 1998.

Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, Boers GJH, den Heijer M, Kluijtmans LAJ, van den Heuve LP, Rozen R. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nature Genetics 10 (1), 111–113, 1995.

Girelli D, Russo C, Ferraresi P, Olivieri O, Pinotti M, Friso S, Manzato F, Mazzucco A, Bernardi F, Corrocher R. Polymorphisms in the factor VII gene and the risk of myocardial infarction in patients with coronary artery disease. New England Journal of Medicine 343 (11), 774–780, 2000.

Golser R, Gorren ACF, Mayer B, Schmidt K. Functional characterization of Glu298Asp mutant human endothelial nitric oxide synthase purified from a yeast expression system. Nitric Oxide : Biology and Chemistry 8 (1), 7–14, 2003.

Green F, Kelleher C, Wilkes H, Temple A, Meade T, Humphries S. A common genetic polymorphism associated with lower coagulation factor VII levels in healthy individuals. Arteriosclerosis and Thrombosis 11 (3), 540–546, 1991.

Guzik TJ, Black E, West NE, McDonald D, Ratnatunga C, Pillai R, Channon KM. Relationship between the G894T polymorphism (Glu298Asp variant) in endothelial nitric oxide synthase and nitric oxide-mediated endothelial function in human atherosclerosis. American journal of Medical Genetics 100 (2), 130–137, 2001.

Hayashi T, Nomura H, Osawa M, Funami J, Miyazaki A, Iguchi A. Nitric oxide metabolites are associated with survival in older patients. Journal of the American Geriatrics Society 55 (9), 1398–1403, 2007.

Herrington DM, Howard TD, Brosnihan KB, McDonnell DP, Li X, Hawkins GA. Reboussin DM, Xu J, Zheng SL, Meyers DA, Bleecker ER. Common estrogen receptor polymorphism augments effects of hormone replacement therapy on E-selectin but not C-reactive protein. Circulation 105 (16), 1879–1882, 2002a.
Herrington DM, Howard TD, Hawkins GA, Reboussin DM, Xu J, Zheng SL, Brosnihan KB, Meyers DA, Bleecker ER. Estrogen-receptor polymorphisms and effects of estrogen replacement on high-density lipoprotein cholesterol in women with coronary disease. New England Journal of Medicine 346 (13), 967–974, 2002b.
Hirschberg K, Gombos T, Dósa E, Somorjai A, Szilágyi Á, Szabó G, Füst G, Entz L. Association between estrogen receptor α gene polymorphisms and early restenosis after eversion carotid endarterectomy and carotid stenting. Atherosclerosis [Electronic publication ahead of print] Jan 29, 2009.
Hoekstra T, Geleijnse JM, Schouten EG, Kluft C. Plasminogen activator inhibitor-type 1: its plasma determinants and relation with cardiovascular risk. Thrombosis and Haemostasis 91 (5), 861–872, 2004.
Hunault M, Arbini AA, Lopaciuk S, Carew JA, Bauer KA. The Arg353Gln polymorphism reduces the level of coagulation factor VII. In vivo and in vitro studies. Arteriosclerosis, Thrombosis, and Vascular Biology 17 (11), 2825–2829, 1997.
Iso H, Folsom AR, Winkelmann JC, Koike K, Harada S, Greenberg B, Sato S, Shimamoto T, Iida M, Komachi Y. Polymorphisms of the β fibrinogen gene and plasma fibrinogen concentration in Caucasian and Japanese population samples. Thrombosis and Haemostasis 73 (1), 106–111, 1995.
Kjaergaard AD, Ellervik C, Tybjærg-Hansen A, Axelsson CK, Grønholdt ML, Grande P, Jensen GB, Nordestgaard BG. Estrogen receptor α polymorphism and risk of cardiovascular disease, cancer, and hip fracture: cross-sectional, cohort, and case-control studies and a meta-analysis. Circulation 115 (7), 861–871, 2007.
Kramsch DM, Franzblau C, Hollander W. The protein and lipid composition of arterial elastin and its relationship to lipid accumulation in the atherosclerotic plaque. The Journal of Clinical Investigation 50 (8), 1666–1677, 1971.
Lane A, Cruickshank JK, Mitchell J, Henderson A, Humphries S, Green F. Genetic and environmental determinants of factor VII coagulant activity in ethnic groups at differing risk of coronary heart disease. Atherosclerosis 94 (1), 43–50, 1992.
Ma J, Stampfer MJ, Hennekens CH, Frosst P, Selhub J, Horsford J, Malinow MR, Willett WC, Rozen R. Methylenetetrahydrofolate reductase polymorphism, plasma folate, homocysteine, and risk of myocardial infarction in US physicians. Circulation 94 (10), 2410–2416, 1996.
Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Clopton P, Steg PG, Westheim A, Knudsen CW, Perez A, Kazanegra R, Herrmann HC, McCullough PA, for the Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. New England Journal of Medicine 347 (3), 161–167, 2002.
McDonald DM, Alp NJ, Channon KM. Functional comparison of the endothelial nitric oxide synthase Glu298Asp polymorphic variants in human endothelial cells. Pharmacogenetics 14 (12), 831–839, 2004.
Metzger IF, Sertório JTC, Tanus-Santos JE. Modulation of nitric oxide formation by endothelial nitric oxide synthase gene haplotypes. Free Radical Biology and Medicine 43 (6), 987–992, 2007.
Mikkola H, Syrjälä M, Rasi V, Vahtera E, Hämäläinen E, Peltonen L, Palotie A. Deficiency in the A-subunit of coagulation factor XIII: two novel point mutations demonstrate different effects on transcript levels. Blood 84 (2), 517–525, 1994.
Nomura H, Hayashi T, Esaki T, Kanda S, Kano H, Hattori A, Iguchi A. Standardization of plasma brain natriuretic peptide concentrations in older Japanese-relationship to latent renal dysfunction and ischemic heart disease. Journal of the American Geriatrics Society 50 (9), 1504–1509, 2002.
Nordström P, Glader CA, Dahlén G, Birgander LS, Lorentzon R, Waldenström A, Lorentzon M. Oestrogen receptor α gene polymorphism is related to aortic valve sclerosis in postmenopausal women. Journal of Internal Medicine 254 (2), 140–146, 2003.
Nuedling S, Kahlert S, Loebbert K, Doevendans PA, Meyer R, Vetter H, Grohé C. 17β-Estradiol stimulates expression of endothelial and inducible NO synthase in rat myocardium in-vitro and in-vivo. Cardiovascular Research 43 (3), 666–674, 1999.
Palmer RM, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 327 (6122), 524–526, 1987.
Pedram A, Razandi M, Aitkenhead M, Levin ER. Estrogen inhibits cardiomyocyte hypertrophy in vitro: antagonism of calcineurin-related hypertrophy through induction of MCIP1. The Journal of Biological Chemistry 280 (28), 26339–26348, 2005.
Pedram A, Razandi M, Lubahn D, Liu J, Vannan M, Levin ER. Estrogen inhibits cardiac hypertrophy: role of estrogen receptor-β to inhibit calcineurin. Endocrinology 149 (7), 3361–3369, 2008.
Pelzer T, Loza PA, Hu K, Bayer B, Dienesch C, Calvillo L, Couse JF, Korach KS, Neyses L, Ertl G. Increased mortality and aggravation of heart failure in estrogen receptor-β knockout mice after myocardial infarction. Circulation 111 (12), 1492–1498, 2005.
Philip I, Plantefeve G, Vuillaumier-Barrot S, Vicaut E, LeMarie C, Henrion D, Poirier O, Levy BI, Desmonts JM, Durand G, Benessiano J. G894T polymorphism in the endothelial nitric oxide synthase gene is associated with an enhanced vascular responsiveness to phenylephrine. Circulation 99 (24), 3096–3098, 1999.
Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood 88 (10), 3698–3703, 1996.
Rees DC, Cox M, Clegg JB. World distribution of factor V Leiden. Lancet 346 (8983), 1133–1134, 1995.
Rosendaal FR, Koster T, Vandenbroucke JP, Reitsma PH. High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). Blood 85 (6), 1504–1508, 1995.
Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Female hormones and thrombosis. Arteriosclerosis, Thrombosis, and Vascular Biology 22 (2), 201–210, 2002.
Rus HG, Niculescu F, Vlaicu R. Tumor necrosis factor-alpha in human arterial wall with atherosclerosis. Atherosclerosis 89 (2–3), 247–254, 1991.
Rus HG, Vlaicu R, Niculescu F. Interleukin-6 and interleukin-8 protein and gene expression in human arterial atherosclerotic wall. Atherosclerosis 127 (2), 263–271, 1996.
Salpeter SR, Walsh JME, Ormiston TM, Greyber E, Buckley NS, Salpeter EE. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes, Obesity & Metabolism 8 (5), 538–554, 2006.
Sapone A, Peters JM, Sakai S, Tomita S, Papiha SS, Dai R, Friedman FK, Gonzalez FJ. The human peroxisome proliferators-activated receptor α gene: identification and functional characterization of two natural allelic variants. Pharmacogenetics 10 (4), 321–333, 2000.
Schuit SC, Oei HH, Witteman JC, Geurts van Kessel CH, van Meurs JB, Nijhuis RL, van Leeuwen JP, de Jong FH, Zillikens MC, Hofman A, Pols HA, Uitterlinden AG. Estrogen receptor α gene polymorphisms and risk of myocardial infarction. JAMA: The Journal of the American Medical Association 291 (24), 2969–2977, 2004.
Srivastava K, Narang R, Sreenivas V, Das S, Das N. Association of eNOS Glu298Asp gene polymorphism with essential hypertension in Asian Indians. Clinica Chimica Acta 387, 80–83, 2008.
Thomas AE, Green FR, Kelleher CH, Wilkes HC, Brennan PJ, Maede TW, Humphries SE. Variation in the promoter region of the β fibrinogen gene is associated with plasma fibrinogen levels in smokers and non-smokers. Thrombosis and Haemostasis 65 (5), 487–490, 1991.
Tsutamoto T, Wada A, Maeda K, Hisanaga T, Mabuchi N, Hayashi M, Ohnishi M, Sawaki M, Fujii M, Horie H, Sugimoto Y, Kinoshita M. Plasma brain natriuretic peptide level as a biochemical marker of morbidity and mortality in patients with asymptomatic or minimally symptomatic left ventricular dysfunction. Comparison with plasma angiotensin II and endothelin-1. European Heart Journal 20 (24), 1799–1807, 1999.
van' t Hooft FM, von Bahr SJ, Silveira A, Iliadou A, Eriksson P, Hamsten A. Two common, functional polymorphisms in the promoter region of the β-fibrinogen gene contribute to regulation of plasma fibrinogen concentration. Arteriosclerosis, Thrombosis, and Vascular Biology 19 (12), 3063–3070, 1999.
Vohl MC, Lepage P, Gaudet D, Brewer CG, Bétard C, Perron P, Houde G, Cellier C, Faith JM, Després JP, Morgan K, Hudson TJ. Molecular scanning of the human PPARα gene: association of the L162V mutation with hyperapobetalipoproteinemia. Journal of Lipid Research 41 (6), 945–952, 2000.
Wells PS, Anderson JL, Scarvelis DK, Doucette SP, Gagnon F. Factor XIII Val34Leu variant is protective against venous thromboembolism: a HuGE (Human Genome Epidemiology) review and meta-analysis. American Journal of Epidemiology 164 (2), 101–109, 2006.
Ye Z, Liu EH, Higgins JP, Keavney BD, Lowe GD, Collins R, Danesh J. Seven haemostatic gene polymorphisms in coronary disease: meta-analysis of 66155 cases and 91307 controls. Lancet 367 (9511), 651–658, 2006.

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REVIEW ARTICLE

Diabetes mellitus and geriatric syndromes

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Diabetes mellitus is associated with an increased prevalence and incidence of geriatric syndrome: functional disabilities, depression, fall, urinary incontinence, malnutrition and cognitive impairment. Geriatric syndrome not only leads to frailty, loss of independence and low quality of life, but also becomes a major obstacle in the treatment and care of diabetic people. The risk factors or contributing factors of geriatric symptoms are micro- and macrovascular complications, age-rated comorbid disease and aging per se. Comprehensive geriatric assessment of geriatric syndrome, including basic activities of daily living, instrumental activities of daily living, gait and balance, visual acuity, the Mini-Mental State Examination, depression scores, history and risk of fall, urination and nutrition, should be performed as part of the care of elderly diabetic patients, in particular old-old patients. Because geriatric syndromes are multifactorial and share risk factors, diabetic people with any geriatric symptoms should be treated with a common concentric strategy, such as supervised exercise therapy including muscle-strengthening training, psychological support, social support for adherence, and good glycemic control with avoidance of hypoglycemia.

Keywords: cognitive impairment, diabetes mellitus, disability, elderly, geriatric syndrome.

Introduction

Diabetes mellitus is more common in the elderly population. At least one-sixth of the elderly population has diabetes mellitus in Japan and other countries.[1,2] The treatment of diabetes mellitus in the elderly population, in particular the old-old people, is often difficult because of impairment of their physical, psychological and cognitive functions, and the lack or shortage of family or social support. Elderly diabetic patients may have increased risk for functional dependency and frailty. Therefore, a comprehensive geriatric assessment may be a necessity in the treatment of elderly patients.[3]

Another important approach to diabetes in the elderly is the assessment, prevention and treatment of geriatric syndrome. The so-called "geriatric syndrome" refers to multifactorial health conditions that occur when the accumulated effects on multiple systems render an old person vulnerable to situational changes.[4] Geriatric syndrome is related to the impairment of multiple systems due to aging as well as age-related disease. Diabetes mellitus is considered to lead to accelerated aging because of both the accumulation of advanced glycation end products, a marker of aging, in the tissues and the high incidence of atherosclerotic disease compared with non-diabetic populations. Also, because the development of diabetic micro- and macrovascular complications is dependent on the duration of diabetes, symptoms of the complications may be concentrated in the elderly. The diabetes population has a high prevalence of geriatric syndrome such as functional disabilities, depression, fall, urinary incontinence, pain and dementia, which occur due to the aging and diabetic complications. The geriatric symptoms lead to frailty, loss of independence and low quality of life. Importantly, these geriatric symptoms are major obstacles in the treatment and care of diabetic people.

In this article, we review geriatric symptoms in diabetes mellitus and discuss an approach to the assessment, prevention, and treatment of geriatric syndromes in diabetic people.

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Diabetes and functional disability

One of the most serious geriatric symptoms is functional disability. Cross-sectional studies in the USA showed that diabetes was associated with a twofold increased risk of being unable to perform daily physical tasks.[5,6] Gregg *et al.* showed that, among 6588 community-dwelling individuals aged 60 years or more, 32% of women and 15% of men reported an inability to walk one-quarter of a mile, do housework or climb stairs, compared with 14% of women and 8% of men without diabetes, respectively.[5] The Women's Health and Aging Study reported that women with diabetes had a 1.6-fold greater risk of basic activities of daily living (bADL) disability (bathing, transferring from bed to chair, using the toilet, dressing and eating) and a 2.3-fold greater risk of severe walking limitation.[6] We assessed the disability of 1135 elderly diabetic outpatients using the Tokyo Metropolitan Institute of Gerontology Index of Competence (TMIG-IC; 13 items), which included instrumental activities of daily living (IADL) (tasks of using public transportation, shopping for daily necessities, preparing meals, paying bill and handling one's own banking), intellectual activity (ability to complete the pension form; to read newspapers, books or magazines; and to be interested in news stories or programs dealing with health) and social role.[7] The prevalence of disability on at least one item of the TMIG-IC was approximately 45%. When we divided the subjects into three age groups, the oldest group (aged ≥80 years) reported a higher prevalence of disabilities for IADL, such as using public transportation, shopping, preparing meals and paying bills, compared with the youngest group (aged 65–69 years) (Fig. 1). A prospective study of women aged 65 years or more in the Study of Osteoporosis Fractures also demonstrated that diabetes was associated with a 2- to 2.5-fold increased incidence of functional disability for doing housework or walking two or three blocks.[8] Coronary heart disease (CHD), obesity (women), stroke (men), peripheral artery disease (PVD), neuropathy, arthritis and depression were important contributors to diabetes-related functional disabilities in US studies.[5,8] In contrast, in a Japanese study, a low sense of well-being, insulin treatment, cognitive impairment and visual impairment were associated with functional disabilities after adjustment for age, sex, body mass index (BMI), duration of diabetes, HbA1c, microangiopathy and macroangiopathy.[7] In addition to diabetic complications, aging per se contributed to diabetes-related disability, which may lead to difficulty in performing self-care activities such as exercise and diet therapy.

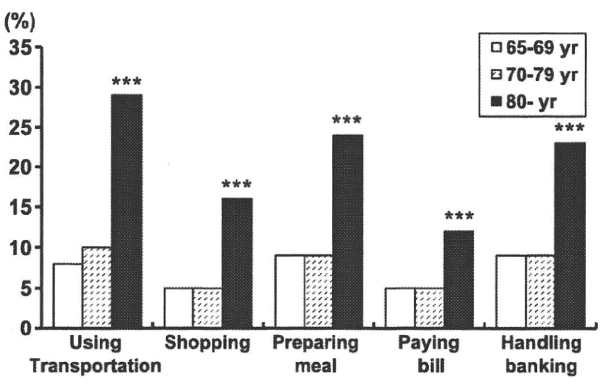

Figure 1 Age-related changes in functional disabilities of elderly patients with diabetes mellitus. The oldest group (aged ≥80 years) reported a higher prevalence of disabilities on tasks for instrumental activities of daily living: public transportation, shopping, preparing meals, paying bills and handling banking) than the youngest group (aged 65–69 years). ***$P < 0.001$.

Diabetes and depression or low sense of well-being

The prevalence and incidence of depressive symptoms are greater in diabetic than in non-diabetic people. Approximately 30% of people with diabetes have depressive symptoms, while 5–10% have major depression.[9] The Health, Aging, and Body Composition Study, a cohort study of subjects aged 70–79 years, showed that diabetic people had an increased incidence of depressed mood compared with those without diabetes (23.5% vs 19.0%; hazard ratio [HR], 1.31; 95% confidence interval [CI], 1.07–1.61).[10] A community-based study in Spanish elderly subjects demonstrated that diabetes was associated with an increased risk of prevalent depression (odds ratio [OR], 1.47; CI, 1.16–1.83) and incident depression (HR, 1.40; CI, 1.03–1.90).[11] Because the presence of comorbid diseases increased the risk of incident depression, diabetes may play a role in the development of depression in the elderly.

The presence of high levels of depressive symptoms based on the Center for Epidemiologic Studies Depression Scale (CES-D) score of 16 or more was associated with diabetic complications, any activities of daily living (ADL) or IADL disabilities, urinary incontinence, visual impairment, poor perceived health status and increased number of hospitalizations.[9]

The impact of depression on disability is much greater in diabetic patients than in non-diabetic subjects. With no diabetes and no major depression as references, the adjusted OR of functional disability was 7.2 for people with diabetes and comorbid major depression, which was high compared with the OR of 2.4 for people with diabetes alone and 3.0 for those who had major depression alone.[12]

Reduced well-being or quality of life should be considered as part of the geriatric syndrome. When well-being, which included the concept of positive feeling of

happiness, life satisfaction and acceptance of aging as well as negative affects, was assessed using the Philadelphia Geriatric Center (PGC) morale scale in elderly people with diabetes, approximately 19% of them had a low sense of well-being (PGC morale score, ≤7). People with a low sense of well-being had 2- to 3-fold increased odds for disability on the TMIG-IC, except for shopping and use of transportation.[7] Multivariate analysis revealed that sex (female), macroangiopathy, high frequency of hypoglycemia, negative social support and reduced positive social support were independently associated with a low sense of well-being.[13]

Interestingly, a low sense of well-being was an independent predictor of stroke after adjustment for conventional risk factors in our 3-year follow-up study.[14] Similarly, depression also predicted stroke and cardiovascular disease independent of the other risk factors.[15,16] The association between depression or a low sense of well-being and atherosclerotic disease may be explained by the activation of platelets,[17] an activated sympathetic nervous system and the increased expression of inflammatory markers. The use of specific antidepressant agents, such as selective serotonin reuptake inhibitors (SSRI), inhibited the activation of platelets in patients with depression[17] and prevented the development of myocardial infarction.[18]

Depression predicted increased mortality, greater incidences of macro- and microvascular complications, and disability in ADL in older people with type 2 diabetes mellitus.[19] The interaction between depression and diabetes in old people (aged ≥65 years) was found to have a synergistic effect on adverse outcomes. Therefore, aggravation of psychological function in diabetic people may lead to adverse outcomes (micro- and macrovascular complications, disabilities and increased mortality) through multifactorial mechanisms.

Diabetes and falling

Falls may lead to fractures, aggravation of glycemic control and reduction of quality of life in diabetic people. Even non-injurious falls can result in a post-fall syndrome characterized by anxiety and reduced physical and social activities.

A growing amount of evidence suggests that diabetes mellitus is one of the major predictors of the risk of falling.[20,21] The Study of Osteoporotic Fractures, which involved 9247 women aged 67 years or more, showed that 18% of older women fell more than once a year. They showed that both non-insulin-treated and insulin-treated people with diabetes had an increased risk of falling compared with non-diabetic people (OR, 1.68; CI, 1.37–2.07; and OR, 2.78; CI, 1.82–4.25, respectively).[20] The Women's Health and Aging Study demonstrated that diabetes was associated with an increased risk of falling among disabled old women.[21] These studies show that poor lower extremity function, poor balance, a history of CHD, a history of arthritis, musculoskeletal pain, depression, poor vision, medication and peripheral neuropathy, overweight and insulin therapy are important predictors of falling among diabetic women.[20,21]

The increased risk of falling may be partially explained by the impairment of gait balance and gait in diabetic people.[22–24] A study reported that diabetic patients had poorer balance during standing in diminished light, and increased sway during standing.[22] Diabetes was associated with an increased risk of gait disturbance due to Parkinson's disease-like symptoms in a 9-year follow up of people aged 75 years and over.[23] Diabetic individuals with peripheral neuropathy had impaired peripheral sensation and reaction time, and had impaired ability to stabilize their body when walking on irregular surfaces.[24] They also had reduced walking speed and step length, and less rhythmic acceleration patterns at the head and pelvis compared with controls.

Diabetes and urinary incontinence

Diabetes is associated with increased risk of both stress incontinence and urge incontinence.[25–27] Furthermore, overflow incontinence can occur as a complication of autonomic neuropathy in diabetic people. Diabetic women have a threefold increased prevalence of urge incontinence and twice the prevalence of stress incontinence.[25] The association between diabetes and urinary incontinence was confirmed with a prospective study of 81 854 women for any incontinence (HR, 1.21; CI, 1.02–1.43) and for severe incontinence (HR, 1.40; CI, 1.15–1.71).[26] A cross-sectional study of postmenopausal women aged 55–75 years showed that 52% of diabetic women with diabetes had some form of incontinence in the past month and 15% had severe incontinence, and that diabetic women were more likely to have severe incontinence or mixed incontinence.[27] The study also showed that diabetes duration, neuropathy, retinopathy and a history of urinary tract infection were independently associated with severe incontinence in multivariate analysis, and that the association decreased after adjustment for BMI. In contrast, a lifestyle intervention that included weight reduction decreased the frequency of stress incontinence in the Diabetes Prevention Program Trial.[28]

Diabetes mellitus and malnutrition

Elderly people with diabetes may be at risk of malnutrition as compared with non-diabetic people. A case-control study showed that community-dwelling diabetic people had significantly lower scores of Mini-Nutritional Assessment (MNA) than non-diabetic subjects.[29] Anorexia due to morbidity (infectious disease,

end-stage renal failure or malignancy), drug adverse effects and excessive dietary restriction may be responsible for the malnutrition in older diabetic people. Because subclinical deficiencies in vitamin B groups (B1, B2, B12, B6 and folate) in the elderly are associated with cognitive impairment or decline,[30] sufficient intake of vitamin and micronutrients may be necessary in elderly patients with diabetes.

Even diabetic patients who are obese or have metabolic syndrome can be modified and overshadowed by malnutrition, which is associated with low BMI and low levels of leptin and insulin.[31] Sarcopenic obesity, which is defined as excess fat with loss of lean body mass, may be a major problem in the diabetic patients. Sarcopenic obesity preceded the onset of IADL disability in a community-dwelling elderly population.[32] The increased production of inflammatory adipokines may alter insulin sensitivity and muscle mass and strength in sarcopenic obesity in diabetic patients.

Malnutrition in the elderly leads to increased mortality, disability and life-threatening complications.[33,34] Because we found that people who had serum albumin levels of less than 3.5 mg/dL showed increased mortality in a 6-year follow-up study of 422 elderly diabetic patients (HR, 4.2; CI, 1.3–13.9) (A Araki *et al.* unpublished data) malnutrition should be included as important geriatric symptoms.

Diabetes and cognitive impairment

Diabetes mellitus is associated with moderate deficits in specific cognitive function domains, such as complex psychomotor skills, speed of information processing, and memory and learning.[35–37] Epidemiological studies have shown that the diabetic population has a 1.6- to 3.0-fold increased risk for Alzheimer's-type dementia and vascular dementia.[38,39] Hyperglycemia,[35–37] advanced glycation end products,[40] recurrent severe hypoglycemia,[41] symptomatic and asymptomatic cerebrovascular disease,[37] polyneuropathy,[42] insulin treatment,[38] hyperinsulinemia or insulin resistance,[43] depression,[44] and low serum albumin[44] were associated with cognitive impairment in diabetes mellitus. Cognitive impairment was predicted by brain structural changes, subcortical atrophy and subcortical white matter hyperintensity, cortical atrophy in the parietal lobe and thalamus, as well as cortical atrophy.[45] Probably decreased cerebral blood flow and hyperglycemia-induced metabolic derangement are involved in the pathogenesis of the diabetic complications in the central nervous system, which refers to diabetic encephalopathy. Cognitive function may be one of the important factors related to poor adherence to diabetic self-care activities, increased frequency of hospitalization, and increased need for assistance in personal care in older adults with diabetes.[46]

Glycemic control in the short term has some favorable effects on cognitive function in diabetic people. In particular, moderate impairment of learning, memory, and complex psychomotor skill was partially improved by glycemic control with oral drugs or insulin therapy for 3 weeks.[40,47]

Although insulin-treated diabetic patients had an increased risk of cognitive impairment or dementia,[38,39] the association may be explained by increased cerebral complications rather than effects of insulin in insulin-treated patients. In contrast, a defect in insulin signaling or insulin resistance in the brain has been proposed as one cause of Alzheimer's disease.[48] Treatment with intranasal insulin, which selectively acted on the central nervous system, improved the impairment of memory saving, attention and functional status in patients in the early stage of Alzheimer's disease.[49] Therefore, insulin may have some beneficial effects on cognition.

Glucose control and geriatric syndrome

Remarkable hyperglycemia may directly cause several forms of geriatric syndrome: functional disability due to general malaise, urinary incontinence due to polyuria, malnutrition due to increased protein catabolism and cognitive impairment. Poor glucose control in the long term also potentially affects forms of geriatric syndrome such as cognitive function and susceptibility to infection.

There is limited data as to what level should be an appropriate treatment goal of HbA1c for elderly people with diabetes. Gao *et al.* demonstrated that, in a longitudinal study of 1139 people aged 65 years and over in England and Wales, diabetic individuals who had HbA1c levels of 7.0% or had a significantly higher risk of all-cause and cardiovascular mortality, and dementia compared with the three tertiles of the subjects (HbA1c: 3.7%–5.2%, 5.3%–5.7%, and 5.8%–6.9%), suggesting a HbA1c goal of 7.0% or less.[50]

Interestingly, glucose control may affect the incidence of falling in people with diabetes. The Health, Aging and Body Composition Study involving a cohort of well-functioning older adults showed that, among those using insulin, HbA1c of 6% or less increased the risk of falls, although no association between HbA1c level and oral hypoglycemic medications was observed.[51] Nelson *et al.* pointed out that the risk of falling in community-dwelling diabetic people aged 75 years or more markedly increased when HbA1c was 7% or less, regardless of frailty status.[52] Although the frequency of hypoglycemia was not assessed in these studies, atypical hypoglycemic symptoms (e.g. unsteadiness, poor coordination, double vision and dizziness) have been considered to cause falling in elderly diabetic individuals.[53] Severe hypoglycemia may lead to transient depression as well as cognitive impairment.[54] Therefore, we consider that, for

well-functioning diabetic people free of geriatric syndrome, a HbA1c level between 6.5% and 7.0% would be an ideal goal in order to prevent severe hypoglycemia, diabetic complications, dementia and death.

In contrast, for elderly people with multiple symptoms of geriatric syndrome (i.e. geriatric syndromes) and multiple morbidities, the glucose control should be individualized. The "Guidelines for improving the care of older persons with diabetes mellitus" proposed that treatment goals for blood glucose in older people with diabetes may be individually determined based on age, life expectancy, patient preference and the presence of geriatric syndrome: depression, pain, falls, incontinence, polypharmacy and cognitive impairment.[55,56] Huang *et al.* calculated expected benefits of intensive glucose control (HbA1c level of 7.0%) versus moderate glucose control (HbA1c level of 7.9%) in a diabetic population 60–80 years of age as a quality-adjusted life expectancy from a decision analysis.[57] They showed that the expected quality of life benefit of intensive control was 106 days at 60–64 years of age and decreased to 52 days at 75–79 years of age with no comorbid illness or functional impairment. They also demonstrated that for people at 60–64 years of age who had had diabetes for 10–15 years the expected benefits decreased from 116 days for those who were at baseline good health (life expectancy, 13.5 years) to 36 days for those with 4 additional mortality index points, which was calculated from comorbid illnesses and functional impairment (life expectancy, 8.0 years) and to 8 days for those with 8 additional mortality index points (life expectancy, 3.9 years). Thus, in some diabetic patients with multiple morbidity and multiple functional impairments (such as dementia, disability and the other three serious diseases), the goal of a HbA1c level of less than 8.0% might be acceptable.

Geriatric syndromes and their risk factors

The prevalence, odds ratio and risk factors of the typical geriatric syndromes are shown in Table 1. Old diabetic people consistently have an increased risk of geriatric syndrome: functional disability, depression, falling, urinary incontinence, malnutrition and cognitive impairment. As shown in Figure 2, the aging per se, diabetic micro- and macrovascular complications (in particular autonomic neuropathy), hyperglycemia and hypoglycemia are risk factors for the geriatric syndromes. Multiple morbidity and lack of social support also may lead to the aggravation of geriatric syndrome in diabetic people. Some forms of geriatric syndrome such as depression and cognitive impairment adversely affect the risk factors: hyperglycemia and micro- and macrovascular complications to form a vicious cycle, leading to the increased mortality. The geriatric syndromes are multifactorial and interrelated, and share risk factors. For example, depression or reduced well-being is thought to be one of risk factors for disability, fall, cognitive impairment and malnutrition.

Assessment of geriatric syndrome

Based on the results discussed above, it is necessary to assess geriatric syndromes when treating diabetic patients, in particular old-old patients. Comprehensive geriatric assessment of geriatric syndromes including bADL, IADL, gait and balance, visual acuity, Mini-Mental State Examination, geriatric depression scores, history and risk of falling and urination status should be performed, as shown in Table 2. The assessment of family or social support, living accommodation and surroundings is also important. The measurement of both supine and standing blood pressures, residual urine volume, and electrocardiogram coefficient of variation of R-R variations may be helpful in the geriatric assessment of diabetic people because autonomic neuropathy may be involved in some geriatric syndromes.

Intervention in geriatric syndrome

The treatment of diabetic patients with geriatric syndrome should focus on a strategy for preventing the aggravation of geriatric syndrome.

The importance of exercise therapy, compared with diet therapy, may be greater in elderly than in younger patients. Muscle-strengthening training, as well as aerobic exercise, led by supervisors or exercise professionals is necessary in order to prevent the worsening of disability and to maintain good glycemic control.

Supervised resistance training for 16 weeks improved the muscle strength of the lower extremities, ADL and glycemic control in elderly patients with diabetes.[58] Supervised exercise may be one of the common strategies for the prevention of forms of geriatric syndromes (disability, depression, fall and cognitive impairment).

A fall prevention program should be implemented for diabetic individuals with geriatric syndrome. Multidisciplinary, multifactorial, health or environmental risk factor screening intervention programs; programs of muscle strengthening and balance training, home hazard assessment and withdrawal of psychotropic medication; and Tai Chi group exercise intervention may be effective in preventing falls in diabetic individuals.[59]

Psychological intervention,[60] such as counseling, group therapy, cognitive behavioral therapy, social support and exercise training,[61] may be necessary for the treatment of old diabetic patients with depressive symptoms or low sense of well-being. Anti-depressive medication, including SSRI drugs, may be indicated in

Table 1 Prevalence, odds ratio, and risk factors for geriatric syndromes in diabetic people

Geriatric syndrome	Ref	Prevalence or incidence	Odds ratio (95% CI)	Risk factors
Disability (inability on 1 or more tasks)	5	Men, 15.2% vs 7.8%; women, 32% vs 14.3%	Men, 2.71 (1.74–4.23); women, 3.27 (2.01–5.38)	CHD, stroke, arthritis, PVD, poor vision, CHD, high BMI, poor vision, stroke, arthritis
Disability (mobility)	6	Mobility disability, 62.2%; ADL disability, 41.2%	Mobility disability, 1.78 (1.06–2.97); ADL disability, 1.65 (1.08–2.52)	PVD, peripheral neuropathy, depression
Disability (any item)	7	45%		Old age, vascular complications, low well-being, low MMSE, low visual acuity, insulin treatment
Disability (any task)	8	Yearly incidence, 9.8% vs 4.8%	Incidence, 2.05 (1.77–2.37)	Old age, high BMI, CHD, arthritis, physical inactivity, severe visual impairment
Depression (CES-D ≥16)	9	31.1% vs 24.1%		CHD, kidney and eye problem, disability, hypertension, incontinence, visual impairment, poorer perceived health status, hospitalization
Depression (CES-D ≥10 or antidepressants)	10	23.5% vs 19.0% for 5.9 years	Incidence, 1.31 (1.07–1.61)	DM-related comorbidities
Depression (psychiatric diagnostic interview)	11	Prevalence, 15.4%, incidence, 16.5%	Prevalence, 1.47 (1.16–1.83; incidence, 1.40 (1.03–1.90)	
Fall (more than once a year)	20	Insulin-treated, 35.4% vs 17.0%; non-insulin-treated, 25.7% vs 17.0%	Insulin-treated, 3.98 (2.25–7.05); non-insulin-treated, 1.53 (1.14–2.04)	Balance, CHD, arthritis, peripheral neuropathy
Fall (any fall)	21	64.9% for 3 years	Incidence, 1.38 (1.04–1.81)	Insulin therapy, high BMI, lower extremity pain, poorer lower extremity performance
Incontinence (stress incontinence) (urge incontinence)	29	Stress incontinence, 30.2% vs 14.4%; urge incontinence, 7.7% vs 26.4%		Neuropathic pain, hysterectomy
Incontinence (very severe)	30	15% vs 7%	Prevalence, 1.78 (1.49–2.12); incidence, 1.97 (1.24–3.12)	Diabetes duration, treatment type, peripheral neuropathy, retinopathy
Dementia, Alzheimer's type, vascular type	38	4.2%	Alzheimer's type, 1.3 (0.9–1.9); vascular type, 2.1 (1.1–4.0)	Insulin treatment
Dementia, Alzheimer's type, vascular type (meta-analysis)	39		Alzheimer's type, OR = 1.4–2.4; vascular type, OR = 2.2–4.2	Stroke, hyperglycemia, insulin treatment, hypertension

ADL, activities of daily living; BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; DM, diabetes mellitus; MMSE, Mini-Mental State Examination; OR, odds ratio; PVD, peripheral artery disease.

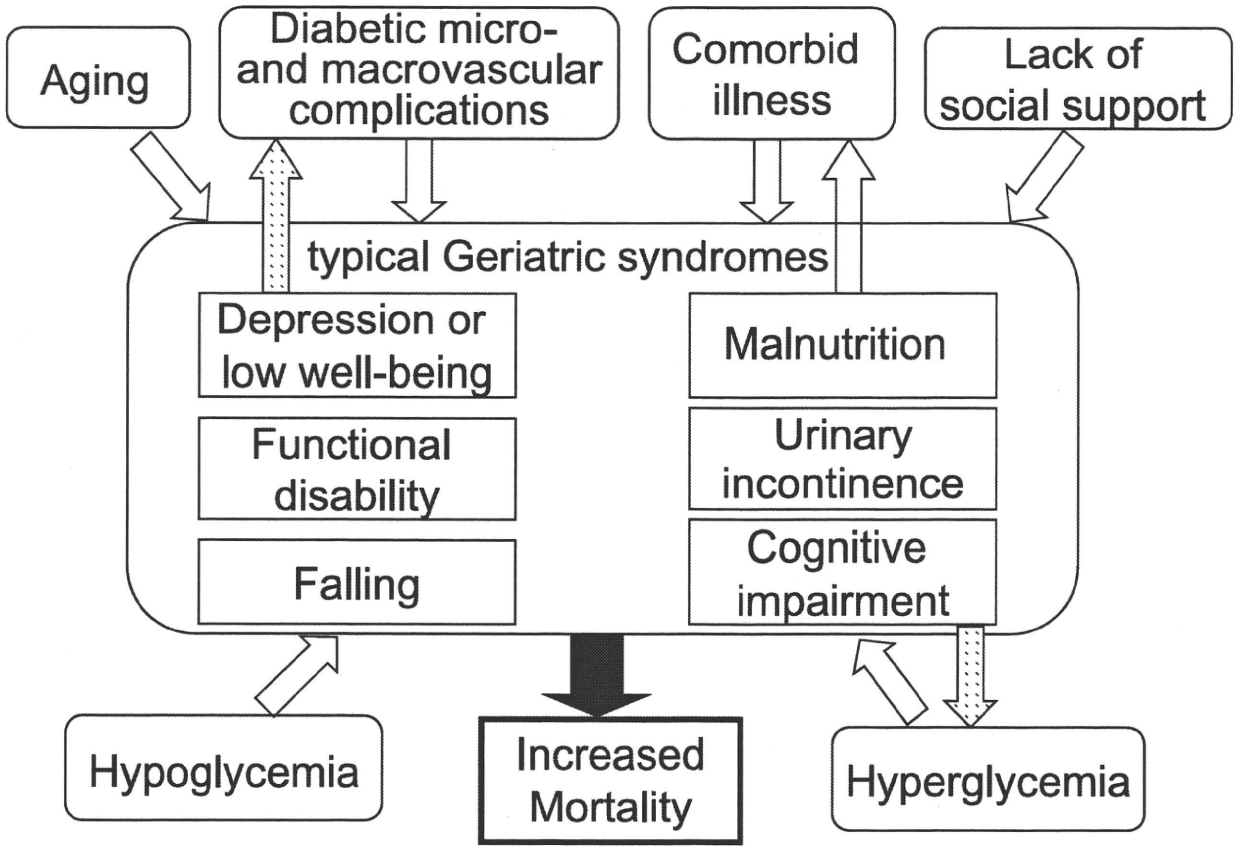

Figure 2 Relation between geriatric syndromes and their risk factors in elderly people with diabetes. Aging, diabetic micro- and macrovascular complications, hyperglycemia, hypoglycemia, multiple morbidity and lack of social support are risk factors for the geriatric syndromes. Some elements of geriatric syndrome such as depression adversely affect the risk factors: micro- and macrovascular complications a hyperglycemia to form a vicious cycle, leading to the increased mortality.

patients with diabetes and comorbid depression for the prevention of diabetic complications and increased mortality.

Diabetic women with urinary incontinence should be given exercise treatment, including pelvic floor muscle training,[62,63] weight reduction,[28] training mobility and toileting skills[64] for stress incontinence. Biofeedback therapy and behavioral training may be also effective for urge incontinence.[65]

Intensive care and social support are necessary for elderly people with diabetes and cognitive impairment. The management of cardiovascular risk factors, community-based supervised exercise, day-service activities and support for adherence to medication or insulin injection regimens may be helpful in the management of patients with both diabetes and cognitive impairment.

The avoidance of hypoglycemia and the ability to cope well with hypoglycemia may be also important for the prevention of falling and maintenance of well-being in elderly diabetic people. Prevention of hypoglycemia requires monitoring of HbA1c and self-monitoring of blood glucose, meticulous adjustment of sulfonylureas and insulin dosage, and educating patients, their families and care staff in coping skills for hypoglycemia and sick days.

Common strategy for geriatric syndrome

Because geriatric syndromes are multifactorial and share risk factors, a concentric approach, focusing on pathways associated with risk factor synergism, may be effective in the care of those who have geriatric syndromes.[4] Therefore, diabetic people with any geriatric symptoms could be treated with a multidisciplinary common concentric strategy: supervised exercise therapy including muscle-strengthening training, psychological support, social support for adherence to anti-diabetic medications or insulin, and good glycemic control with avoidance of hypoglycemia. Further studies are necessary including randomized trials of the efficacy of

Table 2 Assessment of typical geriatric syndromes in diabetes mellitus

Geriatric syndrome	Tools and risk assessment
Disability	Basic activities of daily living (ADL), instrumental ADL
Depression or low quality of life	15-Item Geriatric Depression Scale (GDS-15, GDS-5), PGC morale scale
Fall	Frequency of fall, gait, balance, blood pressures (supine and standing)
Urinary incontinence	Frequency and severity of incontinence, postvoid residual urine volume, nocturia
Dementia	Mini-Mental State Examination (MMSE)
Malnutrition	Subjective global assessment (SGA), Mini-Nutritional Assessment (MNA), objective data assessment (e.g. serum albumin, BMI, lymphocyte number)
Visual disturbance	Visual acuity

multidisciplinary common strategies based on geriatric syndrome in diabetic individuals.

References

1 Sekikawa A, Tominaga M, Takahashi K *et al.* Prevalence of diabetes and impaired glucose tolerance in Funagata area, Japan. *Diabetes Care* 1993; **16**: 570–574.
2 The DECODE Study Group. Age- and sex-specific prevalence of diabetes and impaired glucose regulation in 13 European cohorts. *Diabetes Care* 2003; **26**: 61–69.
3 Bourdel-Marchasson I, Berrut G. Caring the elderly diabetic patient with respect to concepts of successful aging and frailty. *Diabetes Metab* 2005; **31**: 5S13–5S19.
4 Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. *J Am Geriatr Soc* 2007; **55**: 780–791.
5 Gregg EW, Beckles GL, Williamson DF *et al.* Diabetes and physical disability among older U.S. adults. *Diabetes Care* 2000; **23**: 1272–1277.
6 Volpato S, Blaum C, Resnick H *et al.* Comorbidities and impairments explaining the association between diabetes and lower extremities disabilities. *Diabetes Care* 2002; **25**: 678–683.
7 Araki A, Nakano T, Oba K *et al.* Low well-being, cognitive impairment and visual impairment were associated with functional disabilities in elderly Japanese patients with diabetes mellitus. *Geriatr Gerontol Int* 2004; **4**: 27–36.
8 Gregg EW, Mangione CM, Cauley JA *et al.* The Study of Osteoporotic Fractures Research Group. Diabetes and incidence of functional disability in older women. *Diabetes Care* 2002; **25**: 61–67.
9 Black SA. Increased health burden associated with comorbid depression in older diabetic Mexican Americans. Results from the Hispanic Established Population for the Epidemiologic Study of the Elderly survey. *Diabetes Care* 1999; **22**: 56–64.
10 Maraldi C, Volpato S, Penninx BW *et al.* Diabetes mellitus, glycemic control, and incident depressive symptoms among 70- to 79-year-old persons: the Health, Aging, and Body Composition Study. *Arch Intern Med* 2007; **167**: 1137–1144.
11 de Jonge P, Roy JF, Saz P, Marcos G, Lobo A; ZARADEMP Investigators. Prevalent and incident depression in community-dwelling elderly persons with diabetes mellitus: results from the ZARADEMP project. *Diabetologia* 2006; **49**: 2627–2633.
12 Egede LE. Diabetes Major depression, and functional disabilities among the U.S. adults. *Diabetes Care* 2004; **27**: 421–428.
13 Araki A, Ito H. Development of elderly diabetes burden scale for elderly patients with diabetes mellitus. *Geriatr Gerontol Int* 2003; **3**: 212–224.
14 Araki A, Murotani Y, Kamimiya F, Ito H. Low well-being is an independent predictor for stroke in elderly patients with diabetes mellitus. *J Am Geriatr Soc* 2004; **52**: 205–210.
15 Ferketich AK, Schwartzbaum JA, Frid DJ *et al.* Depression as an antecedent to heart disease among women and men in the NHANES I study. *Arch Intern Med* 2000; **160**: 1261–1268.
16 Ohira T, Iso H, Satoh S *et al.* Prospective study of depressive symptoms and risk of stroke among Japanese. *Stroke* 2001; **32**: 903–908.
17 Markovitz JH, Shuster JL, Chitwood WS *et al.* Platelet activation in depression and effects of sertraline treatment: an open-label study. *Am J Psychiatry* 2000; **157**: 1006–1008.
18 Sauer WH, Berlin JA, Kimmel SE. Selective serotonin reuptake inhibitors and myocardial infarction. *Circulation* 2001; **104**: 1894–1898.
19 Black SA, Markides KS, Ray LA. Depression predicted increased incidence of adverse health outcomes in older Mexican Americans with type 2 diabetes. *Diabetes Care* 2003; **26**: 2822–2828.
20 Schwartz AV, Hillier TA, Sellmeyer DE *et al.* Older women with diabetes have a higher risk of falls: a prospective study. *Diabetes Care* 2002; **25**: 1749–1754.
21 Volpato S, Leveille SG, Blaum C, Fried LP, Guralnik JM. Risk factors for falls in older disabled women with diabetes: the Women's Health and Aging Study. *J Gerontol A Biol Sci Med Sci* 2005; **60**: 1539–1545.
22 Petrofsky JS, Cuneo M, Lee S, Johnson E, Lohman E. Correlation between gait and balance in people with and without Type 2 diabetes in normal and subdued light. *Med Sci Monit* 2006; **12**: CR273–CR281.
23 Arvanitakis Z, Wilson RS, Schneider JA, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and progression of rigidity and gait disturbance in older persons. *Neurology* 2004; **63**: 996–1001.
24 Menz HB, Lord SR, St George R, Fitzpatrick RC. Walking stability and sensorimotor function in older people with diabetic peripheral neuropathy. *Arch Phys Med Rehabil* 2004; **85**: 245–252.
25 Brown JS, Vittinghoff E, Lin F *et al.* Prevalence and risk factors for urinary incontinence in women with type 2 diabetes and impaired fasting glucose: findings from the National Health and Nutrition Examination Survey (NHANES) 2001–2002. *Diabetes Care* 2006; **29**: 1307–1312.
26 Lifford KL, Curhan GC, Hu FB, Barbieri RL, Grodstein F. Type 2 diabetes mellitus and risk of developing urinary incontinence. *J Am Geriatr Soc* 2005; **53**: 1851–1857.

27 Jackson SL, Scholes D, Boyko EJ, Abraham L, Fihn SD. Urinary incontinence and diabetes in postmenopausal women. *Diabetes Care* 2005; **28**: 1730–1738.

28 Brown JS, Wing R, Barrett-Connor E *et al.* Diabetes Prevention Program Research Group. Lifestyle intervention is associated with lower prevalence of urinary incontinence: the Diabetes Prevention Program. *Diabetes Care* 2006; **29**: 385–390.

29 Turnbull PJ, Sinclair AJ. Evaluation of nutritional status and its relationship with functional status in older citizens with diabetes mellitus using the mini nutritional assessment (MNA) tool–a preliminary investigation. *J Nutr Health Aging* 2002; **6**: 185–189.

30 La Rue A, Koehler KM, Wayne SJ, Chiulli SJ, Haaland KY, Garry PJ. Nutritional status and cognitive functioning in a normally aging sample: a 6-y reassessment. *Am J Clin Nutr* 1997; **65**: 20–29.

31 Bonin-Guillaume S, Herrmann FR, Boillat D *et al.* Insulinemia and leptinemia in geriatric patients: markers of the metabolic syndrome or of undernutrition? *Diabetes Metab* 2006; **32**: 236–243.

32 Baumgartner RN, Wayne SJ, Waters DL, Janssen I, Gallagher D, Morley JE. Sarcopenic obesity predicts instrumental activities of daily living disabilities in the elderly. *Obes Res* 2004; **12**: 1995–2004.

33 Cederholm T, Jagren C, Hellstrom K. Outcome of protein-energy malnutrition in elderly medical patients. *Am J Med* 1995; **98**: 67–74.

34 Sullivan DH, Bopp MM, Roberson PK. Protein-energy undernutrition and life-threatening complications among the hospitalized elderly. *J Gen Intern Med* 2002; **17**: 923–932.

35 Perlmuter LC, Hakami MK, Hodgson-Harrington C *et al.* Decreased cognitive function in aging non-insulin-dependent diabetic patients. *Am J Med* 1984; 77: 1043–1048.

36 Reaven GM, Thompson LW, Nahum D, Haskins E. Relationship between hyperglycemia and cognitive function in older NIDDM patients. *Diabetes Care* 1990; **13**: 16–21.

37 Araki A, Ito H. Asymptomatic cerebral infarction on brain MR images and cognitive function in elderly diabetic patients. *Geriatr Gerontol Int* 2002; **2**: 206–214.

38 Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee DE, Breteler MM. Association of diabetes mellitus and dementia: the Rotterdam Study. *Diabetologia* 1996; **39**: 1392–1397.

39 Cukierman T, Gerstein HC, Williamson JD. Cognitive decline and dementia in diabetes-systematic overview of prospective observational studies. *Diabetologia* 2005; **48**: 2460–2469.

40 Araki A, Ito H. Glucose metabolism, advanced glycation endproducts, and cognition. *Geriatr Gerontol Int* 2004; **4**: S108–S110.

41 Langan SJ, Deary IJ, Hepburn DA, Frier BM. Cumulative cognitive impairment following recurrent severe hypoglycemia in man. *Diabetologia* 1991; **34**: 337–344.

42 Ryan CM, Williams TM, Finegold DN, Orchaed TJ. Psychomotor slowing is associated with distal symmetrical polyneuropathy in adults with diabetes mellitus. *Diabetes* 1992; **41**: 107–113.

43 Kalmijn S, Feskens EJ, Launer LJ, Stijnen T, Kromhout D. Glucose intolerance, hyperinsulinemia, and cognitive function in a general population of elderly men. *Diabetologia* 1995; **38**: 1096–1102.

44 Umegaki H, Iimuro S, Kaneko T *et al.* Factors associated with low mini mental state examination scores in elderly Japanese diabetes mellitus patients. *Neurobiol Aging* 2008; **29**: 1022–1026.

45 Sakurai T, Yokono K. Comprehensive studies of cognitive impairment of elderly with type 2 diabetes. *Geriatr Gerontol Int* 2006; **6**: 159–164.

46 Sinclair AJ, Girling AJ, Bayer AJ. Cognitive dysfunction in older subjects with diabetes mellitus: impact on diabetes self-management and use of care services. All Wales Research into Elderly (AWARE) Study. *Diabetes Res Clin Pract* 2000; **50**: 203–212.

47 Gradman TJ, Laws A, Thompson LW, Reaven GM. Verbal learning and/or memory improves with glycemic control in older subjects with non-insulin-dependent diabetes mellitus. *J Am Geriatr Soc* 1993; **41**: 1305–1312.

48 de la Monte SM, Tong M, Lester-Coll N, Plater M Jr, Wands JR. Therapeutic rescue of neurodegeneration in experimental type 3 diabetes: relevance to Alzheimer's disease. *J Alzheimers Dis* 2006; **10**: 89–109.

49 Reger MA, Watson GS, Green PS *et al.* Intranasal insulin improves cognition and modulates β-amyloid in early AD. *Neurology* 2008; **70**: 1–9.

50 Gao L, Matthews FE, Sargeant LA, Brayne C, MRC CFAS. An investigation of the population impact of variation in HbA1c levels in older people in England and Wales: from a population based multi-centre longitudinal study. *BMC Public Health* 2008; **8**: 54.

51 Schwartz AV, Vittinghoff E, Sellmeyer DE *et al.* Health, Aging, and Body Composition Study. Diabetes-related complications, glycemic control, and falls in older adults. *Diabetes Care* 2008; **31**: 391–396.

52 Nelson JM, Dufraux K, Cook PF. The relationship between glycemic control and falls in older adults. *J Am Geriatr Soc* 2007; **55**: 2041–2044.

53 Jaap AJ, Jone GC, McCrimmon RJ, Deary IJ, Frier BM. Perceived symptoms of hypoglycemia in elderly type 2 diabetic patients treated with insulin. *Diabet Med* 1998; **15**: 398–401.

54 Strachan MW, Deary IJ, Ewing FM, Frier BM. Recovery of cognitive function and mood after severe hypoglycemia in adults with insulin-treated diabetes. *Diabetes Care* 2000; **23**: 305–312.

55 Brown AF, Mangione CM, Saliba D, Sarkisian CA; California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. *J Am Geriatr Soc* 2003; **51**: S265–S280.

56 Durso SC. Using clinical guidelines designed for older adults with diabetes mellitus and complex health status. *JAMA* 2006; **295**: 1935–1940.

57 Huang ES, Zhang Q, Gandra N, Chin MH, Meltzer DO. The effect of comorbid illness and functional status on the expected benefits of intensive glucose control in older patients with type 2 diabetes: a decision analysis. *Ann Intern Med* 2008; **149**: 11–19.

58 Castaneda C, Layne JE, Munoz-Orians L *et al.* A randomized controlled trial of resistance exercise training to improve glycemic control in older adults with type 2 diabetes. *Diabetes Care* 2002; **25**: 2335–2341.

59 Gillespie LD, Gillespie WJ, Robertson MC, Lamb SE, Cumming RG, Rowe BH. Interventions for preventing falls in elderly people. *Cochrane Database Syst Rev* 2003; **4**: CD000340.

60 Rubin RR, Peyrot M. Psychosocial problems and interventions in diabetes. A review of the literature. *Diabetes Care* 1992; **15**: 1640–1657.

61 Fox KR. The influence of physical activity on mental well-being. *Public Health Nutr* 1999; **2**: 411–418.

62 Balmforth JR, Mantle J, Bidmead J, Cardozo L. A prospective observational trial of pelvic floor muscle training for

female stress urinary incontinence. *BJU Int* 2006; **98**: 811–817.
63 Kim H, Suzuki T, Yoshida Y, Yoshida H. Effectiveness of multidimensional exercises for the treatment of stress urinary incontinence in elderly community-dwelling Japanese women: a randomized, controlled, crossover trial. *J Am Geriatr Soc* 2007; **55**: 1932–1939.
64 van Houten P, Achterberg W, Ribbe M. Urinary incontinence in disabled elderly women: a randomized clinical trial on the effect of training mobility and toileting skills to achieve independent toileting. *Gerontology* 2007; **53**: 205–210.
65 Tadic SD, Zdaniuk B, Griffiths D, Rosenberg L, Schäfer W, Resnick NM. Effect of biofeedback on psychological burden and symptoms in older women with urge urinary incontinence. *J Am Geriatr Soc* 2007; **55**: 2010–2015.

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ORIGINAL

Hypoglycemia due to Ectopic Secretion of Insulin-like Growth Factor-I in a Patient with an Isolated Sarcoidosis of the Spleen

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Abstract. Hypoglycemia is reported to be one of the manifestations of a patient with hypothalamic sarcoid infiltrates due to impaired counter-regulation of glucose. But, without hypothalamic lesion, patients with sarcoidosis would not be expected to have hypoglycemia. We recently identified a patient with an isolated sarcoidosis of the spleen who had experienced frequent fasting hypoglycemia which completely disappeared after splenectomy. During hypoglycemia, serum insulin was undetectable. Endocrinological examination revealed no abnormality. The objective was to investigate whether the patient's hypoglycemia was due to ectopic secretion of an insulin-mimetic factor by the splenic sarcoidosis. Serum insulin-like growth factor-I (IGF-I) and IGF-II were measured by RIA. Serum visfatin and free IGF-I were by ELISA. A high molecular weight form of IGF-II, termed "big" IGF-II, was identified by Western blotting. Tissue IGF-I was quantified by real time RT-PCR after RNA extraction. Before operation, total and free serum IGF-I, serum IGF-II and serum visfatin were within reference range. Big IGF-II was not detected in patient's serum extract. After operation, hypoglycemia did not recur and serum insulin returned to normal, while serum IGF-I decreased by half the preoperative level. RT-PCR revealed that mRNA level of IGF-I in the sarcoidosis tissue was about 1.8-fold greater than that in the normal spleen tissue. These data suggest that ectopic secretion of IGF-I by the splenic sarcoidosis and its direct access to the liver via the portal vein might cause fasting hypoglycemia mainly by suppressing hepatic gluconeogenesis.

Key words: Hypoglycemia, Sarcoidosis, Insulin-like growth factor-I

SARCOIDOSIS is a chronic inflammatory disease of unknown etiology. Over 90% of patients with sarcoidosis present with pulmonary findings at the time of diagnosis. Extra-pulmonary involvement is common, including the liver, eyes, central nervous system, lymph nodes, and joints. It has been reported that hypoglycemia can be one of the manifestations of patients with pituitary/hypothalamic sarcoid infiltrates [1] due to impaired counter-regulation of glucose [2]. However, if it were not for the pituitary/hypothalamic lesion, patients with sarcoidosis would not be expected to have hypoglycemia. Here, we describe a patient with an isolated sarcoidosis of the spleen who had experienced frequent fasting hypoglycemia which completely disappeared after splenectomy.

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Methods

Western blot analysis

Serum samples (0.2 mL) from the patient and a normal subject were extracted with acid-ethanol (12.5% 2N HCl/87.5% ethanol), neutralized with 0.855M Tris, and dried in a Speed Vac concentrator (Savant Instruments, Hickville, NY). For immunoblotting, serum extracts were electrophoresed on a 16% SDS-polyacrylamide gel under non-reducing conditions, and the size-fractionated proteins were then electroblotted onto a nitrocellulose sheet, which was blocked with 5% (wt/vol) skim milk, and then incubated with a mouse anti-insulin-like growth factor-II (IGF-II) monoclonal antibody (Upstate Biotechnology). After extensive washing, the sheet was incubated with horseradish peroxidase-conjugated anti-mouse IgG, and the complexes were detected using an enhanced chemiluminescence (ECLplus) system (Amersham).

Real-time quantitative reverse transcriptase-polymerase chain reaction (RT-PCR)

Total RNA was extracted from the surgically resected sarcoidosis tissue and normal spleen tissue using ISOGEN (Wako, Osaka, Japan), and cDNA synthesized using SuperScript II Reverse Transcriptase (Invitrogen Japan, Tokyo, Japan), Random Primer Hexa-deoxyribonucleotide mixture (TaKaRa, Japan), dNTP Mixture(TaKaRa, Japan) and RNaseOUT Recombinat Ribonuclease Inhibitor (Invitrogen Japan, Tokyo, Japan). IGF-I and IGF-II mRNA level was quantified with real-time quantitative RT-PCR using qPCR Supermix-UDG with ROX (Invitrogen Japan, Tokyo, Japan) following the manufacture's protocol. PCR primers were synthesized by Greiner Bio-one (Tokyo, Japan). The forward and reverse primers for the human IGF-I (Assay ID: Hs01547656_m1) and the human IGF-II (Assay ID: Hs01005963_m1) were used from inventory of TaqMan Gene Expression Assays. As an endogenous control gene, TaqMan Ribosomal RNA Control Reagents (Applied Biosystems, Foster City, CA, USA) was used.

Measurements of serum visfatin and free IGF-I

Serum concentrations of visfatin and free IGF-I were determined by commercial solid-phase enzyme-linked immunosorbent assay kits (AdipoGen Inc., Incheon, South Korea and Diagnostic Systems Laboratories, Inc., Webster, Texas, respectively). The intra- and inter-assay coefficients of variation for visfatin were 2.3-9.1% and 4.7-7.2%, respectively. The intra- and inter-assay coefficients of variation for free IGF-I were 3.6-4.8% and 6.2-11.1%, respectively.

Immunohistochemistry

The immunohistochemical study was performed by the polymer-based visualization technology using an EnVision Dako ChemMate kit (K5027, Dako, Kyoto, Japan). The paraffin sections were deparaffinized, hydrated, and incubated in primary antibodies according to the protocol provided by the manufacturer. The primary antibodies were a rabbit polyclonal anti-insulin (L1859, Dako), anti-glucagon (L1813), and anti-somatostatin (L1840) antibodies.

Case Report

A 71-year old woman was admitted to our hospital after experiencing recurrent episodes of cold sweats and palpitation for 5 months. These symptoms developed when she was hungry or early in the morning, and then disappeared after eating. It was found that plasma glucose level was very low (21 mg/dL) when she experienced the symptoms, but she had not been taking any hypoglycemic agents. She did not smoke or drink and had no family history of endocrine disorders or diabetes.

At the time of admission, she was 143 cm tall and weighed 43 kg (body mass index: 19.6 kg/m^2). Physical examination was unremarkable and chest films were normal. Biochemical data were all within the normal limits except that serum potassium level was low (Table 1). Endocrinological examination revealed no abnormality in basal blood hormone levels, including GH (0.54 ng/mL), LH (24.3 mIU/mL), FSH (39.8 mIU/mL), PRL (3.8 ng/mL), ACTH (8.5 pg/mL), TSH (2.22 μU/mL), cortisol (21.9 μg/dL), free triiodothyronine (3.18 pg/mL) and free thyroxine (1.20 ng/dL). Magnetic resonance imaging revealed no abnormality in the pituitary gland and the hypothalamic region. When she experienced the symptoms, venous sampling was performed. Venous sampling indicated that the plasma glucose level was 30 mg/dL and serum immunoreactive insulin (IRI) as well as C-peptide level was undetectable (Table 1). Thus, insulinoma as well as pituitary/adrenal insufficiency as a cause of her hypoglycemia were excluded.

Abdominal computed tomography showed a mass

Table 1. Laboratory and endocrine data before and after splenectomy

Parameter	Before operation	After operation	Reference range
Fasting plasma glucose (mg/dL)	30	91	65 - 110
Fasting serum IRI (μU/mL)	<1.0	2.2	<17.0
Fasting serum C-peptide (ng/mL)	<0.2	0.6	1.1 - 3.3
Serum IGFBP-3 (μg/mL)	1.73	1.34	1.99 - 3.20
Serum IGF-I (ng/mL)	116	52	38 - 207
Serum IGF-II (ng/mL)	854	846	414 - 1248
Serum potassium (mEq/L)	2.5	3.5	3.5 - 5.0

IGFBP-3; insulin-like growth factor binding protein -3.

in the spleen with a central contrast enhancement effect. The corresponding mass was also detected by gallium-67 scintigraphy. The findings strongly suggested a condition called non-islet cell tumor hypoglycemia (NICTH), however, serum levels of IGF-I and IGF-II were not elevated (Table 1). Serum level of free IGF-I was 0.35 ng/mL (reference range: 0.11-0.42). A high molecular weight form of IGF-II [3] was not detected in patient's serum extract by Western blotting (Figure 1). We also found that serum level of visfatin, which had been shown to exert insulin-mimetic effects [4], was not elevated; the serum visfatin level was 0.9 ng/mL (reference range: 1-10). Serum level of insulin autoantibodies, high levels of which also might be a causative factor for hypoglycemia [5], was less than 0.4% (reference range: < 0.4%). Likewise serum insulin receptor autoantibodies [6] were not detected. In addition, serum level of proinsulin was 8.6 pmol/L (reference range: 6.4-9.4).

Although we failed to obtain firm evidence that the splenic mass was producing substance(s) which could cause hypoglycemia, a diagnostic as well as possibly therapeutic splenectomy was obviously required. She underwent operation; the splenic mass was completely resected surgically. Postoperative course was uneventful. Plasma glucose levels increased to 94 mg/dL just after operation and remained between 92-173 mg/dL even after cessation of continuous glucose infusion. She had no hypoglycemic episodes thereafter. Postoperatively, fasting plasma glucose, serum IRI and serum C-peptide increased, as expected (Table 1). Serum potassium also returned to normal level. Notably, serum level of IGF-II did not appreciably change, while that of IGF-I decreased by half the preoperative level (Table 1).

As shown in Figure 2A, the spleen had a solid, elastic hard mass (6.0 x 5.7 x 6.0 cm in size). Pathological examination revealed numerous non-necrotizing epithelioid granuloma with Langerhans-type multinucleate giant cells (Figure 2B). The splenic hilar lymph nodes showed the same granulomatous inflammation. The acid-fast or Grocott staining was negative. These findings were characteristic of sarcoidosis. Immunoreactivity against somatostatin, insulin or glucagon was not detected in the sarcoidosis tissue by immunohistochemical analysis (Figure 2C). As shown in Figure 3, steady-state mRNA levels of IGF-I and IGF-II in the sarcoidosis tissue were about 1.8-fold greater than and 80-fold less than those in the normal spleen tissue, respectively.

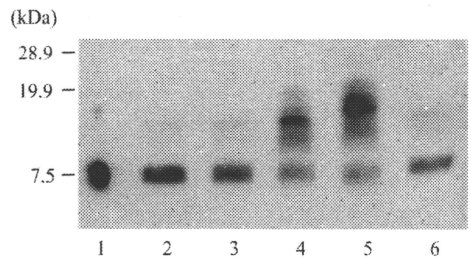

Fig. 1. Western immunoblot analysis of IGF-II. Lane 1, IGF-II control; lane 2, patient's serum, preoperative; lane 3, patient's serum, postoperative; lane 4-5, sera from NICTH patients; lane 6, healthy control serum.

Discussion

Our present observation was that a patient with an isolated sarcoidosis of the spleen experienced insulin-independent hypoglycemia, and the symptom disappeared after splenectomy. It was most possible that the splenic sarcoid lesion produced some substance(s)

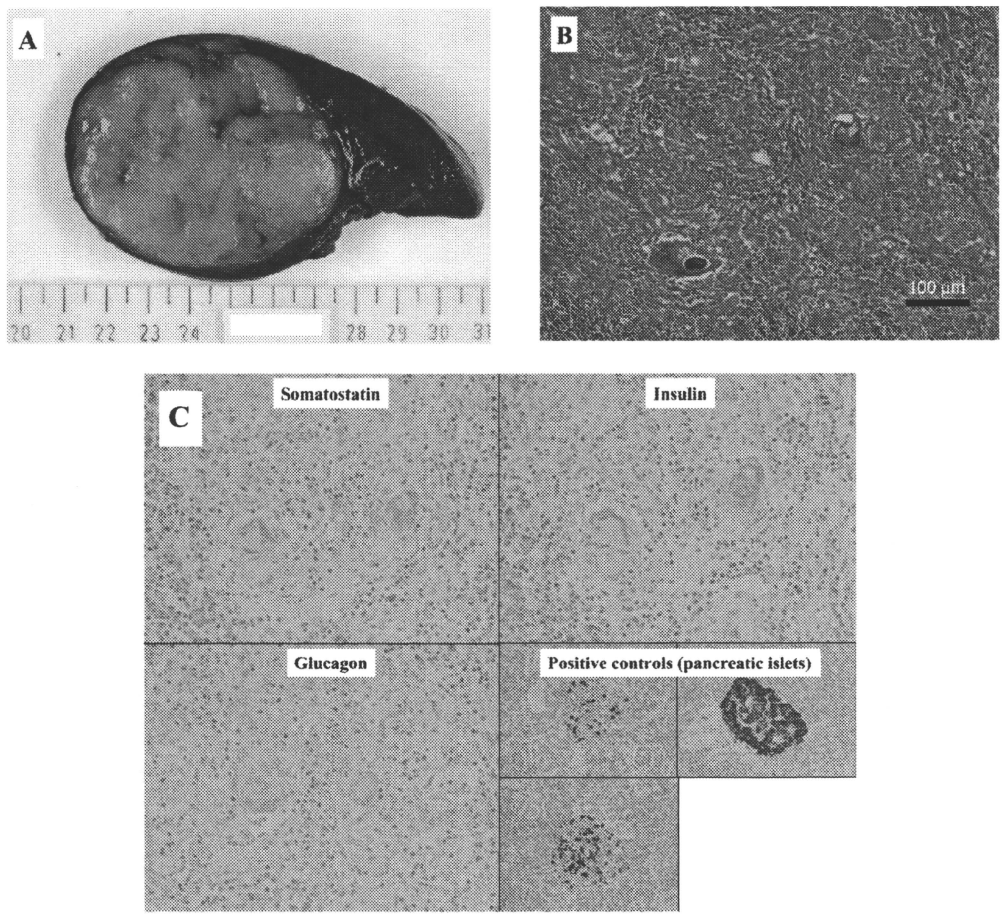

Fig. 2. Cut section of the spleen. (A) Gross appearance: a well-demarcated, yellow-white, solid mass (6.0 x 5.7 x 6.0 cm in size). (B) Microscopic appearance: non-necrotizing granulomatous inflammation with Langerhans-type multinucleate giant cells. The giant cells contain intracellular calcification (Schaumann body). HE stain. (C) Immunohistochemistry: immunoreactivity against somatostatin (upper left), insulin (upper right) and glucagon (lower left) is not detected in the sarcoidosis tissue.

which could cause hypoglycemia. However, serum level of IGF-II was not elevated and, more importantly, the high molecular weight form of IGF-II was not detected (Figure 1). Likewise serum levels of IGF-I and free IGF-I were within reference range, but after splenectomy, the IGF-I level decreased by half the preoperative level (Table 1). RT-PCR revealed that IGF-I mRNA level in the sarcoidosis tissue was about 1.8-fold greater than that in the normal spleen tissue (Figure 3).

One case report has described a patient with recurrent hypoglycemia due to paraneoplastic secretion of IGF-I by metastasizing large-cell carcinoma of the lung [7]. In this case, total and free serum IGF-I was increased (692 ng/mL and 27.2 ng/mL, respectively), and after chemotherapy with carboplatinum/etoposide, the lung nodules largely regressed, and serum IGF-I became normal. Our present case, however, showed relatively low serum IGF-I level which was not expected to cause hypoglycemia under the ordinary conditions [8]. Anatomically, IGF-I produced by the splenic sarcoidosis goes directly to the liver via the portal vein. Although we could not find a precise measurement of hepatic extraction rate of IGF-I in the literature, that of insulin is reported to be about 70% in the basal state [9]. Therefore, it is possible that, after hepatic extraction and dilution in the systemic circulation, IGF-I concentration might be substantially reduced in the peripheral vein where we measured and, hence, the concentration of IGF-I in the portal

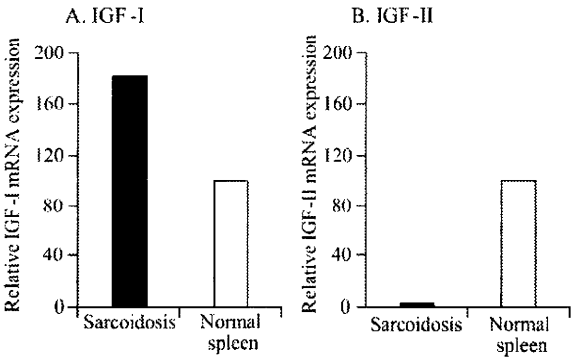

Fig. 3. Expression of IGF-I and IGF-II genes in sarcoidosis and normal spleen tissues. Expression of (A) IGF-I mRNA and (B) IGF-II mRNA in sarcoidosis and normal spleen tissues as determined by RT-PCR is shown as the ratio of each mRNA to that of rRNA.

vein might be much higher than that in the peripheral vein, which was sufficient to suppress hepatic gluconeogenesis in the present case. Furthermore, it seems also possible that partial hypopituitarism might facilitate the onset of hypoglycemia in this patient since basal levels of GH and ACTH were relatively low. Unfortunately, the patient denied further examination to evaluate pituitary GH and ACTH reserve, and the possibility has remained to be elucidated.

It has been shown that the localization of activated immune cells, primarily activated oligoclonal CD4+ T cells and macrophages together with the release of various pro-inflammatory cytokines and growth factors such as IGF-I, determines the immune phenomena as well as the development and fate of the sarcoid granuloma [10]. In pulmonary sarcoidosis, increased level of IGF-I released from activated alveolar macrophages is considered to stimulate collagen synthesis by pulmonary fibroblasts [11]. It is, thus, quite reasonable that an extra-pulmonary sarcoid granuloma, such as sarcoidosis of the spleen found in the present case, could also produce IGF-I.

Isolated granulomatous disease confined to the spleen is rare. Currently, the literature documents only four prior cases of sarcoidosis presenting with isolated splenic lesions [12, 13]. Usually, splenectomy and subsequent histopathologic examination are required for definitive diagnosis as well as neoplastic exclusion. Once diagnosed, patients require continual follow-up for systemic manifestations and associated complications of sarcoidosis. So far, hypoglycemia has not been reported in these 4 cases.

Finally, it should be noted that some unknown factor(s) secreted by the sarcoidosis tissue might cause hypoglycemia through insulin-independent mechanism in our patient. But, at present, the hypoglycemia appeared to be due mainly to ectopic secretion of IGF-I. Further study is necessary to solve an enigma.

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References

1. Jawadi MH, Hanson TJ, Schemmel JE, Beck P, Katz FH (1980) Hypothalamic sarcoidosis and hypopituitarism. *Horm Res* 12: 1-9.
2. Féry F, Plat L, van de Borne P, Cogan E, Mockel J (1999) Impaired counterregulation of glucose in a patient with hypothalamic sarcoidosis. *N Engl J Med* 340: 852-856.
3. Fukuda I, Hizuka N, Ishikawa Y, Yasumoto K, Murakami Y, Sata A, Morita J, Kurimoto M, Okubo Y, Takano K (2006) Clinical features of insulin-like growth factor-II producing non-islet-cell tumor hypoglycemia. *Growth Horm IGF Res* 16: 211-216.
4. Xie H, Tang SY, Luo XH, Huang J, Cui RR, Yuan LQ, Zhou HD, Wu XP, Liao EY (2007) Insulin-like effects of visfatin on human osteoblasts. *Calcif Tissue Int* 80: 201-221.
5. Uchigata Y, Hirata Y (1999) Insulin autoimmune syndrome (IAS, Hirata disease). In: Eisenbarth G (ed) Endocrine and organ specific autoimmunity. RG Landes, Austin: 133-148.
6. Rodriguez O, Collier E, Arakaki R, Gorden P (1992) Characterization of purified autoantibodies to the insulin receptor from six patients with type B insulin resistance. *Metabolism* 41: 325-331.
7. Nauck MA, Reinecke M, Perren A, Frystyk J, Berishvili G, Zwimpfer C, Figge AM, Flyvbjerg A, Lankisch PG, Blum WF, Klöppel G, Schmiegel W, Zapf J (2007) Hypoglycemia due to paraneoplastic se-

cretion of insulin-like growth factor-I in a patient with metastasizing large-cell carcinoma of the lung. *J Clin Endocrinol Metab* 92: 1600-1605.
8. Guler HP, Zapf J, Schmid C, Froesch ER (1989) Insulin-like growth factors I and II in healthy man: estimations of half-lives and production rates. *Acta Endocrinol* 121: 753-758.
9. Toffolo G, Campioni M, Basu R, Rizza RA, Cobelli C (2006) A minimal model of insulin secretion and kinetics to assess hepatic insulin extraction. *Am J Physiol Endocrinol Metab* 290: 169-176.
10. Kunkel SL, Chensue SW, Strieter RM, Lynch JP, Remick DG (1989) Cellular and molecular aspects of granulomatous inflammation. *Am J Respir Cell Mol Biol* 1: 439-447.
11. Allen JT, Bloor CA, Knight RA, Spiteri MA (1998) Expression of insulin-like growth factor binding proteins in bronchoalveolar lavage fluid of patients with pulmonary sarcoidosis. *Am J Respir Cell Mol Biol* 19: 250-258.
12. Zia H, Zemon H, Brody F (2005) Laparoscopic splenectomy for isolated sarcoidosis of the spleen. *J Laparoendosc Adv Surg Tech* A 15: 160-162.
13. Giovinale M, Fonnesu C, Soriano A, Cerquaglia C, Curigliano V, Verrecchia E, De Socio G, Gasbarrini G, Manna R (2009) Atypical sarcoidosis: case reports and review of the literature. *Eur Rev Med Pharmacol Sci* 1: 37-44.

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PHARMACOGENETICS

Effect of *MDR1* C3435T polymorphism on lansoprazole in healthy Japanese subjects

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Abstract
Background and aims The effect of multidrug resistance transporter gene 1 (*MDR1*) on the bioavailability and kinetics of several substrates has not yet been fully elucidated. We evaluated the influence of *MDR1* C3435T polymorphism on the pharmacokinetics and pharmacodynamics of lansoprazole in Japanese subjects.
Methods Fifteen healthy volunteers with the rapid extensive metabolizer genotype of *CYP2C19* were classified into three *MDR1* C3435T genotype groups: C/C (n=5), C/T (n=5), and T/T (n=5). Lansoprazole 30 mg was administered orally for 15 days. The intragastric pH and plasma lansoprazole levels were determined on days 1 and 15.
Results On day 1, the mean C_{max} of lansoprazole in the T/T group was significantly higher than that in the C/C or C/T groups (T/T 1,248, C/C 618, C/T 607 ng/ml; P=0.038). On day 15, similar *MDR1* genotype-dependent differences were observed in the C_{max} of lansoprazole, although smaller than the differences observed on day 1. In contrast, the intragastric pH attained after lansoprazole administration did not differ among *MDR1* genotype groups on either day 1 or day 15.
Conclusion Although the sample size was small, our study demonstrated that the *MDR1* C3435T polymorphism influenced the pharmacokinetics, but not the pharmacodynamics (i.e., intragastric pH), of lansoprazole in rapid metabolizers of CYP2C19.

Keywords Lansoprazole · *MDR1* · Polymorphism · CYP2C19

Abbreviations

CYP2C19	Cytochrome P450 2C9
Helicobacter pylori	*H. pylori*
IM	Intermediate metabolizer
MDR1	Multidrug resistance transporter gene 1
PPI	Proton-pump inhibitor
PM	Poor metabolizer
RM	Rapid metabolizer

Introduction

Proton-pump inhibitors (PPIs) such as lansoprazole, omeprazole, rabeprazole, esomeprazole, and pantoprazole are in

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current clinical use as potent gastric-acid inhibitors. PPIs inhibit gastric-acid secretion by interaction with H^+/K^+-ATPase in gastric parietal cells [1, 2]. The major indication for PPIs is acid-related diseases, such as peptic ulcer, gastroesophageal reflux disease (GERD), and Zollinger-Ellison syndrome [3–7]. PPIs are also used to eradicate *Helicobacter pylori* (*H. pylori*) infection in combination with antimicrobial agents such as clarithromycin (CAM), metronidazole (MNZ), and amoxicillin (AMPC) [8–10].

PPIs are mainly metabolized in the liver by cytochrome P450 isoenzyme 2C19 (CYP2C19), an enzyme whose activity varies due to genetic differences. The genotypes of *CYP2C19* are classified into three groups: rapid metabolizer (RM=**1/*1*), intermediate metabolizer (IM=**1/*X*), and poor metabolizer (PM=**X/*X*, where **X*=**2* or **3*) [11]. The pharmacokinetics and pharmacodynamics of PPIs differ by *CYP2C19* genotype [12, 13]: during PPI treatment, plasma PPI and intragastric pH levels are lowest in the RM group and highest in the PM group. These genotype-dependent differences in pharmacokinetics and pharmacodynamics of PPIs are reflected in the cure rates for *H. pylori* infection following a PPI-based treatment regimen [11, 14]. Factors other than *CYP2C19* polymorphism that affect the cure rates of *H. pylori* infection include bacterial susceptibility to clarithromycin [15], smoking, and compliance, among others. However, inter-individual differences in clinical outcomes are still observed even in individuals who exhibit similarities with regard to these factors, suggesting that other factors influence the pharmacokinetics and pharmacodynamics of PPIs.

MDR1 codes the P-glycoprotein (P-gp), a component of adenosine triphosphate (ATP)-binding-cassette (ABC) transporters [16]. P-gp functions as the energy-dependent exporter of substances from cells and prevents accumulation of potentially toxic and also carcinogenetic substances and metabolites in cells. P-gp expression represents one of the most important mechanisms for the failure of chemotherapeutic treatment of cancer [17]. P-gp is expressed on the surface of not only cancer cells but also normal cells such as hepatocytes, enterocytes, and endothelial cells of brain blood vessels. Genetic differences affect the expression of *MDR1* [18]. A synonymous single nucleotide polymorphism (SNP) in exon 26 (C3435T) has sometimes been reported to be associated with altered P-gp activity [18]. Plasma levels of digoxin, a representative substrate of *MDR1*, have been found to differ among *MDR1* C3435T genotype groups [19].

Lansoprazole is a substrate of P-gp [20], but the impact of *MDR1* C3435T polymorphism on the pharmacokinetics and pharmacodynamics of lansoprazole has not been fully elucidated. Recent clinical studies have revealed that lansoprazole-based therapies for *H. pylori* infection are affected by *MDR1* C3435T polymorphism [21, 22]). However, several reports have indicated that P-gp activity is also affected by the G2677A/T (Ala893Thr or Ala893Ser) and/or C1236T (synonymous) polymorphism [23, 24]. Interestingly, *MDR1* C3435T is in linkage disequilibrium with other polymorphisms such as G2677A/T and C1236T. Meta-analysis has suggested that these haplotypes, rather than the single polymorphism, may be more predictive of P-gp activity [25]. Here, we investigated whether *MDR1* C3435T polymorphism as well as haplotypes affected the pharmacokinetics and pharmacodynamics of lansoprazole in healthy Japanese subjects with the rapid metabolizer genotype of *CYP2C19*.

Methods

Eighty healthy Japanese subjects were invited to be genotyped for *CYP2C19* and *MDR1* C3435T and serologically tested for *H. pylori* infection as described below. Of these, 15 with the RM genotype of *CYP2C19* (**1/*1*) and different *MDR1* C3435T genotypes were enrolled into this study. All participants were seronegative for *H. pylori* infection and had different *MDR1* C3435T genotypes (*MDR1* 3435C/C=5, C/T=5, T/T=5), with no history of peptic ulcer, hepatic disorders, cardiovascular disorders, renal diseases, or other serious conditions. Participants had consumed no alcohol or taken any drugs for at least 1 month prior to this study.

Participants were given a single daily oral dose of 30 mg lansoprazole (Takepron, Takeda Pharmaceutical, Osaka, Japan) at 0800 for 15 days. Intragastric pH was monitored 24 h/day, and blood samples were collected at 0, 0.5, 1, 2, 3, 5, 7, 10, and 24 h after drug administration on days 1 and 15. Meals with the same contents were served at 0800, 1230, and 1800 on days 1 and 15, with caloric counts measuring 300, 600, and 800 kcal, respectively. All subjects gave written informed consent, and the study protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine.

Genotyping of *CYP2C19* and *MDR1*

CYP2C19 genotyping was performed by PCR-RFLP using DNA extracted from whole blood [26]. Those subjects homozygous for the 1* allele (**1/*1*) were defined as RMs of *CYP2C19*.

MDR1 C3435T polymorphisms were identified by PCR-RFLP as reported previously [27] and classified as C/C, C/T, or T/T polymorphism. *MDR1* C1236T and G2677A/T genotypes were similarly determined in all subjects and classified as C/C, C/T, or T/T for C1236T, and as G/G, G/T, G/A, A/T, or T/T for G2677A/T [28].