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Review Article

Aging-related Genes

Hiroshi Shimokata [1], Fujiko Ando [1,2]

1) Department for Development of Preventive Medicine, National Center for Geriatrics and Gerontology
2) Department of Sports and Health Sciences, Faculty of Health and Medical Sciences, Aichi Shukutoku University

Abstract

Genetic factors affect an individual's maximum possible lifespan. In humans, the average lifespan is about 40 years shorter than the maximum lifespan. Any gene that influences the development of a disease is called a disease-susceptibility gene. The impacts of disease-susceptibility genes on aging and average lifespan would be much stronger than the impacts of aging genes on maximum lifespan. Multiple genes are associated with the aging process and age-related diseases, and gene-to-gene interactions are important, as are gene-environment interactions; the interactive effects of lifestyle are especially important. A broad-scale, long-term longitudinal study that includes detailed examinations of medicine, nutrition, physical activity, and psychology in a community-dwelling population is necessary for comprehensive genetic epidemiological study of aging and age-related diseases. Risk of disease to individuals can be more effectively assessed with data on genetic, lifestyle, and environmental factors. The most appropriate health education, lifestyle modifications, and health examination protocols could be then implemented in an individualized manner to prevent diseases and aging processes based on these personalized risk assessments.

KEY WORDS: aging, gene, epidemiology, longitudinal study, lifespan

Aging and genes

Japan is the world leading country with long living poeple. Nevertheless, until recently, few Japanese people lived more than 100 years. However, the number of centenarians has recently begun to increase rapidly; in 2012, there were 51,376 men and women aged 100 years or older in Japan. It is no longer inconceivable for a regular person to live for 100 years or more.

The lifespan of individual organisms varies based on species. The maximum lifespan for humans is currently 120 years, at most. The maximum lifespan in each species is determined by genes. Do longevity genes that increase maximum life-span exist? If such longevity genes exist, what is the function of these genes in the human body? Perpetual youth and longevity is a dream of people worldwide, and extensive research is currently being performed to clarify the mechanism of aging using new molecular and genetic methodologies [1] to identify for longevity genes.

Search for an aging gene

Progeria (Hutchinson–Gilford progeria syndrome) is a rare genetic disease with symptoms that resemble the acceleration of the regular aging process [2]. The first symptoms manifest in neonates and infants. In one year, a patient with progeria undergoes physical aging equivalent to that requiring over 10 years in an unaffected person. The average lifespan of patients with progeria is about 13 years. The incidence of progeria is very low, at only 1 person in every 4 to 8 million live births. The typical symptoms of progeria are growth insufficiency, a localized scleroderma-like skin condition, wrinkled skin, loss of eyesight, hair loss, atherosclerosis, cardiovascular disease, and renal failure. However, cognitive development and function are usually normal. A point mutation in position 1824 of the lamin A (LMNA) gene has been identified as the cause of progeria [3].

Werner syndrome, also called adult progeria or progenoid syndrome, is another very rare genetic disease characterized by the appearance of premature aging. Symptoms of Werner syndrome are short stature, low body weight, absence of a teenage growth spurt, graying of hair, bilateral cataracts, hoarseness of the voice, and thickening of the skin. These symptoms appear after the age of 10. Patients with Werner syndrome generally die of atherosclerotic disease or cancer sometime between the ages of 40 and 60. In humans, Werner syndrome is an autosomal recessive disorder caused by a point mutation in the WRN gene on chromosome 8 [4]. About 1,200 cases have been reported, and 80% of these patients are Japanese.

Dr. Hiroshi Shimokata, MD, Ph.D.
Department for Development of Preventive Medicine, National Center for Geriatrics and Gerontology
36 Gengo, Morioka-cho, Obu, Aichi 474-8511, Japan
Tel : +81-562-46-2311 / Fax: +81-562-46-8249 / E-mail: hiroshi@ncgg.go.jp

The incidence of Werner syndrome is 3 per 100,000 live births in Japan.

The LMNA and WRN genes, which are responsible for progeria and Wener syndrome respectively, cause pathological aging processes, but do not regulate normal aging processes. The frequency of genotypes unrelated to lifespan did not differ between younger people and older people in a cross-sectional study [5] (***Fig. 1-A***). However, the frequency of certain genotypes changes with aging. A genotype with a high frequency among older people could represent a "longevity genes" that serves to prolong lifespan or to protect against age-related diseases (***Fig. 1-B***). In contrast, a genotype with a lower than average frequency among older people could represent an "aging gene" or a "gene resulting in shorter life expectancy" (***Fig. 1-C***).

Table 1 shows a list of genes associated with longevity based on the findings of a cross-sectional study of age difference in genotype frequency [5]. Most of these genes are related to a molecular pathway involved in nutrient metabolism, especially lipid or glucose metabolism, or in endocrine regulation.

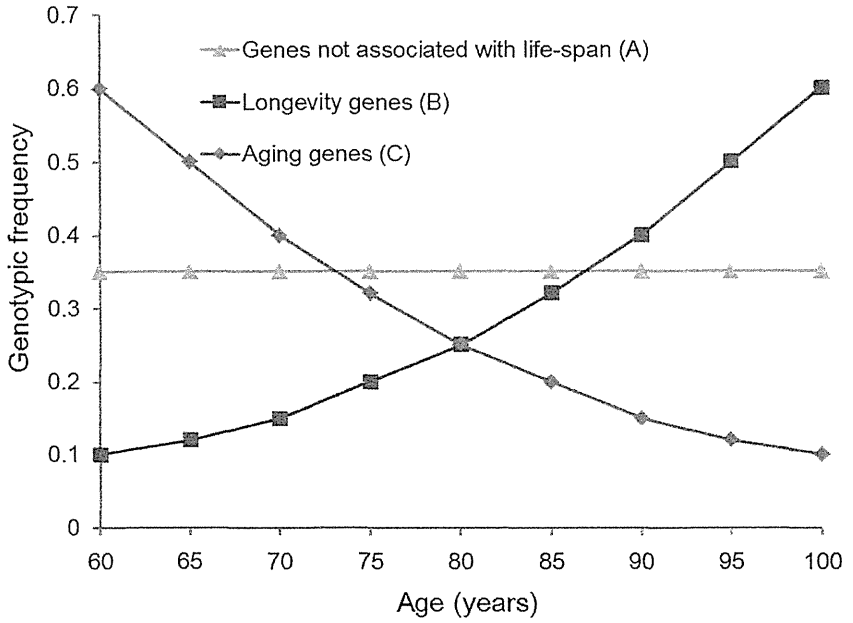

Fig. 1. **Genotypic frequency by age in genes not associated with lifespan (A), longevity genes (B), and aging genes (C) (Modified form Barzilai *et al.*, 2010 [5]).**

Table 1 Genes associated with longevity

Gene	Longevity	Relevant biological action	Chromosomal loci
Klotho (KL gene)	+	Insulin sensitivity, modulation of IGF-I and vitamin D	13q12
Silent mating type information regulation 2 homolog 1 (SIRT1)	+	Regulates epigenetic gene silencing and suppresses recombination of rDNA, associated with insulin action/sensitivity	10q21.3
Catalase (CAT)	+	Antioxidant that protects cells from hydrogen peroxide	11p13
Mammalian target of rapamycin (mTOR)	−	Modulates insulin, IGF, and mitogen function	1P36
IGF-I/insulin (FOXO)	−	Transcription factors that take part in cell growth and differentiation	12q23–23
GH	−	Stimulates growth, production of IGF-I	17 q22-q24
TSHβ	+	Production of TSH	1p13
Thyrotropin receptor (TSHR)	+	Production of T4 and T3	14q31
CETP	+	Facilitates the transport of cholesteryl esters and triglycerides between the lipoproteins	16q21
APOC-3	+	Inhibits lipoprotein lipase and hepatic lipase	11q23.1-q23.2
Adiponectin (AdipoQ)	+	Modulates glucose and fatty acid metabolism	3q27

Modified form Barzilai *et al.*, 2010 [5]

Aging genes and disease susceptibility genes

It is very rare for a human being to live 120 years; most people die from one of many diseases before reaching 120 years of age. Currently, the average human lifespan is thought to be about 40 years shorter than the maximum lifespan. Several lifestyle-related diseases, such as dyslipidemia, hypertension, diabetes, atherosclerosis, and cardiovascular disease, accelerate the aging process. The relationship between atherosclerosis and aging is particularly strong, as indicated by "a man is as old as his arteries". Susceptibility to lifestyle-related disease is influenced by genetic factors. Any gene that influences the development of disease is known as disease-susceptibility gene. The impact of disease-susceptibility genes on aging and average lifespan is thought to be much larger than the impact of aging genes on maximum lifespan.

Although disease-susceptibility genes determine the susceptibility of an individual to disease, including lifestyle-related diseases, a person with a specific disease-susceptibility gene does not always have the disease. Lifestyle or environmental factors might have much stronger effects on pathogenesis than any of the direct effects of the gene. For example, it should be possible to develop a new method for preventing a disease by investigating differences in lifestyle or environmental factors between individuals with and without disease in a group with a specific disease susceptibility allele. Moreover, investigation of longitudinal changes in modifiable risk factors such as lifestyle should be useful. A better understanding of changes in the incidence of a disease should be helpful for preventive genetic counseling; for example, a person with a specific disease-associated genotype may be able to reduce their personal risk of developing the respective disease if they double their physical activity.

Molecular epidemiology of aging

Genotypes related to aging or age-related disease are, in most cases, not single but multiple, and effects of genotypes are influenced by gene-to-gene interactions and gene-environment interactions. Thus, the analysis of genotypes is often difficult [6].

Case-control or association studies of genetic factors that affect aging or age-related diseases compare the frequency of genotypes in a group of cases with those in a control group. Usually, a relatively small number of cases and controls are examined in a case-control study. To date, many association studies have been conducted to identify genetic factors that affect or cause diseases and clinical condition. However, in most of these studies, gene-gene interactions and gene-environment interactions were not examined.

Affected sib-pair linkage analysis is a type of genome-wide analysis in which researchers study sib-pairs that are affected by a specific disease to identify disease-causing alleles [7]. Although significant linkage can be located in specific loci, identification of the actual disease-causing allele is usually difficult.

Calpain-10A, a member of the calpain-like cysteine protease family, was identified as a type 2 diabetes susceptibility gene in a genome-wide screen of affected sib-pairs of Mexican-American descent [8]. However, findings from other studies indicate that no association between the calpain-10 gene and diabetes exists in other population [9,10]. The results often differ based on the quality of the cohorts, especially for diseases such as diabetes, as numerous genes are related to glucose metabolism and obesity.

Findings based on affected sib-pair linkage analysis can be highly problematic. Collecting a large sample of sib-pair cases is often difficult, environmental factors are usually excluded, and the required genome-wide analyses are very costly. Association studies are better suited for the investigation of aging and age-related diseases because these involve many genotypes and many environmental factors. A large cohort is necessary for such analyses because each disease-related genotype may contribute a small amount to the onset of disease and because there are usually significant interactions with lifestyle and environmental factors. For example, in the analysis of dyslipidemia, contribution of genotype should be controlled for age, body size, diet, physical activity level, and among other factors. Multivariate and longitudinal analyses that account for changes in many examination results are essential in large cohort studies.

Epidemiologists and biostatisticians with experience in clinical medicine and human genome studies should develop methodologies for comprehensive and systematic assessments of many genotypes, lifestyles, and environmental factors in studies of molecular epidemiology. A large number subjects are necessary in epidemiological analyses of the associations between a disease and combinations of relevant genotypes. For example, in the case of combination of two genotypes with 10 percent mutation rate, the subject with both mutations is only 1 percent. To assess interactions between rare mutations at two different genes, a larger number of subjects are necessary than single mutation.

Based on whole-genome sequencing, the human genome encodes 30,000 genes, and in many cases, a single gene is highly pleiotropic because it has multiple roles and functions in multiple organs. For example, variants in the apolipoprotein ε4 gene are associated with lipid metabolism and atherosclerosis [11], and with Alzheimer's disease [12] and with osteoporosis [13]. A single allele of a gene may influence the aging process as well as the incidence of multiple age-related diseases, and the effect of the allele may be influenced by lifestyle, environmental factors, or both.

For the above-mentioned reasons, at least 2,000 middle-aged or elderly men and women should be selected, if possible, from a community-dwelling population as a basic cohort for a genetic epidemiological study of aging and age-related disease. Many alleles and candidate genes should be genotyped or, if possible, a genome-wide analysis of single nucleotide polymorphisms should be performed, and various life and environmental factors, medical findings, and disease markers should be assessed in a systematic way for each individual in the cohort. Moreover, for the assessment of time-dependent changes in lifestyle choices and environment factors, a comprehensive longitudinal study in which the subjects are observed repeatedly over time is desirable.

Research on the association of genotypes with common age-related diseases or disabilities that is controlled for many background factors can be accomplished with a nested case-control study design in which subjects with and without disease or disability are in the basic cohort. Research on genetic associations with differences in clinical parameters such as blood pressure, serum cholesterol level, and bone mineral density are also possible. For important geriatric diseases including Alzheimer's disease, Parkinson's disease, and femoral neck fracture, it is difficult to recruit enough affected patients from a single community-dwelling population to conduct a genetic association study. However, case-control study design is feasible if the patient group with the disease is recruited from collaborating hospitals and the control group without the disease is selected from the basic cohort.

Longitudinal epidemiological studies

Accumulation of basic data on aging is indispensable for the molecular epidemiological study of aging and age-related disease. The National Center for Geriatrics and Gerontology (NCGG) Research Institute (former National Institute for Longevity Sciences: NILS) is the leading national research center for aging and geriatrics; it is located in Obu City in the suburbs of Nagoya, Japan. In 1996, the Laboratory of Long-term Longitudinal Studies was established within the Department of Epidemiology, NILS; the initiative was focused on a new longitudinal study of aging in Japan. In October 1997, a trial run of the examinations was conducted, and in November 1997, we started the NILS-Longitudinal Study of Aging (NILS-LSA), a large-scale and comprehensive longitudinal study of aging in Japan [14]. Every day, six to seven participants were examined at the NILS-LSA Examination Center (***Fig. 2***). The first wave of the examinations finished in April 2000, and 2,267 participants (both male and female) had completed the examinations. The participants were examined every 2 years, and in July 2012, the seventh wave of examinations was completed.

The research area was defined as the neighborhood of NCGG, which included Obu City (population 79,000) and Higashiura Town (population 48,000). This area is located south of Nagoya, and is a bedroom town and also an industrial area of the Toyota group, and the area has many orchards and farms; therefore, the research area included both urban and rural characteristics. The research area is located at the center of Japan, and the climate is close to the average for all of Japan. We examined how representative this area is of Japan by conducting a national postal questionnaire of prefecture-stratified random samples of 3,000 households from all prefectures in Japan, and found that the lifestyle choices in the research were typical of all areas in Japan. Therefore, we expected that the results of the examinations in this area will be representative of Japan.

The participants in the baseline examinations of the NILS-LSA were males and females aged 40 to 79 years old. The population of Obu City and Higashiura Town was stratified by both age and gender, and participants were randomly selected from resident registrations in cooperation with the local governments. To test sex differences, the study cohort included equal numbers of males and of females; moreover, the numbers of participants within each decade (40s, 50s, 60s, 70s) were also to be equal. There are some dropout participants in each wave of the examination. These dropout participants were replaced newly recruited age- and sex-matched samples randomly selected from the resident registration except the participants over 79 years old. And, new participants, males and females aged just 40 years, were recruited every year. Recruitment and follow-up are expected to be much easier with volunteers than with randomly selected participants. However, because samples comprising volunteers generally tend to be interested in health, findings from samples comprising volunteers would produce biased results. Consequently, samples should comprise randomly selected participants in order observe the aging process of ordinary Japanese who live ordinary lives.

The participants were examined from 8:50 am to 4:00 pm at a special examination center within a facility at the NCGG. To examine 2,400 males and females in 2 years, that is, 1,200 males and females per year, six or seven participants were to be examined each day, 4 days a week, from Tuesday to Friday, 200 days (50 weeks) a year. We took advantage of the fact that all participants could be examined at the center; therefore, we could conduct detailed examinations that included medical evaluations as well as examinations of exercise physiology, body composition, nutrition, and psychology. Each examination was to be extensive and the most up-to-date, aiming at the internationally highest level in geriatrics and gerontology.

From the beginning of the study, blood samples for gene analysis were collected from almost all participants. There would be no other accumulation of DNA specimens with very detailed back ground information in a community-dwelling population in Japan and other countries. To date, 230 genotypes have been examined, and the associations between genotypes with age-related diseases and parameters of aging controlling for various background factors including nutrition and physical activity have been investigated.

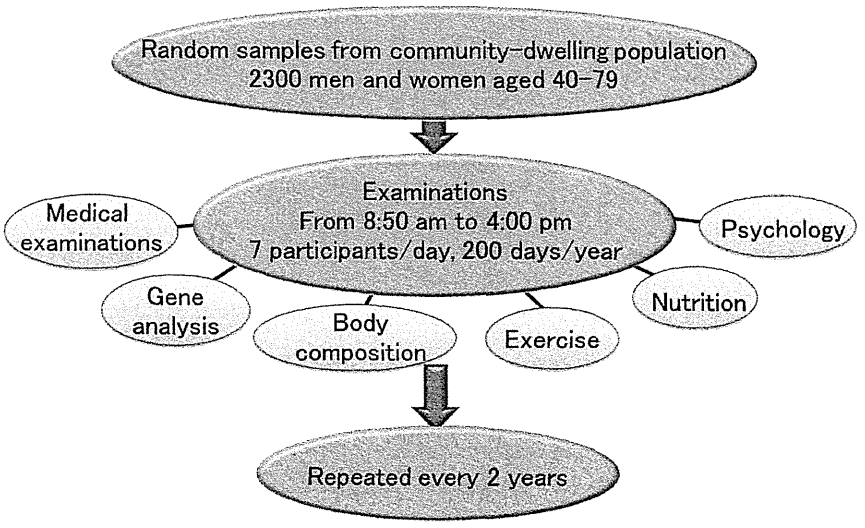

Fig. 2. **Implementation of the National Institute for Longevity Sciences, Longitudinal Study of Aging (NILS-LSA).**

Genotype and bone mineral loss with aging

Age-related changes in bone mineral density (BMD) were examined via dual-energy x-ray absorptiometry (DXA) and a peripheral quantitative CT (pQCT) in the NILS-LSA. We found 31 genotypes that were associated with BMD (***Table 2***). These are results from association studies between genotypes of candidate genes and BMD by DXA or pQCT.

Fig. 3 shows the effects of the estrogen receptor (ERα) Xbal genotype on the relationship between BMD and lean body mass in post-menopausal women [30]. BMD tends to be higher with more muscle mass estimated as lean body mass, and the effect of lean body mass is larger in AG/GG type than in AA type of ERα Xbal genotype. We suspect that, for the purpose of preventing osteoporosis, an increase in muscle mass is more effective in people with the AG/GG type than in those with the AA type.

BMD is higher in AA type in a cohort with low muscle mass, but BMD is lower in AA type in a cohort with large muscle mass. Findings from analyses of cohorts with different muscle mass reveal that there may be an inverse association between genotype and BMD. Lack in analysis of interaction between gene and life-style would be one of the causes of poor reproducibility in genome research. Thus, comprehensive analyses of the interaction with detailed data from nutrition surveys and lifestyle examinations including smoking, alcohol drinking, and physical activity are essential in the study of Anti-Aging and disease prevention.

Gene and age-related cognitive impairment

Many genes are likely to influence cognitive function, but the associations between genetic polymorphisms and age-related cognitive impairment are unclear. There are significant differences in age-related cognitive decline among individuals.

Klotho is a type I membrane protein that shares sequence similarity with members of the glycosidase family [31], and it

Table 2 Newly found or confirmed associations between genotypes and bone mineral density (BMD) based on NILS-LSA findings

Genes and genotypes		Effects on BMD	Ref.
Calcium metabolism related hormones and receptors			
VDR	Vitamin D receptor (A-3731G)	Femoral neck BMD is high in men with CC type	15
ESR1	Estrogen Receptor α (PP/pp)	BMD is low in elderly women with CC type	16
ESR1	Estrogen Receptor α(XX/xx)	BMD is low in elderly women with GG type	16
OST	Osteocalcin (C298T)	BMD is low in premenopausal women with TT type	15
ADR	Androgen receptor (CAG repeat)	BMD is low in premenopausal women with frequent CAG repeat	17
CYP17A1	Cytochrome P450,family 17, subfamily A, polypeptide 1 (T-34C)	BMD is low in postmenopausal women with CC type	18
Cytokines growth hormones and receptors			
IL6	Interleukin-6 (C-634G)	Radial BMD is low in postmenopausal women with GG type	15
TGFB	Transforming growth factor-β1 (T29C)	Radial BMD is high in elderly women with CC type	19
OPG	Osteoprotegerin (T950C)	Radial BMD is low in premenopausal women with CC type	20
OPG	Osteoprotegerin (T245G)	Femoral neck BMD is low in pastmenopausal women with GG type	20
CCR	Chemokine receptor 2 (G190A)	BMD is high in postmenopausal women and middle-aged men and with AA type	21
Bone matrix related protein			
MMP1	Matrix metalloproteinase-1 (1G/2G at-1607)	Radial BMD is low in postmenopausal women with 2G/2G type	22
MMP9	Matrix metalloproteinase-9 (C-1562T)	BMD is low in men with CT/TT type	23
COL	Collagen type1 (G-1997T)	BMD is low in postmenopausal women with GG type	24
ICAM1	Intercellular adhesion molecule-1 (Lys469Glu)	BMD is low in postmenopausal women with AA type	25
PLOD1	Procollagen-lysine 2-oxyglutarate 5-dioxygenase (Ala99Thr)	BMD is low in pre and postmenopausal women with GA/AA type	25
CX37	Connexin 37 (Pro319Ser)	BMD is low in men with TT type	25
Others			
KLOT	Klotho (G-395A)	BMD is low in pre and postmenopausal women with GG type	17
MTP	Microsomal triglyceride transfer protein (G-493T)	BMD is high in premenopausal women with TT type	18
VLDLR	VLDL receptor (triplet repeat)	BMD is high in men with more than 8 CGG repeat	18
ALAP	Adipocyte-derived leucine aminopeptidase (Lys528Arg)	BMD is high in premenopausal women with GG type	25
LIPC	Hepatic lipase (C-514T)	BMD is low in postmenopausal women with TT type	25
CNR2	Cannabinoid receptor 2 gene (A/G, rs2501431)	BMD is low in pre and postmenopausal women with AA/AG type	25
PON1	Paraoxonase-1 (Gln192Arg)	BMD is low in postmenopausal women with GG type	26
PON1	Paraoxonase-1 (Met55Leu)	BMD is low in postmenopausal women with TT type	26
PON2	Paraoxonase-2 (Cys311Ser)	BMD is low in postmenopausal women with CC type	26
DRD4	Dopamine D4 Receptor (C-521T)	BMD is low in men with CC type	27
FOXC2	Forkhead box C2 (C-512T)	BMD is low in men and women with T allele	28
PLN	Perilipin (C1243T)	BMD is low in men with C allele	28
MAOA	Monoamine oxidase A (uVNTR)	BMD is low in women with repeat less than 4	29
SH2B1	Src-homology-2-B (Ala484Thr)	BMD is low in women with A allele	29

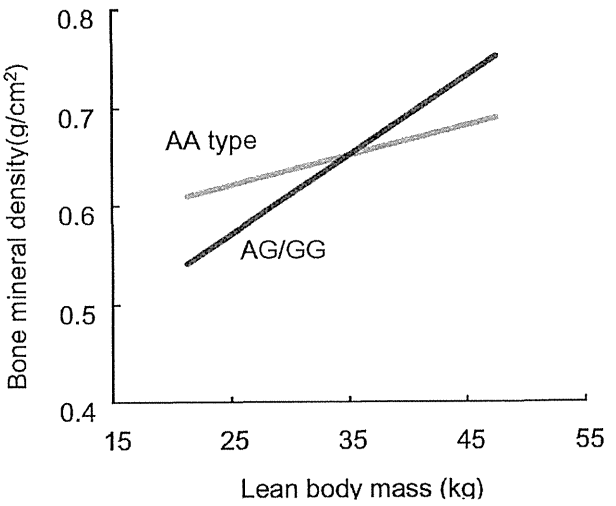

Fig. 3. **The effects of the estrogen receptor (ERα) XbaI genotype on the relationship between BMD and lean body mass in post-menopausal women. The BMD tends to be higher in women with more muscle mass as estimated as lean body mass, and the effect of lean body mass is larger in AG/GG type than in AA type of ERα XbaI genotype (modified from Kitamura *et al.*, 2007 [30]).**

is a fundamental regulator of aging in mice [32]. Mice lacking this protein exhibit multiple aging phenotypes and age-related disorders, including a shortened lifespan, reduced spontaneous activity, arteriosclerosis, infertility, skin atrophy, premature thymic involution, pulmonary emphysema, and osteopenia, although the function of klotho remains to be determined [31,33]. A human homolog of the mouse klotho gene was isolated and its structure was determined [34]. Cognitive impairment was previously shown in klotho gene mutant mice aged seven weeks or over [35]. The klotho gene may be mediate age-related changes in cognitive function in humans.

The effects of klotho gene genotype on cognition were examined in the NILS-LSA [36]. The subjects comprised 2,234 participants in the NILS-LSA aged 40 to 79 years. The klotho gene promoter polymorphism G-395A was identified, and cognitive function was assessed using the Japanese Wechsler Adult Intelligence Scales - Revised Short Forms (JWAIS-R SF) and Mini Mental State Examination (MMSE). The differences in cognitive function were compared between the GG type and GA/AA type of the klotho gene G-395A polymorphism. There was no significant difference in IQ between the GG type and GA/AA type in the subjects aged 40 to 59 years. However, the IQ level was significantly different in terms of the klotho genotype for subjects aged 60 to 79 years (p=0.004). The mean and SE of IQ levels of the subjects with the GG type and the GA/AA type at nucleotide –395 were 99.8 ± 0.5 and 102.6 ± 0.8, respectively. There were also significant differences in three subtests within the JWAIS-R SF: Information, Similarities, and Picture Completion for subjects aged 60 to 79 years. Also, the MMSE score was slightly lower for the GG type than for the GA/AA type (p=0.099).

There were statistically significant differences in cognitive function for klotho gene promoter polymorphism G-395A only in subjects aged 60 or over. This polymorphism may be associated with age-related cognitive impairment, and not associated with cognitive development during childhood to adolescence.

A new genetic strategy for Anti-Aging and prevention of age-related disease

The impact of genetic surveys could be enormously helpful for preventive treatments of geriatric disease as well as Anti-Aging. Previously, associations between disease and genotype were usually investigated by association studies of a specific genotype and a specific disease in molecular epidemiology research. However, we should clarify the following to apply results of epidemiological study to Anti-Aging medicine and preventive medicine: 1) the penetration rates of the genotypes in Japanese; 2) contribution rate to incidence of disease by each susceptibility genotype; 3) factors associated with development of disease in carriers of disease susceptibility genotype; 4) interactive effects with other genotypes; and 5) other physiological effects of the genotype.

These can be investigated in community-dwelling populations and patient cohorts that have detailed background data. Risk of disease can be estimated with the aid of accumulated data. The best-suited education and modification of lifestyles and the content and frequency of examinations for each individual can be determined based on the risk estimation can be applied for disease prevention and Anti-Aging.

Conflict of interest statement

The authors declare no financial or other conflicts of interest in the writing of this paper.

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Aging Clinical and Experimental Research

SHORT COMMUNICATIONS

Slower adaptation to driving simulator and simulator sickness in older adults

Naoko Kawano[1,2,5], Kunihiro Iwamoto[1], Kazutoshi Ebe[3], Branko Aleksic[1], Akiko Noda[4], Hiroyuki Umegaki[5], Masafumi Kuzuya[5], Tetsuya Iidaka[1] and Norio Ozaki[1]

[1]Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, [2]Research Team for Promoting Independence of the Elderly, Tokyo Metropolitan Institute of Gerontology, Tokyo, [3]Toyota Central R&D Labs., Inc., Nagakute, [4]Department of Biomedical Sciences, Chubu University, Kasugai, [5]Department of Geriatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan

ABSTRACT. ***Background and aims:*** *Methods of assessing driving abilities in the elderly are urgently needed. Although the driving simulator (DS) appears to be a safe and cost-effective method of objectively evaluating driving performance, it may pose adaptation problems for elderly adults. In this study, we examined age-related adaptation deficits on the DS.* ***Methods:*** *Healthy young adults (n=15) and healthy elderly persons (n=17) completed some neuropsychological tests, and then performed a road-tracking task with the DS, which was repeated four times (Trials 1-4).* ***Results:*** *After simulated driving in DS, simulator sickness (SS) was observed in 18.8% of participants. The frequency of SS was 29.4% in elderly adults and 6.7% in young adults, and 17.6% of the elderly participants dropped out of the experiment. Performance on the Necker cube copying task was significantly correlated with the onset of SS. Driving performance also showed a significant interaction between group and trial, for both driving accuracy and vehicle speed. In addition, the performance of elderly adults significantly improved between trials 1 and 4, reaching a plateau in trial 4, whereas that of young adults did not change across trials.* **Conclusion:** *This study provides preliminary evidence of slower adaptation to a DS-based driving task by older adults, which was associated with cognitive aging. Age affected driving accuracy and velocity when a road-tracking task was simply repeated. It is concluded that the capacity of elderly people to adapt to DS environments should be taken into consideration when evaluating their performance on DS tasks.*
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INTRODUCTION

The proportion of licensed drivers over the age of 65 has increased with respect to two or three decades ago, and this number is expected to increase even further over the next few decades. It has been established that age-related decline, in both cognitive and perceptual and physical abilities, is associated with an increased risk of being involved in a traffic accident (1, 2). Identifying unsafe elderly drivers is therefore a critical issue in terms of individual and public safety (3, 4), and geriatric clinicians have been faced with the task of categorizing senior citizens into "safe" *vs* "unsafe" drivers (5). Valid methods for assessing the driving abilities of elderly people are urgently required.

While many consider road testing to be the gold standard by which to evaluate driving competence, road tests are costly and may be dangerous if the driver is incompetent. Although the driving simulator (DS) appears to be a safe and cost-effective method for objective evaluation of driving performance (6-9), DS applications are not without limitations, particularly when elderly adults are concerned. One important problem concerns the slower adaptation to simulation environments observed in elderly persons. When using a DS to evaluate the driving performance of elderly adults, it is necessary to discriminate between true driving abilities and age-related adaptation deficits specific to the simulator environment.

Simulator sickness (SS), or simulator adaptation syndrome, has been defined as a set of symptoms similar to those experienced after exposure to virtual interfaces, as well as to flight and driving simulators. Symptoms include headache, sweating, dry mouth, drowsiness, disorientation, vertigo, nausea, dizziness, and vomiting (10). One expla-

Key words: Driving simulator, elderly drivers, simulator sickness, learning effect, slow adaptation.

Correspondence: Naoko Kawano, Department of Psychiatry, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya-shi, 466-8550, Japan.
E-mail: n-kawano@med.nagoya-u.ac.jp

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nation is that symptoms are caused by a mismatch between visually perceived movements and the sense of movement perceived by the vestibular system, what is called the sensory conflict theory (10). Although SS is caused by several factors, aging is known to be one of them. Some studies have reported that older participants experience more SS in driving simulators than younger participants (10, 11). Cognitive variables may also play a certain role in SS; however, systematic studies have not investigated the relationship between SS and these variables, which is hindering the use of DS as an assessment tool for elderly persons with cognitive impairment.

In order to examine whether age-related adaptation deficits affect DS performance, we asked both elderly adults and young adults (controls) to drive a DS on four separate occasions, one immediately after the other, and compared the adaptation process between the two groups. In the present study, we focused on two specific markers of adaptation: the influence of simple repetition on task performance, and the occurrence frequency of SS. We also carried out a preliminary search to identify cognitive functions related to SS in elderly persons.

METHODS

Participants

We recruited 15 healthy young adults and 17 healthy elderly persons over 60 years of age. The participants were naïve with regard to this study, and were paid for their participation. They all had normal or corrected-to-normal vision, and reported no history of any psychotropic medication use, head injury with loss of consciousness, secondary neurological disorders, or drug intoxication.

None of the elderly participants showed any signs of general cognitive decline. Medical histories (including stabilograph assessment results and MRI scans) were obtained and carefully reviewed, to exclude any individuals with neuropsychiatric disease. Elderly participants with a diagnosis of dementia, and/or those with Mini-Mental State Examination (MMSE) (12) scores of 23 or less, and/or a Logical Memory delayed recall subtest score of 12 or lower on the Wechsler Memory Scale-Revised (WMS-R) (13) were excluded.

The ethics committee of the Nagoya University School of Medicine approved this study, and written informed consent was obtained from each subject prior to participation.

Tasks

Driving performance. Daily driving skills associated with traffic accidents were measured by a road-tracking task, which required participants to drive at a constant speed of 100 km/h while maintaining their vehicles at the center of a gently winding road. According to Park et al., SS emerges at a high rate in this type of DS situation, which includes high speed and multiple turns (14).

The standard deviation of the lateral position (SDLP; in cm), which indicates weaving, and the velocity (km/h) of the vehicle were used as performance measures. Recordings were made every 20 ms during the test, which lasted for 5 minutes. Details regarding the DS (manufactured by Toyota Central R&D Labs., Inc.) configuration and driving tasks used are available elsewhere (9, 15).

Evaluation of driving with the simulator was performed after neuropsychological testing was complete. Before starting the test, each driver was familiarized with the simulator by driving for a maximum of 5 minutes on a two-lane highway with no other traffic. The driving task was then repeated four times by each participant (trials 1-4).

Cognitive functions. Cognitive functions were assessed by structured performance tests selected to represent a broad range of cognitive domains, including those measured in previous studies related to complex driving tasks (16). To assess attention and executive function, the forward and backward digit span subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (17) and the paper-based Stroop Test (18) were completed. The Clock Drawing Test (CDT) (19) and Necker cube copying task (20) were completed to assess visuospatial function in elderly adults. An experienced psychologist examined all participants by the above test battery.

RESULTS

Participants were healthy young adults (n=15, 5 women and 10 men; age range, 29-43 years) and healthy elderly persons (n=17, 7 women and 10 men; age range, 60-79 years). SS was observed in 18.75% (6/32) of participants after simulated driving. The frequency of SS was 29.41% (5/17) in elderly adults and 6.67% (1/15) in young adults. This difference was not statistically significant (p=0.229, Fisher's exact test). Three elderly adults failed to complete the trials due to SS, and the data from one younger adult were excluded from following analyses, due to a mechanical problem. One-way Analysis of Variance (ANOVAs) were conducted for each neuropsychological task. The demographic characteristics of participants are listed in Table 1. The main effect of group was significant for the Stroop test ($F_{(1,26)}$=18.70, p=0.002), whereas no main effects were found for the WAIS-R digit span forward and backward tasks. Differences in cognitive functions between age groups are listed in Table 2.

In order to identify cognitive functions related to the onset of SS in elderly participants, the correlation between SS and each cognitive task score in the elderly group was analyzed. The results of Spearman's rank correlation method indicated that only the performance of the Necker cube copying test was significantly associated with the onset of SS ($\rho_{(15)}$= -0.68, p=0.002). SS was also associated with dropping out of the task (ρ(15)= -0.49,

Table 1 - *Demographic data of each age group: means ± standard deviations.*

	Elderly adults (n=14)	Young adults (n=14)
Female/male	5/9	5/9
Age (years)	66.6±4.7	35.2±5.0
Education (years)	15.1±3.0	16.0±0.0
Duration of holding a driving license (years)	43.7±7.2	15.1±5.4
Cognitive characteristics		
Mini-Mental State Examination	28.1±1.9	
WMS-R Logical Memory: immediate recall	21.2±5.9	
WMS-R Logical Memory: delayed recall	19.3±7.0	

WMS-R: Wechsler Memory Scale-Revised.

p=0.030). Table 3 lists the association between SS and each cognitive task score in the elderly group.

Figure 1 shows task performance trends from baseline to each time-point after repeating. To examine whether age-related adaptation deficits could be observed on the DS task, 2 (Group: young adults, elderly adults) × 4 (Trial: 1 to 4) factorial ANOVAs were carried out on driving performance measures. The results are summarized in Figure 1. For SDLP, the analysis revealed the main effects of group and trial ($F_{(1,26)}$=11.85, p=0.002; $F_{(3,78)}$=8.37, p=0.001). The interaction between group and trial was also significant ($F_{(3,78)}$=3.41, p=0.038). Following-up this interaction, we found a significant simple effect of group in all trials ($F_{(1,26)}$=11.09, p=0.003; $F_{(1,26)}$=13.87, p=0.001; $F_{(1,26)}$=8.50, p=0.007; $F_{(1,26)}$=5.41, p=0.028) and also a significant simple trial effect in elderly adults ($F_{(3,24)}$=8.03, p=0.001), but no such effect in young adults. Multiple comparisons with the Bonferroni adjustment were performed, and significant differences were found between trial 1 and 2 and trial 4 in the elderly group (p=0.001; p=0.001).

As regards velocity, analysis revealed the main effects of group and trial ($F_{(1,26)}$=15.95, p=0.001; $F_{(3,78)}$=15.07, p<0.001). The interaction between group and trial was also significant ($F_{(3,78)}$=11.72, p<0.001). Following up this interaction, a significant simple effect of group was found in all trials ($F_{(1,26)}$=21.86, p<0.001; $F_{(1,26)}$=12.85, p=0.001; $F_{(1,26)}$=9.62, p=0.005; $F_{(1,26)}$=7.70, p=0.010), together with a significant simple trial effect in elderly adults ($F_{(3,24)}$=12.67, p<0.001), but no such effect in young adults. Multiple comparisons with the Bonferroni adjustment were performed, and significant differences were found between trial 1 and 2 and trial 4 in the elderly group (p<0.001; p=0.044). These results showed that the performance of elderly adults improved from trial 1 to trial 4, whereas that of young adults did not change across trials. Moreover, by trial 4, the performance of the elderly group had reached a plateau.

Correlational analyses were conducted to examine the relationship between the road-tracking task trial and the neuropsychological task performance of each group. In the elderly group, there were significant negative correlations between SDLP values in the trial 3 and 4 and scores on the WAIS-R backward digit span subtest ($r_{(12)}$= -0.77, p=0.001; $r_{(12)}$= -0.60, p=0.023), and significant positive correlations between driving performance in trial 2, 3 and 4 and performance on the Stroop test ($r_{(12)}$=0.54, p=0.047; $r_{(12)}$=0.59, p=0.025; $r_{(12)}$=0.59, p=0.027). In the young group, there were significant positive correlations between SDLP values in trial 2 and scores on the WAIS-R forward digit span subtest ($r_{(12)}$=0.59, p=0.035), as well as significant negative correlations between SDLP values in trial 3 and performance on the Stroop test ($r_{(12)}$= -0.62, p=0.024). No sig-

Table 2 - *Neuropsychological scores of each age group: means ± standard deviations.*

	Elderly adults (n=14)	Young adults (n=14)	*p* (one-way ANOVA)
Clock Drawing Test	8.5±1.2		
Necker cube copying (correct/any distortion)	9/5		
WAIS-R: digit span forward	6.9±2.6	7.8±2.5	0.159
WAIS-R: digit span backward	7.4±2.5	6.7±2.0	0.667
Stroop Test (sec)	13.1±6.3	5.8±4.3	0.002

WAIS-R: Wechsler Adult Intelligence Scale-Revised.

Table 3 - *Association between occurrence of simulator sickness (SS) and cognitive functions in elderly group.*

	Simulator sickness			
	Onset SS (frequency of SS: 5/17)		SS in drop-outs (frequency of SS: 3/17)	
	Spearman's ρ	p	Spearman's ρ	p
Cognitive functions				
Clock Drawing Test	-0.34	0.142	-0.04	0.845
Necker cube copying	-0.68	0.002	-0.49	0.030
WAIS-R: digit span forward	-0.29	0.197	0.09	0.700
WAIS-R: digit span backward	-0.26	0.241	-0.17	0.445
Stroop Test	0.40	0.058	0.21	0.314

WAIS-R: Wechsler Adult Intelligence Scale-Revised.

nificant correlations were detected in the elderly group for velocity. In the young group, there were significant negative correlations between speed in trial 2 and scores on the WAIS-R forward digit span subtest ($r_{(12)}$= -0.62, p=0.022), as well as significant positive correlations between speed in trial 2 and performance on the Stroop test ($r_{(12)}$= -0.57, p=0.043).

DISCUSSION

Human behavior is dependent on dynamic interactions between people and their environment. The effects of normal aging on adaptation to the environment are controversial. Specifically, some studies have found no age-related adaptation deficits (21, 22), whereas others suggest that aging results in both slower adaptation and a reduced ability to adapt (23, 24). The present study demonstrates that aging affects both the occurrence of SS and the influence of simply repeating tasks on performance. Our results point toward the limitations of a DS to screen for unsafe elderly drivers. Protocols specifically designed to test the driving ability of senior citizens should be developed.

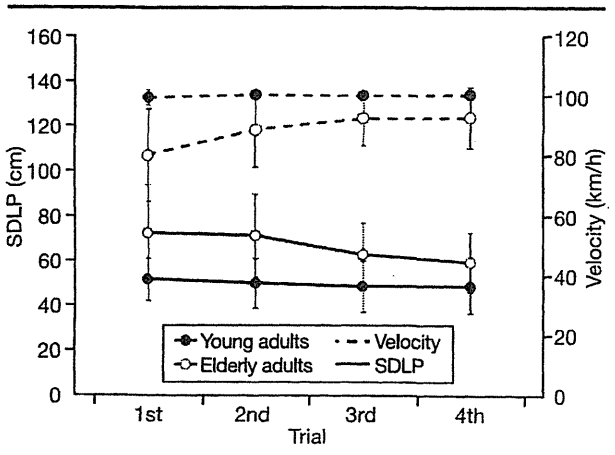

Fig. 1 - *Trends of task performances from baseline to each time point after task repetition.*

Our findings indicate that SS was typically observed in elderly adults. In addition, as 17.6% of our elderly drivers dropped out of the study because of SS, this result corroborates previous research (10, 11, 14). Brooks et al. speculated that one explanation of SS is the increased balance and dizziness problems experienced with aging (10). However, our older participants had no neuropsychiatric history and had normal stabilographic assessment results. This study demonstrates an association between SS onset and visuospatial function as measured by the Necker cube copying test, indicating that the increased SS in elderly people is caused by cognitive aging associated with visuospatial cognition. This finding suggests that people with compromised visuospatial cognition, such as patients with Alzheimer's disease, are more vulnerable to SS than normal elderly people.

Our study also demonstrates that the low driving accuracy of elderly persons is correlated with a decline in attention markers on later trials. Conversely, such a simple linear pattern was not found in younger adults. Rather, on the middle trials (2, 3), low driving accuracy and low velocity were correlated with high performance on attention tasks. These results suggest that variations in DS performance due to age-related adaptation deficits disappear across repeated tasks, and that DS performance directly reflects individual differences in attention and executive function. As the effects of aging on adaptive visuomotor mechanisms are a potential confounding factor (21-23, 25), the driving ability of elderly persons should be evaluated after they have reached a DS performance plateau. Repeating the driving task three times is an effective technique for adaptation to this type of DS. In addition, young adults had a different link between cognitive characteristics and adaptation to the DS in comparison with elderly adults.

This study has several limitations. The first is that the degree of SS was not quantified. However, drop-outs who experienced severe SS were all elderly, which supports the hypothesis that SS is an age-related adaptation deficit. A second limitation was the small sample size, which should be taken into consideration when interpreting the results. Lastly, no dementia patients participated in this study.

In conclusion, this study provides preliminary evidence concerning the slower adaptation to DS-based driving tasks associated with cognitive aging in older adults. Age affected driving accuracy and velocity when a simple road-tracking task was repeated. It is concluded that DS assessment of driving skills must be performed after a certain level of practice. The external validity of DS should also be further investigated. In order to standardize DS tasks as assessment tools, further research is needed on the effects of SS on simulator performance.

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Geriatrics Gerontology Medline Indexed

Geriatr Gerontol Int 2013; **13:** *28–34*

REVIEW ARTICLE

Cognitive dysfunction: An emerging concept of a new diabetic complication in the elderly

Hiroyuki Umegaki,[1] Toshio Hayashi,[1] Hideki Nomura,[1,2] Madoka Yanagawa,[1] Zen Nonogaki,[1] Hirotaka Nakshima[1] and Masafumi Kuzuya[1]

[1]*Department of Geriatrics, Nagoya University Graduate School of Medicine, and* [2]*Department of Geriatrics, Ajima Clinic, Nagoya, Japan*

The incidence of type 2 diabetes mellitus (T2DM) has risen, and this trend is likely to continue. Recent advances suggest that T2DM is a risk factor for cognitive decline. We are now encountering novel complications of T2DM, namely cognitive dysfunction and dementia. Although the treatment strategy for diabetic patients with neurocognitive dysfunction has received a great deal of attention, the appropriate level of glycemic control for the prevention of the development and/or progression of cognitive decline in elderly diabetic patients remains to be elucidated. Another issue in diabetic treatment in patients with cognitive dysfunction is the selection of medicines. The best choice and combination of antidiabetic medications for the preservation of cognition should also be studied. Ample studies suggest that exercise helps to preserve cognitive function, although existing evidence does not necessarily indicate its effectiveness exclusively in diabetic patients. Exercise is a helpful non-pharmacological therapy. Considering the progressive aging of the worldwide population, more research to investigate the best way to manage this population is important. **Geriatr Gerontol Int 2013; 13: 28–34.**

Keywords: Alzheimer's disease type dementia, hypoglycemia, insulin resistance, neurocognitive assessment, vascular dementia.

Introduction

The incidence of type 2 diabetes mellitus(T2DM) has risen, and this trend is expected to continue.[1] Recent remarkable advances in pharmacological therapy in T2DM have resulted in a wide variety of treatments. Many large clinical trials have been carried out, and a variety of interventions are now available to prevent and treat the classic microvascular and macrovascular complications that occur with DM, so that people are living longer with the condition.[2] Recent studies suggested that T2DM is a risk factor for cognitive dysfunction and dementia in the elderly. With the increase in the number of elderly individuals with DM, the number of diabetic patients with cognitive dysfunction has been increasing. We are now encountering novel complications of T2DM that are not targeted by the current management strategies. As one of these new targets, cognitive impairment and dementia in patients with T2DM has generated a great deal of interest, and diabetic treatment in this population that takes brain protection into consideration should be provided.

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Correspondence: Dr Hiroyuyki Umegaki MD PhD, Department of Geriatrics, Nagoya University Graduate School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan. Email: umegaki@med.nagoya-u.ac.jp

Cognitive impact of T2DM

Large epidemiological studies have shown the cognitive impacts of T2DM. In the Rotterdam Study,[3] T2DM patients showed an increased risk of developing dementia. The study also showed that patients treated with insulin were at a 4.3-fold higher relative risk for dementia. The Hisayama Study showed that the incidence of all-cause dementia, Alzheimer's disease (AD) and vascular dementia were significantly higher in patients with diabetes than in those with normal glucose tolerance[4] The same study showed that systemic insulin resistance was associated with the pathogenic process of AD, neuritic plaques formation.[5] The Religious Orders Study, which observed some 800 nuns and priests longitudinally for 9 years, showed that diabetic people had a 65% increased risk of developing AD.[6] The Honolulu Asia Aging Study, a cohort of Japanese Americans in Hawaii, showed that the diabetic population had a 1.8-fold higher risk of developing AD and a 2.3-fold risk of vascular dementia.[7,8]

Prospective trials also suggested that T2DM caused cognitive function to deteriorate in the elderly.

A diagnosis of diabetes increased the odds of cognitive decline 1.2-fold to 1.7-fold (95% CI 1.3–2.3) in several neurocognitive assessments.[9] A recent systematic review of large prospective trials reported that T2DM increased the risk of AD by a factor of 1.59 (range 1.15–2.7).[10] Another systematic review reported that T2DM has a risk of vascular dementia of 2.0–4.2.[9,11]

The advances in the research in this field strongly suggest that T2DM is a risk factor for cognitive dysfunction or dementia.[12,13]

Assessment of diabetes-associated cognitive dysfunction

To screen patients with cognitive impairment, several neuropsychological assessment tools might be applied. The Mini-Mental State Examination (MMSE) is an assessment scale for global cognition including orientation, memory, calculation, verbal ability and constructional disability.[14] A full score is 30, and a cut-off point of 23 out of 24 is usually used for the screening of dementia. The MMSE subset analysis identified impaired attention and calculation as specific characteristics of DM patients,[15] whereas patients with AD had lower scores in temporal orientation and recall.[16]

As a part of a large cohort study of older DM patients (Japanese Research of Cholesterol and Diabetes Mellitus, UMIN000000516 Japan CDM), we carried out MMSE on diabetic patients aged older than 65 years in a diabetic outpatient clinic (52 males, 61 females; mean age 74.7 ± 4.6 years). Of these patients, 75 were aged less than 75 years (younger-old mean age 69.9 ± 4.7 years) and 38 patients were aged older than 75 years (older-old mean age 80.7 ± 4.4). In the younger-old group, 76.0% of patients (57/75) had a MMSE score of more than 24 (mean score 25.3 ± 4.7), and in the older-old group, 52.6% (20/38) had a MMSE score of more than 24 (mean score 24.2 ± 4.6). This small assessment showed that many diabetic patients had lower cognitive scores indicative of dementia, especially in the older-old.

Diabetes affects a wide range of cognitive domains.[17] Among the domains affected by T2DM, cognitive speed might provide early detection of diabetes-related cognitive decline[18,19] The digit symbol substitution test (DSST) is a test of cognitive speed that can be carried out relatively easily. It consists of a number (e.g. nine) of digit-symbol pairs (followed by a list of digits). Under each digit, the patient is asked to write down the corresponding symbol as quickly as possible. The number of correct symbols written within the allowed time (e.g. 90 or 120 s) is measured.

In clinical settings, the diagnosis of dementia is generally made based on the Diagnostic and Statistical Manual of Mental Disorders III revised criteria in patients with or without DM.[20] The disturbance in memory impairment with at least one of the following is required for the diagnosis of dementia: abstract thinking, judgement, higher cortical function and personality changes interferes with work or social activities. The leading cause of dementia in diabetic patients is AD, as is those without DM. DM patients often have cerebrovascular disease, and clinical-pathological studies support the notion that vascular lesions aggravate the deleterious effects of AD pathology by reducing the threshold for cognitive impairment.[21]

Pathogenesis of diabetes-associated cognitive dysfunction

The precise mechanisms underlying T2DM-related cognitive dysfunction or the development of dementia, especially AD-type dementia, remain to be elucidated; however, several hypothetical mechanisms have been proposed (Fig. 1). To develop pharmacological and non-pharmacological strategies for treating the diabetic elderly with cognitive impairment, elucidating the pathogenesis of this complication might be essential.

High glucose concentration, a major pathological characteristic of diabetes, might have toxic effects on neurons in the brain through osmotic insults and oxidative stress, and the maintenance of chronic high glucose also leads to the enhanced formation of advanced glycation end-products (AGE).[22] AGE couple with free radicals and create oxidative damage, which in turn leads to neuronal injury,[23] and they also reactivate microglia, the resident innate immune cells in the brain. A wealth of evidence shows that activated microglia can become deleterious and damage neurons.[24]

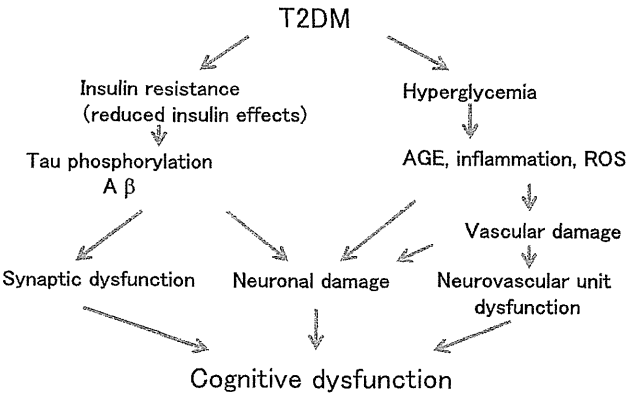

Figure 1 Pathogenesis of type 2 diabetes mellitus (T2DM)-associated cognitive dysfunction. Cognitive dysfunction in T2DM is induced by multiple pathways. Insulin resistance might be associated with Alzheimer's disease pathology, and hyperglycemia induces advanced glycation end-products (AGE) formation, inflammation and reactive oxygen species (ROS) production, which might lead to neuronal damage and neurovascular dysfunction.

T2DM, especially in conjunction with obesity, is characterized by insulin resistance and/or hyperinsulinemia. Insulin degrading enzyme (IDE) catabolizes insulin in the liver, kidneys and muscles.[25,26]

It is generally agreed that insulin located within the brain is mostly of pancreatic origin, having passed through the blood–brain barrier, although there is debate about the amount of insulin that is produced de novo within the central nervous system.[27] Major known actions of insulin in the brain include control of food intake (through insulin receptors located in the olfactory bulb and thalamus) and effects on cognitive functions, including memory.[28,29] Insulin also regulates acetylcholine transferase expression, which is an enzyme responsible for acetylcholine (ACh) synthesis. ACh is a critical neurotransmitter in cognitive function, and it might be relevant to neurocognitive disorders in diabetics.[30] Recent basic research showed that insulin signaling in the central nervous system prevents the pathological binding of amyloid beta (Aβ) oligomers.[31] Aβ oligomers are soluble molecules that attach with specificity to particular synapses, acting as pathogenic ligands.[32]

Insulin has multiple important functions in the brain, as aforementioned. These functions are disrupted in insulin-resistant states. The transport of insulin into the brain across the blood–brain barrier is reduced in insulin-resistance-associated hyperinsulinemia, and insulin levels in the brain are subsequently lowered.[33,34] Intranasal insulin showed some benefits in early AD patients.[35] With intranasal administration, insulin bypasses the periphery and the blood–brain barrier, reaching the brain and cerebrospinal fluid within minutes through extracellular bulk flow transport along olfactory and trigeminal perivascular channels, as well as through more traditional axonal transport pathways.[36,37]

Some basic research suggests that insulin signaling is involved in AD-related pathology through its effects on the Aβ metabolism and tau phosphorylation.[38] Insulin signaling activates PI3K/Akt pathway, which leads to inactivation of glycogen synthase kinase-3β (GSK-3β). GSK-3β regulates tau phosphorylation, one of the main pathological components in AD. Less insulin signaling might also induce increased activity of GSK-3β, which leads to the enhanced phosphorylation of tau protein and the formation of neurofibrillary tangles.[39] Decreased insulin signaling reduces the synthesis of several proteins, including IDE. IDE degrades Aβ as well as insulin, and reduced amounts of IDE might result in greater amyloid deposition. The results of pathological assessments in AD with or without DM, however, are highly controversial.[40,41] More research would be warranted to elucidate the relevance of insulin and insulin resistance in the underlying mechanism of T2DM-assocaiated cognitive dysfunction.

Diabetic patients often have ischemic brain lesions.[42] Even asymptomatic cerebral infarctions have affects on the cognition in elderly diabetic patients.[18,43] On cerebral magnetic resonance imaging, white matter hyperintensities and lacunae, both of which are frequently observed in the elderly, are generally viewed as evidence of small vessel disease in the brain (white matter lesions and lacunae). Small vessel diseases affect cognitive function in older diabetics.[18,44] DM also affects the function of microvascular endothelial cells. The deterioration of the endothelial cell function leads to the disruption of blood–brain barrier function, which might induce neuroinflammatory reactions and neurodegeneration.[45] The endothelial cells play a critical role in the control of hemodynamic coupling among neuronal, glial and vascular components; that is, "neurovascular units". Dysfunction of "neurovascular units" might have some impact on cognition in diabetic patients.[46]

Treatment of vascular risk factors including T2DM was reportedly associated with a lower conversion rate from mild cognitive impairment to AD[47] or slower cognitive decline in AD patients.[48] Comprehensive management in DM patients should be warranted.

Treatment and management of diabetic patients with cognitive impairment

T2DM is associated with cognitive dysfunction; however, it has not yet been made clear whether glycemic control leads to the preservation or improvement of cognitive function. Several prospective studies[19,49,50] have shown that higher glycated hemoglobin (HbA1c) levels at baseline are associated with cognitive decline. A recent prospective study by Christman *et al.*, however, showed that HbA1c levels at baseline had no effects on cognitive function.[51] A large cohort study, the Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes (ACCORD-MIND) trial, has found that HbA1c levels were cross-sectionally associated with worse performance on several cognitive functional tests.[52] However, the results of the interventional study were rather disappointing.[53] Although total brain volume in the intensive glycemic control group was significantly greater than in the standard treatment group after 40 months, there was no significant difference in cognitive assessment. The results of the study, however, should be interpreted cautiously because of the early drop-outs in the intervention group.

In the ACCORD-MIND study, the intensive control group achieved a HbA1c level of 6.6% compared with 7.5% in the standard treatment group. Several smaller studies involving less intensive glycemic treatment, however, indicated that modest cognitive decrements in patients with T2DM are partially reversible with the improvement of glycemic control,[54–59] although not invariably.[60] Postprandial hyperglycemia is associated

with atherosclerosis and diabetic complications,[61] and a control of postprandial hyperglycemia might prevent cognitive decline in older diabetic individuals.[59] These studies suggested that metabolic control might have beneficial effects in terms of cognitive function; however, the appropriate levels of blood glucose control remain unclear. In contrast, a recent report has suggested that a history of severe hypoglycemic episodes is associated with a greater risk of dementia.[62] The diabetic control in this population should be balanced between the merits of treatment and the risk of hypoglycemia.

Another issue related to the treatment that pertains to cognitive dysfunction is the selection and combination of antidiabetic medicines. The Rotterdam Study reported that insulin use increased the incidence of dementia.[3] However, many confounding factors must be considered when interpreting the results of that study. The patients who used insulin might have had worse diabetic control, a longer history and more complications, and these factors might have some impact on the incidence of dementia. Greater insulin resistance means that a greater amount of insulin is required to control the blood glucose level. The association of the use of an excessive amount of insulin with insulin resistance status might be undesirable, the appropriate prescription of insulin for maintaining a desirable blood glucose level has not yet been determined for individuals with insulin resistance. A small study reported that pioglitazone, an insulin sensitizer, has some beneficial effects on cognition in AD.[63] Comprehensive management in combination with insulin use would be necessary to achieve appropriate glycemic control, and efforts to reduce insulin resistance would be warranted.

Recently, a new class of diabetic pharmacological treatments known as incretin-related medicines has emerged. Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), whose activity is reduced in insulin resistance, have been implicated in central nervous system function, including cognition, synaptic plasticity and neurogenesis.[64] An animal study showed that GLP-1 prevented the neurodegenerative developments in AD model mice.[65] Further clinical investigation from the perspective of brain protection is warranted.

Many studies suggested that exercise has the potential to protect brain function. A systematic review of the Cochran database by Angevaren *et al.* reported the effects in elderly individuals without known cognitive impairment, and another systematic review of a prospective cohort study by Hamer *et al.* reported that exercise reduces the risk of incidence of dementia by 28% and of AD by 45%.[66,67]

Exercise also has effects on patients with mild cognitive impairment and dementia.[68] Although existing evidence does not indicate the effects of exercise on the protection of brain function exclusively in the diabetic population, exercise has multiple established effects on diabetic patients, including the improvement of insulin resistance. Studies to investigate the effects of exercise on diabetic cognitive dysfunction are warranted.

Cognitive dysfunction is associated with poor ability of self-care in elderly diabetics, and the use of both health and social services.[69] In addition, physical function is often more compromised in those with cognitive impairment. Individuals with DM with cognitive impairment might have difficulty carrying out the daily tasks of DM self-care effectively,[70] which might result in worse glycemic control than in individuals without cognitive impairment. A study reported that cognitively impaired DM patients were at increased risk of mortality and functional disability.[71] The relationship between cognition and self-management ability might be bidirectional. While it could be that poor self-management practices lead to poorer metabolic control and therefore brain dysfunction, cognitive deterioration would lead to changes in self-management ability.

A depressive mood is often comorbid with dementia,[72] especially in diabetics.[73] Depressed mood might also be associated with cognitive impairment and might interfere with effective self-management.[74–77]

People with dementia often experience behavioral and psychological symptoms of dementia (BPSD) during the course of their illness. The management of dementia is complicated by BPSD, such as psychosis, depression, agitation, aggression and disinhibition. BPSD also disrupts the daily diabetes care routine, with "denial" of having diabetes or memory loss (anosognosia) being the most disruptive.[78] Caregivers often report that caring for both diabetes and dementia is highly burdensome, that they feel overwhelmed by BPSD, and that they want more support from family and from the patients' healthcare providers.

To control BPSD, antipsychotic medication is sometimes prescribed. Antipsychotic drugs, especially second-generation drugs including olanzapine and quetiapine, have the potential to induce weight gain and elevate plasma glucose levels.[79] The use of these drugs in demented diabetic patients should be avoided.

Conclusion

Cognitive dysfunction might be a novel class of diabetic complication in the elderly. The management of diabetic patients with this complication is challenging and presents many unresolved problems. Considering the progressive aging of the worldwide population, it will be important to carry out investigations to improve our understanding of the association between T2DM and cognitive dysfunction, and to determine the best way to manage these populations.

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Disclosure statement

Nothing to declare.

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ORIGINAL ARTICLE: BEHAVIORAL AND SOCIAL SCIENCES

Day-care service use is a risk factor for long-term care placement in community-dwelling dependent elderly

Masafumi Kuzuya,[1] Sachiko Izawa,[1,2] Hiromi Enoki[1,3] and Jun Hasegawa[1]

[1]Department of Community Healthcare & Geriatrics, Nagoya University Graduate School of Medicine, Nagoya, [2]Department of Health and Nutrition, Faculty of Psychological and Physical Science, Aichi Gakuin University, Nisshin and [3]Department of Health and Medical Science, Aichi Shukutoku University, Nagakute, Japan

Aims: To identify predictors of long-term care placement and to examine the effect of day-care service use on long-term care placement over a 36-month follow-up period among community-dwelling dependent elderly.

Methods: This study was a prospective cohort analysis of 1739 community-dwelling elderly and 1442 caregivers registered in the Nagoya Longitudinal Study for Frail Elderly. Data included the clients' demographic characteristics, basic activities of daily living, comorbidities, and use of home care services, including the day-care, visiting nurse, and home-help services, as well as caregivers' demographic characteristics and care burden. Analysis of long-term care placement over 36 month was conducted using Kaplan–Meier curves and multivariate Cox proportional hazards models.

Results: Among the 1739 participants, 217 were institutionalized at long-term care facilities during the 36-month follow-up. Multivariate Cox regression models, adjusted for potential confounders, showed that day-care service use was significantly associated with an elevated risk for long-term care placement within the 36-month follow-up period. Participants using a day-care service two or more times/week had significantly higher relative hazard ratios than participants not using such a service.

Conclusion: The results highlight the need for effective measures to reduce the long-term care placement of day-care service users. Policy makers and practitioners must consider implementing multidimensional support programs to reduce the caregivers' willingness to consider long-term care placement. **Geriatr Gerontol Int 2012; 12: 322–329.**

Keywords: community, day-care service, elderly, long-term care placement, nursing home.

Introduction

Japan introduced a universal-coverage long-term care insurance (LTCI) program in April 2000.[1,2] This program brought a radical change from traditional, family-based care toward elderly care involving socialization and the integration of medical care and welfare

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Correspondence: Dr Masafumi Kuzuya MD PhD, Department of Community Healthcare & Geriatrics, Nagoya University Graduate School of Medicine, 65 Tusruma-cho, Showa-ku, Nagoya 466-8550, Japan. Email: kuzuya@med.nagoya-u.ac.jp