ピー 1998;16:164—167.
5) 下方浩史：加齢研究の方法—横断的研究と縦断的研究. 新老年学（折茂 肇編），東京大学出版会，東京，1999, p281—290.
6) 下方浩史，安藤富士子：健康科学における縦断加齢研究. 健康支援 1999;1:11—19.
7) Shimokata H, Ando F, Niino N: A new comprehensive study on aging-the National Institute for Longevity Sciences. Longitudinal Study of Aging (NILS-LSA). J Epidemiol 2000;10:S1—S9.
8) 下方浩史：長期縦断研究の目指すもの. Geriatric Medicine 1998;36:21—26.
9) 下方浩史，安藤富士子，新野直明：老化に関する長期縦断疫学研究. Advances in Aging and Health Research 1998, 長寿科学振興財団，東京，1999, p59—69.
10) Funakoshi A, Miyasaka K, Matsumoto H, Yamamori S, Takiguchi S, Shimokata H, et al.: Gene structure of human cholecystokinin (CCK) type-A receptor: Body fat content is related to CCK type A receptor gene promoter polymorphism. FEBS Lett 2000;466:264—266.
11) Yamada Y, Ando F, Niino N, Shimokata H: Transforming Growth Factor-betal Gene Polymorphism and Bone Mineral Density. JAMA 2001;285:167—168.

Abstract

Trends Geriatric Disease Research Evaluated by Long-term Longitudinal Study

Hiroshi Shimokata and Fujiko Ando

The number of patients with geriatric diseases will rapidly increase in our aging society. Geriatric diseases tend to progress chronically and disturb the daily activity of the elderly patients. Care for the elderly patients requires a great deal of manpower. The prevention and treatment of geriatric disease are urgent issues that must be addressed. A comprehensive longitudinal study of aging and geriatric disease was started at the National Institute for Longevity Sciences (NILS) in 1997. The participants of the NILS longitudinal study of aging (NILS-LSA) were 2,267 men and women from a local community population. The participants are examined at the NILS and followed up every two years. An outline of the system and examinations of the NILS-LSA is shown. The latest results from the NILS-LSA research including geriatric disease-related genotypes and risk factors for mild cognitive impairment (MCI) are also presented.
Key words: *Longitudinal study, Geriatric disease, genotype, Life-style, Cognitive impairment*
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Department of Epidemiology, National Institute for Longevity Sciences

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中高年者における日常生活視力と矯正視力

野村　秀樹[*1]　浅野　和子　田辺　直樹[*2]　棚橋　尚子[*3]
安藤富士子[*4]　新野　直明　下方　浩史　三宅　養三[*5]

*1 国立療養所中部病院眼科　*2 東海中央病院眼科　*3 中部労災病院眼科
*4 国立長寿医療研究センター疫学研究部　*5 名古屋大学医学部眼科学教室

要約　40歳以上の一般住民2,263名について，日常生活視力と5m矯正視力を測定した。日常生活視力は，通常使用している遠用眼鏡での視力と定義した。日常生活視力，矯正視力ともに高年齢群ほど低視力の割合が多かった（$p<0.001$）。日常生活視力が0.5未満の頻度は，40歳台8.6%，50歳台6.2%，60歳台7.5%，70歳台16.0%であり，矯正視力では，40歳台0%，50歳台0.5%，60歳台1.2%，70歳台5.6%であった。日常生活視力が0.5未満で矯正視力が0.5以上である頻度は，全体の7.7%であり，50・60歳台に比べ，70歳台で有意に多かった（$p<0.05$）。高齢者では適切な屈折矯正により日常の視力が改善される可能性があることを示す所見である。

Presenting and best-corrected visual acuity in Japanese over forty years of age

Hideki Nomura[*1]　Kazuko Asano　Naoki Tanabe[*2]　Naoko Tanahashi[*3]
Fujiko Ando[*4]　Naoakira Niino　Hiroshi Shimokata　Yozo Miyake[*5]

*1 Dept of Ophthalmol, Chubu National Hosp　*2 Dept of Ophthalmol, Tokai Central Hosp
*3 Dept of Ophthalmol, Chubu Rosai Hosp　*4 Dept of Epidemiol, National Institute for Longevity Sciences
*5 Dept of Ophthalmol, Nagoya Univ Sch of Med

Abstract. We evaluated the presenting and best-corrected visual acuity in 2,263 persons in the general community over forty years of age. The presenting visual acuity was defined as that measured by eyeglasses currently in use. The elder group had a higher incidence of impaired presenting and corrected visual acuity ($p<0.001$). The incidence of presenting visual acuity of less than 0.5 was 8.6% in the fifth decade, 6.2% in the sixth, 7.5% in the seventh, and 16.0% in the eighth. That of best-corrected visual acuity was 0% in the fifth decade, 0.5% in the sixth, 1.2% in the seventh, and 5.6% in the eighth. The incidence of best-corrected visual acuity of 0.5 or over among persons with presenting visual acuity of less than 0.5 was 7.7% in the whole series. This incidence was significantly higher in persons in the eighth decade than in those in the sixth and seventh ($p<0.05$). The findings show that presenting visual acuity may improve in elderly persons with the use of suitable eyeglasses.

Rinsho Ganka (Jpn J Clin Ophthalmol) 56(3)：293-296, 2002

緒言

人口の高齢化に伴い，わが国においては視覚障害を有する高齢者数も増加している[1]。視覚障害の主な原因疾患は糖尿病網膜症，緑内障などである[2]。これまでの報告では，主に疾患との関連を明らかにするために，矯正視力値を用いて視力障害が検討されてきた。しかし，日常生活視力もまたactivities of daily living（ADL）やquality of life（QOL）に大きな影響を与えると考えられる。海外では日常生活視力が低い場合に，その原因として屈折矯正の不足が多いことが報告されている[3~5]。今回，一般地域住民を対象に日常生活視力と矯正視力を測定し，年齢群別に視力の分布を

別刷請求先：野村秀樹（のむら・ひでき）〒474-8511 大府市森岡町源吾36-3　国立療養所中部病院眼科
Reprint requests to：Hideki Nomura　Department of Ophthalmology, Chubu National Hospital. 36-3 Gengo Morioka-cho Obu-shi, 474-8511 JAPAN

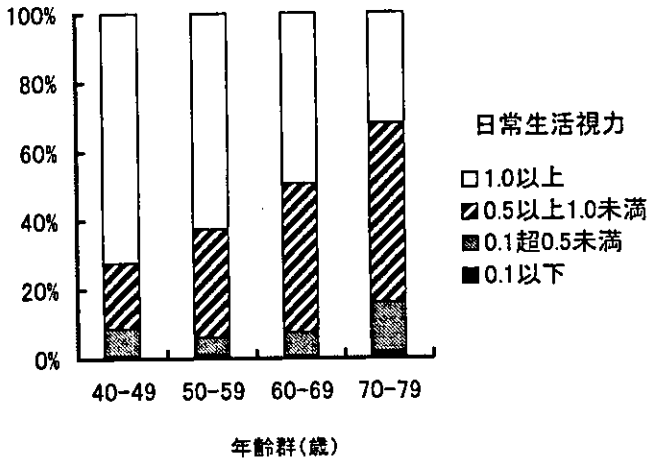

図 1　日常生活視力の年齢群別分布
日常生活視力は高年齢群ほど低視力の割合が多い有意な傾向がみられた（Cochran-Mantel-Haenszel：$p<0.001$）。

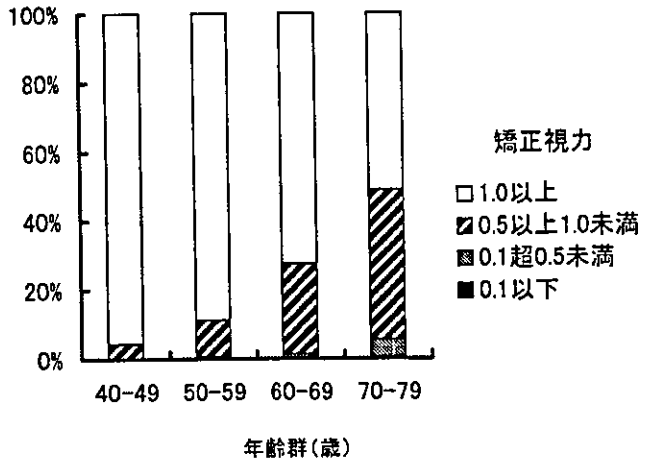

図 2　矯正視力の年齢群別分布
矯正視力は高年齢群ほど低視力の割合が多い有意な傾向がみられた（Cochran-Mantel-Haenszel：$p<0.001$）。

検討した。

方法

対象は，国立長寿医療研究センターにおける老化に関する長期縦断疫学調査（National Institute for Longevity Sciences-longitudinal study of aging：以下，NILS-LSA）[6,7]の第1回目調査（1997年11月から2000年4月まで）に参加した2,267名のうち，日常生活視力検査および矯正視力検査を施行した2,263名（男性1,134名，女性1,129名，年齢40～79歳）である。NILS-LSAの対象者は，愛知県大府市および東浦町における40歳から79歳までの在住者を性・年齢別に層化し，無作為抽出法により選ばれた一般地域住民である。

調査は，すべての対象者から文書によるインフォームドコンセントを得た後，国立長寿医療研究センター内の疫学調査センターで行われた。

視力検査は日本眼科医会の指針[8]に従い，検査距離は5mとした。はじめに日常生活視力を測定した。今回の研究では，日常生活で使用している遠見用眼鏡を装用して測定した視力値を，日常生活視力として定義した。日常生活において遠見用眼鏡を使用していない場合は，裸眼視力を日常生活視力とした。つぎにオートレフラクトメータ（ニデックARK700A）により得られた屈折異常値を参考に，自覚的に最良となる矯正視力を測定した。

分析には，日常生活視力，矯正視力それぞれにつき各対象者の左右眼で，よいほうの視力値を用いた。対象者を10歳ごとの年齢群別に4群に分け，視力の基準値を0.1，0.5，1.0として視力の分布を算出し，Cochran-Mantel-Haenszel法により，日常生活視力および矯正視力と年齢群との関係を検討した。また，日常生活視力が0.5未満で，適切な屈折矯正により矯正視力が0.5以上となる場合を視力障害改善群とし，その頻度を年齢群別に算出しχ^2検定により年齢群差を検討した。また，視力障害改善群において，矯正視力がよいほうの眼における屈折異常の球面等価値および乱視度数を，オートレフラクトメータの値から算出し，その分布と年齢群との関係をCochran-Mantel-Haenszel法により検討した。矯正視力が両眼ともに同じ場合には，右眼の屈折値を採用した。年齢群別の対象者数は，40歳台569名，50歳台567名，60歳台570名，70歳台557名である。

結果

日常生活視力検査結果を図1に示す。日常生活視力の分布（0.1以下，0.1を超え0.5未満，0.5以上1.0未満，1.0以上）は，40歳台0.9%，7.7%，19.0%，72.4%，50歳台1.2%，4.9%，31.2%，62.6%，60歳台0.7%，6.8%，43.0%，49.5%，70歳台2.0%，14.0%，42.1%，32.0%であった。同様に矯正視力の分布は，40歳台0.0%，0.0%，4.4%，95.6%，50歳台0.2%，0.4%，10.8%，88.7%，60歳台0.2%，1.1%，26.1%，72.6%，70歳台0.4%，5.2%，43.3%，51.2%であった（図2）。日常生活視力および矯正視力ともに，高年齢群ほど低視力の割合が多い有意な傾向がみられた（Cochran-

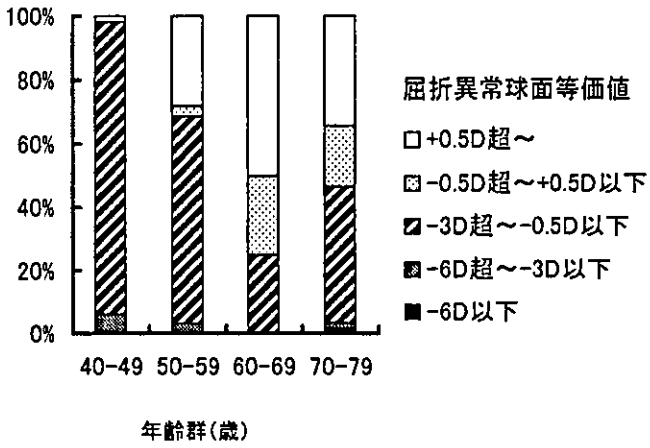

図 3　視力改善群（日常生活視力 0.5 未満かつ矯正視力 0.5 以上）における屈折度球面等価値の年齢群別分布
高年齢群で遠視および正視の割合が多い有意な傾向がみられた（Cochran-Mantel-Haenszel：$p<0.001$）。

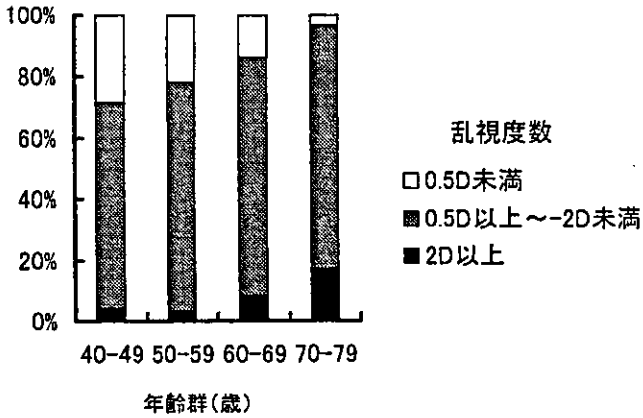

図 4　視力改善群（日常生活視力 0.5 未満かつ矯正視力 0.5 以上）における乱視の年齢群別分布
高年齢群でより強い乱視の割合が多い有意な傾向がみられた（Cochran-Mantel-Haenszel：$p<0.001$）。

Mantel-Haenszel：$p<0.001$）。

視力障害改善群は全体で 175 名（7.7%）であった。年齢群別では 40 歳台で 49 名（8.6% [95%信頼区間：7.0～10.4%]），50 歳台で 32 名（5.6% [3.7～7.5%]），60 歳台で 36 名（6.3% [4.9～7.7%]），70 歳台で 58 名（10.4% [8.6～12.2%]）であった。70 歳台における視力改善群の割合は，50 歳台および 60 歳台に比較して有意に多かった（χ^2 検定：$p=0.003$，$p=0.013$）。70 歳台と 40 歳台とでは有意な差を認めず，また 70 歳台以外の 3 群間にも，有意な差を認めなかった。視力障害改善群の屈折球面等価値および乱視度数の分布を図 3，4 に示す。球面等価値に関して，40 歳台では 1 名を除き全員が軽度もしくは中等度近視であり，50 歳台でも近視の割合が 7 割近くを占めた。一方，60 歳台および 70 歳台では近視の割合は半数以下であり，高年齢群で遠視および正視の割合が多い有意な傾向を認めた（Cochran-Mantel-Haenszel：$p<0.001$）。また，乱視に関しても，高年齢群でより強い乱視の割合が多い有意な傾向を認めた（Cochran-Mantel-Haenszel：$p=0.005$）。

考按

今日まで，わが国において，中高年者における視力に関する疫学調査は少ない。これまでの報告の大半は，対象者が施設入居者[9,10]や，眼科外来患者の一部[11]であり，一般地域住民を対象とした視力に関する疫学調査の結果は，ほとんど報告されていない。また，臨床的研究においても日常生活視力を用いて検討することは稀である。しかし，ADL や QOL と視力との関連を検討する場合，今回定義したような日常生活視力の影響が，矯正視力の影響を上回る可能性があると考えられる。実際に，筆者らが行っている転倒に関する調査では，日常生活視力と転倒との有意な関係が示されている[12]。

今回の検討の結果，適切な屈折矯正を行うことにより日常生活視力が 0.5 未満から 0.5 以上へ改善できる割合は 70 歳台で 10.4%であり，50・60 歳台よりも有意に多かった。一方，70 歳台と 40 歳台とでは有意差がなかった。40 歳台では屈折矯正に余地のある対象者の屈折異常は軽度近視が多く，むしろ近見に関しては有利であり，自ら低矯正の状態を選択している可能性があるためと考えられる。70 歳台で屈折矯正に余地のある場合は，近見に関しても不利である遠視や乱視の可能性が高い。高齢者では運転免許証の更新に伴う検眼など，視力を測定する機会も少なくなるため，無意識に放置している場合も少なくないと推測される。

これまでの代表的な中高年者における矯正視力調査として，市川の報告[11]がある。これは眼科外来患者のうちで視力障害を主訴とせず，少なくとも瞳孔領の水晶体に混濁のない者を対象としている。それによると，平均矯正視力は 45 歳から 75 歳までほぼ直線的に下降し，75 歳を過ぎると視力はさらに加速度的に低下する。矯正視力 1.0 以上の割合は 40 歳で 90%以上，50 歳で約 80%，60

歳で70%程度，70歳で約半数，80歳で約10%と推定される。今回の研究では矯正視力1.0以上の割合が，40歳台95.6%，50歳台88.7%，60歳台72.6%，70歳台51.2%であり，市川の報告よりもやや良好な結果と思われるが，その理由の一部に対象者の選択方法の差が考えられる。

本研究では，対象者自身の所有する眼鏡を使用した遠見視力を，日常生活視力として定義した。しかし日常生活における視環境は，焦点が遠方から近距離までさまざまに変化し，コントラストや色・照度もさまざまである。今後は多様な視環境に対応した日常生活視力の評価法の検討が必要になると思われる。

NILS-LSAは調査センターに来所可能な人を対象としているため，施設入居者や介護の必要な高齢者は参加困難である。それにより対象者に若干の偏りが生じるため，今回の結果が日本人全体の視力を示しているとはいえない。しかし，日常生活視力と矯正視力に関し，一般地域住民を対象とした大規模な疫学調査はほかに少なく，現在の日本人の視力を検討する上で有用なデータであろう。今回の結果から，高年齢群においてADLやQOLに影響を与える日常生活視力に関し，適切な屈折矯正が行われていない可能性があり，70歳台では約10人に1人の割合であった。今後は高齢者検診などにおいて視力検査を実施し，高齢者の良好な視力維持のための啓蒙を進める必要があると思われる。

文献

1) 中島　章：失明予防と眼遺伝．日眼会誌　86：1834-1858，1980
2) 中江公裕・小暮文雄・長屋幸郎・他：わが国における視覚障害の現況．厚生の指標　38：13-22，1991
3) Tielsch JM, Sommer A, Witt K et al：Blindness and visual impairment in an American urban population. The Baltimore Eye Survey. Arch Ophthalmol 108：286-290, 1990
4) Liou HL, McCarty CA, Jin CL et al：Prevalence and predictors of undercorrected refractive errors in the Victorian population. Am J Ophthalmol 127：590-596, 1999
5) Weih LM, vanNewkirk MR, McCarty CA et al：Age-specific causes of bilateral visual impairment. Arch Ophthalmol　118：264-269, 2000
6) Shimokata H, Ando F, Niino N：A new comprehensive study on aging-the National Institute for Longevity Sciences, longitudinal study of aging (NILS-LSA). J Epidemiol　10 (Suppl 1)：S1-S9, 2000
7) Nomura H, Tanabe N, Nagaya S et al：Eye examinations at the National Institute for Longevity Sciences-longitudinal study of aging：NILS-LSA. J Epidemiol　10 (Suppl 1)：S18-S25, 2000
8) 日本眼科医会学校保健部：視力検査の要点について．日本の眼科　69：1433-1435，1998
9) 大江健一：老年者の視力．眼科　13：445-448，1971
10) 戸張幾生：老人と眼疾患（その1）―老人の視力について―．日本の眼科　47：161-165，1976
11) 市川　宏：老化と眼の機能．臨眼　35：9-26，1981
12) Niino N, Nomura H, Kozakai R et al：Visual function and falls among community-dwelling elderly people. Gerontology　47 (suppl 1)：386, 2001

J Hum Genet (2002) 47:243–248

ORIGINAL ARTICLE

Yoshiji Yamada · Michiko Fujisawa · Fujiko Ando
Naoakira Niino · Masashi Tanaka · Hiroshi Shimokata

Association of a polymorphism of the transforming growth factor-β1 gene with blood pressure in Japanese individuals

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Abstract Transforming growth factor-β1 (TGF-β1) is an important regulator of blood pressure (BP) and vascular remodeling, and thus may contribute to the pathogenesis of hypertension. A T→C transition at nucleotide 869 of the *TGF-β1* gene results in a Leu→Pro substitution at amino acid 10 of the signal peptide. We have now examined the possible association of the 869T→C polymorphism of the *TGF-β1* gene with BP and the prevalence of hypertension in 2241 community-dwelling Japanese individuals (1126 men and 1115 women). TGF-β1 genotype was determined by an allele-specific polymerase chain reaction method. For women, both systolic and diastolic BP was significantly higher in individuals with the *CC* genotype than in those with the *TT* or *TC* genotype. No significant association between *TGF-β1* genotype and BP was detected in men. The frequency of the *CC* genotype was significantly higher in women with hypertension than in those with normal BP. These results suggest that the *TGF-β1* gene at chromosome 19q13.1 may be a candidate susceptibility locus for hypertension in Japanese women.

Key words Transforming growth factor-β1 · Gene polymorphism · Blood pressure · Hypertension · Population-based study

Introduction

The regulation of blood pressure (BP) involves both the integration of a variety of biological systems that control the structure and tone of the vasculature and the volume and composition of body fluid, as well as the adaptation of these systems to constantly changing physiological needs (Lalouel and Rohrwasser 2001). Hypertension is a complex multifactorial and polygenic disorder that is thought to result from an interaction between an individual's genetic background and various environmental factors (Lifton et al. 2001). Recent advances in genetic epidemiology have revealed that certain genetic variants, including polymorphisms in the genes encoding angiotensinogen (Jeunemaitre et al. 1992), the β3 subunit of G proteins (Siffert et al. 1998), and the β2-adrenergic receptor (Bray et al. 2000), increase the risk of hypertension.

Transforming growth factor-β (TGF-β) is the prototype of a large family of cytokines (Heldin et al. 1997). Three isoforms of TGF-β (TGF-β1, -β2, and -β3) have been identified in mammals, and these isoforms exhibit similar biological properties. TGF-β directly stimulates the synthesis of extracellular matrix proteins and inhibits matrix degradation (Roberts et al. 1992a). It may influence BP by stimulating both the production of endothelin-1 by vascular endothelial cells (Kurihara et al. 1989) and the release of renin from juxtaglomerular cells of the kidney (Antonipillai et al. 1993). Li et al. (1999) demonstrated a positive correlation between the circulating concentration of TGF-β1 and BP in humans. In addition, the upregulation of TGF-β1 expression was shown to be associated with cardiovascular and renal alterations in individuals with hypertension (August et al. 2000).

Several single-nucleotide polymorphisms (SNPs) have been detected in the TGF-β1 gene, including a 869T→C (Leu10Pro) transition at codon 10 and a 914G→C (Arg25Pro) transversion at codon 25 in the region encoding the signal peptide of this protein (Derynck et al. 1987; Cambien et al. 1996; Grainger et al. 1999). Cambien et al. (1996) showed that the 914G→C polymorphism was associated with hypertension, with the *C* allele reflecting a lower systolic pressure and a lower frequency of a history of hypertension. Suthanthiran et al. (2000) showed that the *C* allele of the 869T→C polymorphism was more frequent in African–Americans than in Caucasian Americans and was

Y. Yamada (✉) · M. Tanaka
Department of Gene Therapy, Gifu International Institute of Biotechnology and Institute of Applied Biochemistry, Yagi Memorial Park, 2193-128 Mitake, Mitake-cho, Kani-gun, Gifu 505-0116, Japan
Tel. +81-574-67-6616; Fax +81-574-67-6627
e-mail: yoyamada@giib.or.jp

M. Fujisawa · F. Ando · N. Niino · H. Shimokata
Department of Epidemiology, National Institute for Longevity Sciences, Aichi, Japan

associated with both a greater abundance of TGF-β1 mRNA in peripheral blood mononuclear cells and higher serum concentrations of the protein. Recently, Rivera et al. (2001) showed that the 869T→C polymorphism was associated with systolic BP measured at rest as well as at moderate and maximal exercise intensities in Caucasians.

Clarification of the role of TGF-β1 in the development of hypertension should be facilitated by characterization of the relations of genetic variants that may affect the production, secretion, or activity of this cytokine to BP in various ethnic groups. We have now studied the relation of the 869T→C polymorphism of the *TGF-β1* gene to both BP and the prevalence of hypertension in community-dwelling Japanese men and women.

Subjects and methods

Study population

The National Institute for Longevity Sciences–Longitudinal Study of Aging (NILS-LSA), a population-based prospective cohort study of aging and age-related diseases, was begun in 1997 (Shimokata et al. 2000). We have examined 2241 participants (1126 men and 1115 women) of the NILS-LSA, all of whom were community-dwelling individuals aged 40 to 79 years and randomly recruited from Obu City and regions close to NILS in Aichi Prefecture, Japan. A total of 1477 participants (746 men and 731 women) had normal BP (systolic BP of <140 mmHg and diastolic BP of <90 mmHg), and 754 individuals (377 men and 377 women) had hypertension (systolic BP of ≥140 mmHg or diastolic BP of ≥90 mmHg, or both) or had taken antihypertensive drugs; the remaining 10 subjects (3 men and 7 women) had borderline hypertension (hypertension and normal BP at the first and second measurements, respectively) and did not take antihypertensive medication. Individuals with congenital malformations of the heart or vessels, valvular heart disease, or renal or endocrinologic diseases that cause secondary hypertension were excluded from the study. BP was measured with subjects in the seated position according to the guidelines of the American Heart Association (Perloff et al. 1993). The study protocol was approved by the Committee on the Ethics of Human Research of National Chubu Hospital and the National Institute for Longevity Sciences, and written informed consent was obtained from each subject.

Genotyping of the *TGF-β1* gene polymorphism

Venous blood (7 ml) was collected from each subject into tubes containing 50 mmol/l ethylenediaminetetraacetate (disodium salt), and genomic DNA was isolated with an automated system (model NA-1000; Kurabo, Osaka, Japan). TGF-β1 genotype was determined by an allele-specific polymerase chain reaction (PCR)–based method, as previously described (Yamada et al. 1998, 2000; Yokota et al. 2000), with two sense primers (S1, 5′-CTCCGG GCTGCGGCTGCTGCT-3′; S2, 5′-CTCCGGGCTGCGG CTGCTGCC-3′) and one antisense primer (AS, 5′-GTTGTGGGTTTCCACCATTAG-3′). Amplification reactions were performed in a total volume of 25 μL containing 0.25 μg of genomic DNA, 10 pmol of each primer, 0.2 mmol/l each of deoxycytidine triphosphate, deoxythymidine triphosphate, deoxyguanosine triphosphate, and deoxyadenosine triphosphate, 0.5 U of *Taq* DNA polymerase (Amplitaq Gold; Perkin Elmer, Foster City, CA, USA), 50 mmol/ KCl, 1.5 mmol/l $MgCl_2$, 1.5% dimethyl sulfoxide, 0.01% gelatin, and 10 mmol/l Tris-HCl (pH 8.3). The thermocycling procedure consisted of an initial denaturation at 94°C for 5 min; 35 cycles of denaturation (94°C for 30 s), annealing (60°C for 30 s), and extension (72°C for 30 s); and a final extension at 72°C for 5 min. The PCR products were analyzed by 1% agarose gel electrophoresis and visualized by ethidium bromide staining. The expected size of the specific amplification product was 346 bp.

Statistical analysis

Data are presented as means ± SD. BP and other quantitative data were compared among TGF-β1 genotypes by one-way analysis of variance and the Tukey-Kramer post hoc test. BP values were analyzed with adjustment for age, body mass index (BMI), smoking status, alcohol consumption, and salt intake by the least squares method in a general linear model. BP values were also subjected to analysis of covariance and the Tukey-Kramer test in a general linear model. Qualitative data were compared by the chi-square test. Allele frequencies were estimated by the gene counting method, and the significance of deviation from Hardy-Weinberg equilibrium was analyzed by the chi-square test. A P value of <0.05 was considered statistically significant.

Results

We examined the effect of TGF-β1 genotype on BP in a total of 1758 subjects (876 men and 882 women), consisting of 1477 individuals with normal BP and 281 untreated individuals (130 men and 151 women) with borderline or mild hypertension (Tables 1 to 3). The characteristics of these subjects are shown in Table 1. The distribution of TGF-β1 genotype was in Hardy-Weinberg equilibrium both in men and in women. For women, the fasting blood sugar concentration was significantly greater in individuals with the *CC* genotype than in those with the *TC* genotype. BMI and serum asparate aminotransferase activity were lower and the serum concentration of creatinine was higher in women with the *TC* genotype than in those with the *TT* genotype. For men, the serum concentrations of total cholesterol and triglycerides were lower in individuals with the *CC* genotype than in those with the *TT* or *TC* genotype. BMI was greater in men with the *TC* genotype than in those with the *TT* genotype.

For women, both systolic and diastolic BP values were significantly greater in individuals with the *CC* genotype

Table 1. Characteristics of 1758 subjects according to TGF-β1 genotype

Characteristic	Men (n = 876)			Women (n = 882)		
	TT	*TC*	*CC*	*TT*	*TC*	*CC*
No. of subjects	238 (27.2%)	441 (50.3%)	197 (22.5%)	266 (30.2%)	465 (52.7%)	151 (17.1%)
Age (years)	55.7 ± 10.8	57.4 ± 12.6	57.6 ± 11.2	57.3 ± 11.4	56.4 ± 10.8	55.3 ± 12.3
BMI (kg/m²)	22.4 ± 3.1	23.0 ± 2.1*	22.7 ± 2.8	23.0 ± 3.3	22.4 ± 2.2*	22.9 ± 3.7
Smoking (pack-year)	23.6 ± 20.0	25.3 ± 18.9	24.3 ± 21.0	1.8 ± 4.9	1.3 ± 6.5	1.8 ± 6.2
Alcohol consumption (g/day)	29.1 ± 37.0	26.0 ± 37.8	23.3 ± 37.8	6.0 ± 17.9	4.7 ± 17.3	5.8 ± 19.7
Salt intake (g/day)	13.3 ± 4.6	13.1 ± 4.2	12.8 ± 4.2	11.3 ± 3.3	11.2 ± 4.3	11.5 ± 3.7
Blood examination						
Hemoglobin (g/dL)	15.6 ± 1.5	15.6 ± 2.1	15.4 ± 1.4	13.6 ± 1.6	13.6 ± 2.2	13.7 ± 1.2
Asparate aminotransferase (IU/L)	26.5 ± 15.4	27.6 ± 16.8	26.7 ± 16.8	25.5 ± 13.0	23.2 ± 13.0‡	23.8 ± 12.3
Alanine aminotransferase (IU/L)	27.9 ± 20.0	27.7 ± 21.0	26.3 ± 21.0	22.4 ± 16.3	19.6 ± 17.3	20.7 ± 17.2
γ-Glutamyl transferase (IU/L)	56.2 ± 70.8	61.5 ± 71.4	57.2 ± 72.8	29.8 ± 24.5	26.7 ± 25.9	29.7 ± 24.6
Total cholesterol (mg/dL)	215 ± 31	212 ± 21	206 ± 28‡	228 ± 33	225 ± 43	227 ± 37
HDL-cholesterol (mg/dL)	57.4 ± 13.9	58.2 ± 12.6	56.2 ± 14.0	66.0 ± 14.7	66.9 ± 15.1	64.5 ± 14.8
Triglycerides (mg/dL)	127 ± 77	139 ± 84	120 ± 84‡	108 ± 49	105 ± 65	113 ± 62
Fasting blood sugar (mg/dL)	104 ± 15	103 ± 21	103 ± 14	99 ± 16	98 ± 22	102 ± 12§
Hemoglobin A_{1c} (%)	5.29 ± 0.62	5.36 ± 0.63	5.29 ± 0.70	5.13 ± 0.49	5.13 ± 0.43	5.23 ± 0.49
Blood urea nitrogen (mg/dL)	16.3 ± 13.9	16.3 ± 14.7	14.6 ± 25.2	13.7 ± 11.4	15.5 ± 13.0	14.4 ± 11.1
Creatinine (mg/dL)	1.00 ± 0.31	1.03 ± 0.21	1.00 ± 0.28	0.76 ± 1.63	0.78 ± 2.16*	0.77 ± 0.12
Sodium (mEq/L)	143 ± 5	143 ± 6	144 ± 9	143 ± 6	142 ± 6	143 ± 5
Potassium (mEq/L)	4.14 ± 1.23	4.20 ± 1.26	4.28 ± 2.24	4.07 ± 1.14	4.22 ± 1.30	4.10 ± 0.98
Calcium (mg/dL)	9.27 ± 0.31	9.27 ± 0.21	9.26 ± 0.28	9.25 ± 0.33	9.27 ± 0.22	9.26 ± 0.37
Magnesium (mg/dL)	2.20 ± 0.15	2.20 ± 0.21	2.21 ± 0.14	2.17 ± 0.16	2.19 ± 0.22	2.17 ± 0.12

Data are means ± SD
BMI, Body mass index
* P = 0.03 versus *TT*, † P = 0.04 versus *TT*, ‡ P = 0.01 versus *TT*, § P = 0.02 versus *TC*

Table 2. Systolic and diastolic BP in 1758 subjects according to TGF-β1 genotype

	Men (n = 876)			Women (n = 882)		
	TT (n = 238)	*TC* (n = 441)	*CC* (n = 197)	*TT* (n = 266)	*TC* (n = 465)	*CC* (n = 151)
Systolic BP (mmHg)	120.0 ± 16.9	121.0 ± 16.8	122.0 ± 18.2	119.7 ± 19.6	118.9 ± 19.4	124.7 ± 18.5*
Diastolic BP (mmHg)	74.9 ± 10.8	75.5 ± 10.5	75.7 ± 11.2	72.3 ± 11.4	72.0 ± 10.8	75.6 ± 11.1†
Adjusted for age (years), BMI (kg/m²), smoking (pack-year), alcohol consumption (g/day), and salt intake (g/day)						
Systolic BP (mmHg)	121.1 ± 16.9	120.1 ± 16.8	122.0 ± 16.8	118.1 ± 17.9	119.0 ± 17.3	123.9 ± 18.5‡
Diastolic BP (mmHg)	75.1 ± 10.8	75.1 ± 10.5	75.9 ± 9.8	72.0 ± 11.4	72.2 ± 10.8	75.4 ± 11.1§

Data are means ± SD
BP, Blood pressure; BMI, body mass index
* P = 0.03 versus *TT*, P = 0.003 versus *TC*; † P = 0.02 versus *TT*, P = 0.001 versus *TC*; ‡ P = 0.006 versus *TT*, P = 0.015 versus *TC*; § P = 0.007 versus *TT*, P = 0.006 versus *TC*

Table 3. General linear model for analysis of factors that affect systolic and diastolic BP in 1758 subjects

	Men (n = 876)				Women (n = 882)			
	Systolic BP		Diastolic BP		Systolic BP		Diastolic BP	
	SRC	*P*	SRC	*P*	SRC	*P*	SRC	*P*
TGF-β1 genotype (*TT* = *TC* = 0, *CC* = 1)	0.038	0.273	0.034	0.318	0.103	0.002	0.113	<0.001
Age (years)	0.123	<0.001	0.035	0.331	0.246	<0.001	0.156	<0.001
BMI (kg/m²)	0.252	<0.001	0.273	<0.001	0.305	<0.001	0.300	<0.001
Smoking (pack-year)	−0.057	0.110	−0.051	0.150	−0.011	0.757	−0.012	0.728
Alcohol consumption (g/day)	0.159	<0.001	0.191	<0.001	0.014	0.681	0.020	0.562
Salt intake (g/day)	−0.064	0.074	−0.030	0.390	−0.026	0.437	−0.033	0.341

Data were subjected to analysis of covariance and the Tukey-Kramer test in a general linear model
BP, Blood pressure; SRC, standardized regression coefficient; BMI, body mass index

Table 4. Association of TGF-β1 genotype with the prevalence of hypertension in 1477 subjects with normal BP and 754 subjects with hypertension

	Men (n = 1123)		Women (n = 1108)	
	Normal (n = 746)	Hypertension (n = 377)	Normal (n = 731)	Hypertension (n = 377)
TGF-β1 genotype				
TT	210 (28.2%)	94 (24.9%)	226 (30.9%)	114 (30.2%)
TC	372 (49.9%)	203 (53.8%)	392 (53.6%)	184 (48.8%)
TT + TC	582 (78.0%)	297 (78.8%)	618 (84.5%)	298 (79.0%)
CC	164 (22.0%)	80 (21.2%)	113 (15.5%)	79 (21.0%)
P (*TT + TC* versus *CC*)		0.770		0.017

Normal, systolic BP of <140 mmHg and diastolic BP of <90 mmHg; hypertension, systolic BP of ≥140 mmHg and/or diastolic BP of ≥90 mmHg
BP, Blood pressure

than in those with the *TT* genotype and those with the *TC* genotype (Table 2). Given that aging, obesity, smoking, excessive alcohol consumption, and increased salt intake are conventional risk factors for hypertension, we analyzed BP values after adjustment for age, BMI, smoking status, alcohol consumption, and salt intake by the least squares method. The association of TGF-β1 genotype with BP did not change after adjustment for these factors. For men, however, no difference in systolic or diastolic BP was detected among TGF-β1 genotypes.

Analysis with a general linear model revealed that TGF-β1 genotype, age, and BMI significantly influenced both systolic and diastolic BP in women (Table 3). In men, BMI and alcohol consumption significantly affected both systolic and diastolic BP, with age affecting only systolic BP.

To clarify further the effect of the *C* allele on BP, we compared the distribution of TGF-β1 genotypes between 1477 individuals with normal BP and 754 individuals with hypertension (Table 4). The frequency of the *CC* genotype was significantly higher in subjects with hypertension than in those with normal BP for women. In contrast, the *C* allele was not associated with the prevalence of hypertension in men.

Discussion

TGF-β1 stimulates the expression of endothelin-1 (Kurihara et al. 1989) and inhibits the production of nitric oxide (Roberts et al. 1992b) in vascular endothelial cells, which would be expected to result in an increase in BP. It also stimulates renin release from juxtaglomerular cells (Antonipillai et al. 1993), which likely results in an increased generation of angiotensin II and a consequent increase in BP. In addition, TGF-β1 promotes the deposition of extracellular matrix proteins on vessel walls, thereby influencing their stiffness and compliance (O'Callaghan and Williams 2000). Thus, TGF-β1 appears to play an important role in the regulation of BP and the development of hypertension. We have now examined the association of variants of the *TGF-β1* gene with both BP and the prevalence of hypertension in community-dwelling Japanese. Our results show that the 869T→C polymorphism of the *TGF-β1* gene is associated with BP in women and that the *CC* genotype is more prevalent in women with hypertension than in those with normal BP.

We failed to detect an association of the 869T→C polymorphism of the *TGF-β1* gene with BP or with the prevalence of hypertension in Japanese men. We previously showed that the *T* allele of this polymorphism is a risk factor for predisposition to myocardial infarction in Japanese men but not in women (Yokota et al. 2000). The reason for these gender-dependent differences in the association of TGF-β1 genotype with hypertension or with myocardial infarction remains unclear.

In an association study of hypertension and myocardial infarction with SNPs in the *TGF-β1* gene, Cambien et al. (1996) showed that the 914G→C (Arg25Pro) polymorphism was associated with the prevalence of hypertension among populations in both France and Northern Ireland. The presence of the *C* (Pro25) allele was associated with lower systolic BP in the control group. Li et al. (1999) also showed that homozygosity for the *G* (Arg25) allele of this polymorphism was more frequent in individuals with hypertension than in normotensive controls in the United States. However, we were unable to detect this polymorphism in 102 Japanese subjects (data not shown). In contrast to our results, Cambien et al. (1996) did not detect an association of the 869T→C polymorphism with either BP or the prevalence of hypertension in their European populations. The distribution of the 869T→C polymorphism in European male control subjects [*TT*, 225 (35.8%); *TC*, 294 (47.2%); *CC*, 107 (17.0%)] (Cambien et al. 1996) was significantly different from that in men [*TT*, 238 (27.2%); *TC*, 441 (50.3%); *CC*, 197 (22.5%); P = 0.0006, chi-square test] and marginally different from that in women [*TT*, 266 (30.2%); *TC*, 465 (52.7%); *CC*, 151 (17.1%); P = 0.056] of our population. Thus, the prevalence of TGF-β1 polymorphisms may differ among races.

Suthanthiran et al. (2000) showed that the distribution of 869T→C genotypes in African-Americans differed significantly from that in Caucasian Americans, in that there was

an excess of the *C* allele in the former when compared with the latter. These researchers also showed that the abundance of TGF-β1 mRNA in peripheral blood mononuclear cells and the serum concentration of TGF-β1 were both greater in individuals with the *CC* or *TC* genotype than in those with the *TT* genotype, consistent with our previous observation that the serum concentration of TGF-β1 increases with the number of *C* alleles (Yamada et al. 1998, 2000; Yokota et al. 2000). Although Suthanthiran et al. (2000) detected an association of the abundance of TGF-β1 mRNA in peripheral blood mononuclear cells and of the serum concentration of TGF-β1 with hypertension, they failed to demonstrate a direct association of the 869T→C polymorphism with the prevalence of hypertension. Rivera et al. (2001) recently showed that the 869T→C polymorphism was associated with systolic BP in Caucasians; the systolic BP of homozygotes for the *T* allele was thus significantly lower than that of homozygotes for the *C* allele, both at rest and at moderate or maximal exercise intensities. In contrast to the observation of Suthanthiran et al. (2000), these researchers observed no difference in allele frequencies between black and white subjects (Rivera et al. 2001). Our results show that the 869T→C polymorphism of the *TGF-β1* gene is associated with BP in Japanese women and that the *CC* genotype is more prevalent among women with hypertension, although the contribution of this polymorphism to hypertension appears to be relatively small.

TGF-β1 is synthesized in a latent form composed of 390 amino acids, with the active protein consisting of two identical disulfide-linked polypeptide chains corresponding to the 112 carboxyl-terminal residues of the precursor (Derynck et al. 1985). The Leu10Pro (869T→C) polymorphism is located in the signal peptide sequence of TGF-β1, which is thought to target newly synthesized protein to the endoplasmic reticulum (Verner and Schatz 1988). We previously showed that the serum concentration of TGF-β1 increases according to the rank order of 869T→C genotypes *TT* < *TC* < *CC* (Yamada et al. 1998, 2000; Yokota et al. 2000). This association suggests that the Leu10Pro substitution may affect the function of the signal peptide, probably influencing intracellular trafficking or export efficiency of the protein. Although the serum concentration of TGF-β1 was not measured in the present study population, our observation that women with the *CC* genotype showed the highest BP is consistent with the previous observation that BP positively correlates with the serum concentration of TGF-β1 (Li et al. 1999).

It is possible that the 869T→C polymorphism of the *TGF-β1* gene is in linkage disequilibrium with some other gene polymorphism that is actually responsible for the development of hypertension. Our results, however, suggest that the *TGF-β1* gene located at chromosome 19q13.1 is a candidate susceptibility locus for hypertension in Japanese women.

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References

Antonipillai I, Le TH, Soceneantu L, Horton R (1993) Transforming growth factor-β is a renin secretagogue at picomolar concentrations. Am J Physiol 265:F531–F541

August P, Leventhal B, Suthanthiran M (2000) Hypertension-induced organ damage in African Americans: transforming growth factor-β1 excess as a mechanism for increased prevalence. Curr Hypertens Rep 2:184–191

Bray MS, Krushkal J, Li L, Ferrell R, Kardia S, Sing CF, Turner ST, Boerwinkle E (2000) Positional genomic analysis identifies the β2-adrenergic receptor gene as a susceptibility locus for human hypertension. Circulation 101:2877–2882

Cambien F, Ricard S, Troesch A, Mallet C, Générénaz L, Evans A, Arveiler D, Luc G, Ruidavets J-B, Poirier O (1996) Polymorphisms of the transforming growth factor-β1 gene in relation to myocardial infarction and blood pressure. Hypertension 28:881–887

Derynck R, Jarrett JA, Chen EY, Eaton DH, Bell JR, Assoian RK, Roberts AB, Sporn MB, Goeddel DV (1985) Human transforming growth factor-β complementary DNA sequence and expression in normal and transformed cells. Nature 316:701–705

Derynck R, Rhee L, Chen EY, van Tilburg A (1987) Intron-exon structure of the human transforming growth factor-β precursor gene. Nucleic Acids Res 15:3188–3189

Grainger DJ, Heathcote K, Chiano M, Snieder H, Kemp PR, Matcalfe JC, Carter ND, Spector TD (1999) Genetic control of the circulating concentration of transforming growth factor type β1. Hum Mol Genet 8:93–97

Heldin C-H, Miyazono K, ten Dijke P (1997) TGF-β signalling from cell membrane to nucleus through SMAD proteins. Nature 390:465–471

Jeunemaitre X, Soubrier F, Kotelevtsev YV, Lifton RP, Williams CS, Charru A, Hunt SC, Hopkins PN, Williams RR, Lalouel J-M, Corvol P (1992) Molecular basis of human hypertension: role of angiotensinogen. Cell 71:169–180

Kurihara H, Yoshizumi M, Sugiyama T, Takaku F, Yanagisawa M, Masaki T, Hamaoki M, Kato H, Yazaki Y (1989) Transforming growth factor-β stimulates the expression of endothelin mRNA by vascular endothelial cells. Biochem Biophys Res Commun 159:1435–1440

Lalouel J-M, Rohrwasser A (2001) Development of genetic hypotheses in essential hypertension. J Hum Genet 46:299–306

Li B, Khanna A, Sharma V, Singh T, Suthanthiran M, August P (1999) TGF-β1 DNA polymorphisms, protein levels, and blood pressure. Hypertension 33:271–275

Lifton RP, Gharavi AG, Geller DS (2001) Molecular mechanisms of hypertension. Cell 104:545–556

O'Callaghan CJ, Williams B (2000) Mechanical strain-induced extracellular matrix production by human vascular smooth muscle cells: role of TGF-β1. Hypertension 36:319–324

Perloff D, Grim C, Flack J, Frohlich ED, Hill M, McDonald M, Morgenstern BZ (1993) Human blood pressure determination by sphygmomanometry. Circulation 88:2460–2470

Rivera MA, Echegaray M, Rankinen T, Pérusse L, Rice T, Gagnon J, Leon AS, Skinner JS, Wilmore JH, Rao DC, Bouchard C (2001) TGF-β1 gene-race interactions for resting and exercise blood pressure in the HERITAGE Family Study. J Appl Physiol 91:1808–1813

Roberts AB, McCune BK, Sporn MB (1992a) TGF-β: regulation of extracellular matrix. Kidney Int 41:557–559

Roberts AB, Vodovotz Y, Roche NS, Sporn MB, Nathan CF (1992b) Role of nitric oxide in antagonistic effects of transforming growth factor-β and interleukin-1β on the beating rate of cultured cardiac myocytes. Mol Endocrinol 6:1921–1930

Shimokata H, Ando F, Niino N (2000) A new comprehensive study on aging — the National Institute for Longevity Sciences, Longitudinal Study of Aging (NILS-LSA). J Epidemiol 10:S1–S9

Siffert W, Rosskorpf D, Siffert G, Busch S, Moritz A, Erbel R, Sharma AM, Ritz E, Wichmann H-E, Jakobs KH, Horsthemke B (1998) Association of a human G-protein β3 subunit variant with hypertension. Nat Genet 18:45–48

Suthanthiran M, Li B, Song JO, Ding R, Sharma VK, Schwartz JE, August P (2000) Transforming growth factor-β1 hyperexpression in

African-American hypertensives: a novel mediator of hypertension and/or target organ damage. Proc Natl Acad Sci USA 97:3479–3484

Verner K, Schatz G (1988) Protein translocation across membranes. Science 241:1307–1313

Yamada Y, Miyauchi A, Goto J, Takagi Y, Okuizumi Y, Kanematsu M, Hase M, Takai H, Harada A, Ikeda K (1998) Association of a polymorphism of the transforming growth factor β1 gene with genetic susceptibility to osteoporosis in Japanese women. J Bone Miner Res 13:1569–1576

Yamada Y, Okuizumi H, Miyauchi A, Takagi Y, Ikeda K, Harada A (2000) Association of transforming growth factor β1 genotype with spinal osteophytosis in Japanese women. Arthritis Rheum 43:452–460

Yokota M, Ichihara S, Lin T-L, Nakashima N, Yamada Y (2000) Association of a T^{29}→C polymorphism of the transforming growth factor-β1 gene with genetic susceptibility to myocardial infarction in Japanese. Circulation 101:2783–2787

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Changes in serum lipid levels during a 10 year period in a large Japanese population
A cross-sectional and longitudinal study

Masafumi Kuzuya [a,*], Fujiko Ando [b], Akihisa Iguchi [a], Hiroshi Shimokata [b]

[a] *Department of Geriatrics, Nagoya University Graduate School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya 466-8550 Japan*
[b] *Department of Epidemiology, National Institute for longevity sciences, 36-3 Gengo, Morioka-cho, Obu-shi, Aich 474-8522, Japan*

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Abstract

To determine the recent secular trends in serum lipid levels and characterize their influence on the aging process, we examined a large cohort of Japanese cross-sectionally and longitudinally. The participants included 80331 Japanese men and women 20–79 years of age, who had received annual health examinations from 1989 to 1998. In cross-sectional analysis, an increase in total and LDL cholesterol as well as triglyceride levels was observed in the population during the period of 1989–1998. The longitudinal changes showed that total and LDL cholesterol increased with age in men between the birth cohorts of the 1920s and 1960s. In women, these cholesterol levels increased in the 1930s and younger cohorts. HDL cholesterol decreased in men of all birth cohorts. However, HDL cholesterol increased in women of the 1940s and younger cohorts. Triglyceride levels increased in men of the 1940s and younger cohorts but decreased in the 1930s and older. Triglyceride levels increased in women of the 1930s and younger. Longitudinal analysis also suggested a birth cohort effect except for the triglyceride level for women. These results suggest that Japanese serum lipid levels continue to increase and that there exist birth cohort effects regarding serum lipid levels in the Japanese population.

Keywords: Serum lipid; Cholesterol; Triglyceride; Cross-sectional study; Longitudinal study

1. Introduction

A number of studies have demonstrated that higher serum cholesterol levels are associated with an increase in subsequent morbidity and mortality due to coronary heart disease [1–3]. Since the 1970s, increasing awareness of dietary and other lifestyle determinants of serum lipid levels has led to recommendations to the general public in the US and many European countries [4,5]. In fact, a decline in serum cholesterol has been observed during past 30 years in these countries [6–8]. Parallel to changes in serum cholesterol levels, coronary heart disease mortality has also declined in these countries [9–11].

Due to the rapid westernization of the Japanese lifestyle, serum lipid levels have been reported to increase after 1960s [12–15]. However, recent trends in Japanese serum lipid levels are controversial. According to a survey of serum lipid levels which has been carried out by the members of the Japan Atherosclerosis Society every 10 years since 1960, no significant change was seen in either total cholesterol or triglyceride levels in the 10 years from 1980 to 1990, although a marked increase was observed in the periods from 1960 to 1980 [16]. However, other surveys observed that Japanese serum cholesterol levels still increased from 1980 to 1990 [17,18]. Although an important issue is whether these trends have persisted into the 1990s, unfortunately no studies examining the recent trend of serum lipid profile have been performed in a large Japanese population after 1990. In addition, almost no study has examined the longitudinal changes in the recent Japanese lipid profile in individuals over time.

* Corresponding author. Tel.: +81-52-744-2364; fax: +81-52-744-2371.
E-mail address: kuzuya@med.nagoya-u.ac.jp (M. Kuzuya).

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The purpose of this study is to examine both secular trends in serum lipids in a large Japanese population and changes in these lipid levels in a single cohort of individuals.

2. Methods

2.1. Study population

Study population was office workers and their families residing in Aichi Prefecture in the central region of Japan. The subjects included 80 331 Japanese (50 056 men and 30 275 women) with an average age of 44.5 years in men, and 43.7 years in women, who had received annual examinations at a health examination center in Japan between 1989 and 1998 (Table 1). Since study population was many and unspecified office workers and their families, the participation rate is unknown. Eight hundred eighty four subjects (1.1% of total subjects, 81 215) who were receiving medication for hyperlipidemia had been excluded. Our cohort included more male than female, since the number of male workers is greater than female in Japan. About 57% of the cohort attended at least one follow-up examination. Average visits for the follow-up examinations were 3.0 times for men and 2.6 times for women. The examinations included an interview and blood chemistry on the same day.

2.2. Laboratory methods

All serum samples were obtained following a 12–14 h fast. Serum was separated promptly and all lipid analyses were conducted at the clinical laboratory in the health examination center. Serum total cholesterol and triglycerides were measured by using enzymatic methods. HDL cholesterol was measured after dextran sulfate–magnesium precipitation. No differences were seen in the sample collection, laboratory apparatus, or techniques used between 1989 and 1998. LDL cholesterol was estimated for samples with triglyceride levels of 400 mg/dl or less by using the method of Friedewald et al. [19].

Table 1
Characteristics of participants, means (S.D.)

	Men	Women
Number of subjects	50 056	30 275
Total number of serum lipid measurements for 10 years	149 763	77 717
Average number of measurement per subject for 10 years	3.0 (2.5)	2.6 (2.2)
Average age (years)	44.5 (9.1)	43.7 (9.2)
Total cholesterol (mg/dl) at initial measurement	196.8 (34.7)	198.0 (36.6)
LDL cholesterol (mg/dl) at initial measurement	114.7 (31.3)	113.4 (33.2)
HDL cholesterol (mg/dl) at initial measurement	54.5 (13.1)	66.7 (14.3)
Triglyceride (mg/dl) at initial measurement	143.5 (102.7)	89.9 (50.7)

2.3. Data analysis

Data were processed and analyzed using the Statistical Analysis System (SAS) version 6.12 [20]. In the cross-section analysis, mean values of each serum lipid in 1989 and 1998 were plotted. The difference of serum lipid levels between 1989 and 1998 were examined using t-test in six age groups divided by decades ranging from 20–29 to 70–79 years.

Longitudinal changes in serum lipid levels were analyzed by a mixed effect model [21,22], which is a type of statistical analysis commonly used for repeated measurements. Responses from points close in time are usually more highly correlated with each other than responses from points far apart in time. Therefore, special methods of analysis are usually needed to accommodate the correlation structure of the repeated measurements. This autoregressive structure was controlled in the mixed effect model. The least-square means for serum lipid values at 50 years of age in each cohort were determined. The trend in cohort difference was tested.

3. Results

3.1. Cross-sectional analysis

Fig. 1 shows the age-specific means of serum lipid levels and a 3-year moving average of serum lipid levels in men and women in 1989 and 1998. The age-specific changes in serum lipid levels were similar in 1989 and 1998. In men, serum total cholesterol level gradually increased from 20–29 up to 50–59 years and no further increase was observed after 50–59 years. In women, serum total cholesterol level dramatically increased from 20–29 up to 60–69 years and then subsequently decreased. These age-related changes were similar in LDL cholesterol levels in men and women. HDL cholesterol levels decreased between 20–29 and 40–49 years and remained unchanged up to 70–79 years in men. In women, HDL cholesterol levels were lower with increasing age. Serum triglyceride levels increased up to 40–49 years, followed by a decline above 50–59 years in men, whereas triglyceride in women increased up to 60–69 years, and then decreased at 70–79 years.

Mean values of serum lipid levels in 1989 and 1998 are shown by age group and gender (Table 2). Significant gender differences existed in lipid levels. Before 40–49 years, total and LDL cholesterol levels in men were

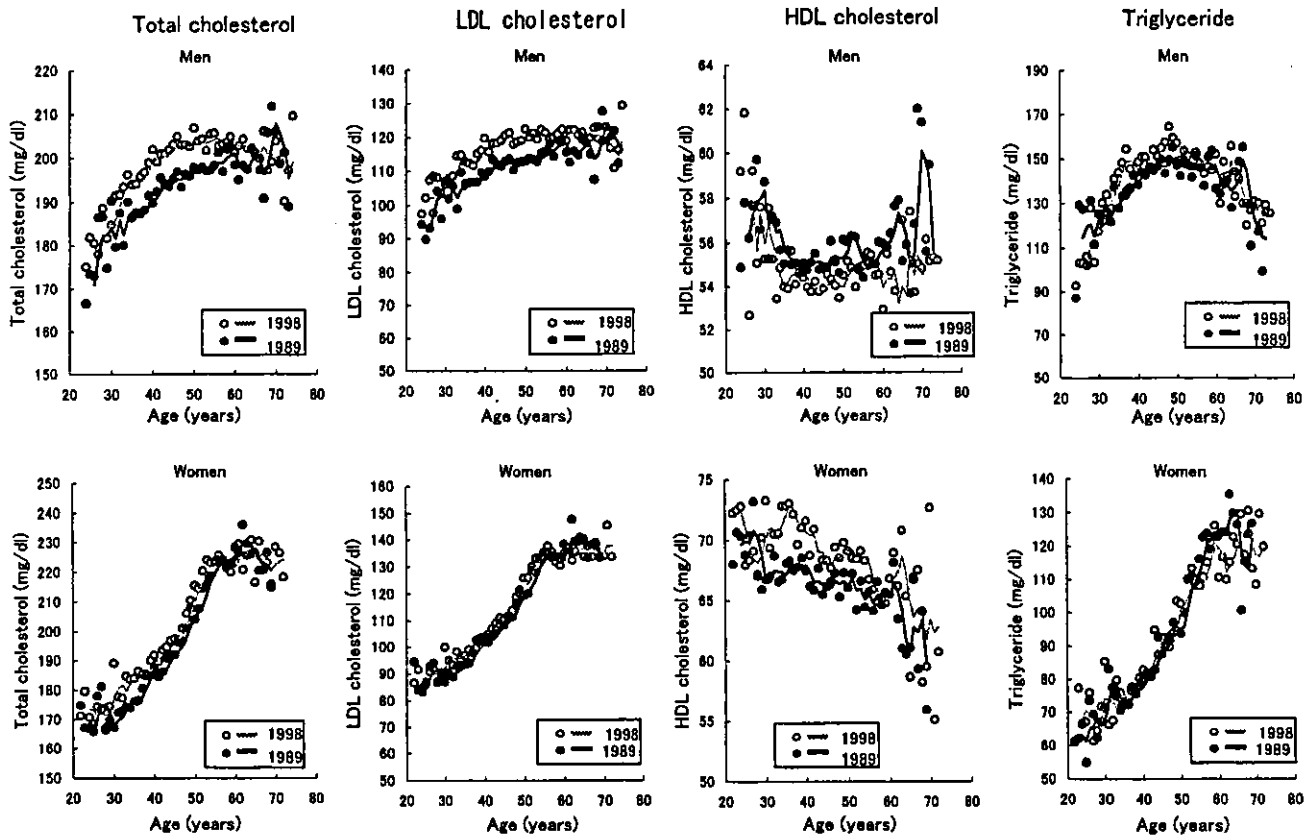

Fig. 1. Effect of aging on serum lipid levels in cross-sectional analysis. The age-specific means of serum lipid levels and a 3-year moving average of serum lipid levels are shown in men and women at 1989 and 1998.

higher than those in women. However, after 50 years of age, women had higher concentrations of serum total and LDL cholesterol than did men. Higher HDL cholesterol levels were observed in women than in men at all age groups. Gender difference in triglyceride levels was also observed in younger age groups, but the difference tended to decrease in older groups. In men, total and LDL cholesterol levels significantly increased and HDL cholesterol decreased in 1998 compared with those in 1989 with age in the third, fourth, fifth, and sixth decades of life. Triglyceride levels increased in 1998 with age in the third, fourth, and fifth decades of life in men. In women, total cholesterol, LDL cholesterol, and HDL cholesterol levels significantly increased in 1998 compared with those in 1989 with age in the third, fourth, and fifth decades of life. Triglyceride levels increased in 1998 with age in the fourth decade of life in women.

3.2. Longitudinal analysis

Longitudinal changes in serum lipid levels by birth cohort in men and women are shown in Fig. 2. These changes indicate the slight birth cohort effect in the serum total cholesterol and LDL cholesterol levels for men, since at most ages, the total and LDL cholesterol values of younger birth cohorts were higher than those of the older birth cohorts. But a birth cohort effect on other lipid levels was not clear in men and women. The shape of these curves also contains information regarding the age effect. In this case, total and LDL cholesterol levels increased with age up to 60 years old in both men and women. Regarding HDL cholesterol level, no significant age effect was observed for men. On the other hand, HDL cholesterol levels decreased with age for women. Triglyceride levels increased with age up to 40–49 years for men and 60–69 years for women.

Table 3 examines the mean change in lipid levels for 1 year by birth cohort and gender using repeated measurements during 10 years on the same individuals. Over the interval, total cholesterol increased significantly with age in men and women from the birth cohorts between the 1930s and 1960s. This indicated that in 55-year-old men and women total cholesterol level increased by 0.51 and 1.19 mg/dl per year, respectively. LDL cholesterol increased significantly with age for men from the birth cohorts between the 1920s and 1960s, indicating that even 64-year-old men still increased LDL cholesterol by 0.51 mg/dl per year. HDL cholesterol decreased significantly in men from the cohorts of the 1930s, 1950s, and 1960s. Triglyceride decreased significantly in men from the birth cohort of the 1930s and increased from

Table 2
Mean and S.D. of serum lipid levels in 1989 and 1998

Age group (years)		20–29		30–39		40–49		50–59		60–69		70–79		Total	
Year		1989	1998	1989	1998	1989	1998	1989	1998	1989	1998	1989	199	1989	1998
Men															
Number of subjects		194	188	3147	2440	5970	5317	3815	4990	796	1344	81	137	14003	14416
Total cholesterol (mg/dl)	Mean	175.9	180.9	187.9	195.2	194.0	202.2	198.5	204.4	198.7	201.9	198.3	201.2	193.9	201.5
	S.D.	(29.0)	(30.2)	(33.5)*	(34.4)*	(33.3)*	(33.1)*	(34.2)*	(34.1)*	(34.0)*	(31.9)*	(36.9)	(30.1)	(33.9)*	(33.8)*
LDL cholesterol (mg/dl)	Mean	97.5	102.2	106.8	113.2	111.4	118.8	115.0	121.0	115.8	120.6	117.1	120.8	111.4	118.6
	S.D.	(27.0)	(28.3)	(29.7)*	(30.2)*	(30.4)*	(30.2)*	(31.4)*	(30.4)*	(31.2)*	(29.1)*	(34.0)	(29.2)	(30.8)*	(30.3)*
HDL cholesterol (mg/dl)	Mean	56.7	58.2	55.4	54.7	55.1	54.0	55.6	54.8	56.5	54.1	57.9	54.8	55.4	54.5
	S.D.	(12.4)	(14.4)	(12.4)*	(13.8)*	(12.7)*	(13.5)*	(13.3)*	(14.6)*	(14.5)*	(14.3)*	(14.5)	(15.7)	(12.9)*	(14.1)*
Triglyceride (mg/dl)	Mean	113.2	104.5	134.2	142.7	145.3	154.4	146.4	149.7	137.0	141.5	116.3	128.5	142.0	148.7
	S.D.	(82.3)	(64.6)	(98.8)*	(116.7)*	(105.4)*	(112.5)*	(96.4)*	(106.1)*	(84.5)	(85.5)	(46.3)	(56.4)	(100.0)*	(108.1)*
Women															
Number of subjects		171	240	1371	1441	2735	3139	1843	2331	314	498	33	53	6467	7702
Total cholesterol (mg/dl)	Mean	170.9	172.3	178.7	185.2	192.5	198.6	216.3	220.5	226.9	225.3	210.5	222.0	197.6	203.8
	S.D.	(28.3)	(25.6)	(29.6)*	(28.2)*	(32.4)*	(31.8)*	(36.0)*	(33.9)*	(37.0)	(32.8)	(38.5)	(37.1)	(36.6)*	(35.1)*
	S.D.	(28.3)	(25.6)	(29.6)	(28.2)	(32.4)	(31.8)	(36.0)	(33.9)	(37.0)	(32.8)	(38.5)	(37.1)	(36.6)	(35.1)
LDL cholesterol (mg/dl)	Mean	89.4	88.6	96.1	98.7	108.6	111.7	128.8	131.3	138.8	135.8	125.0	134.2	112.8	116.2
	S.D.	(23.9)	(22.3)	(26.1)*	(25.6)*	(29.6)*	(29.2)*	(33.1)*	(31.6)*	(35.2)	(29.5)	(34.1)	(37.1)	(33.1)*	(32.2)*
HDL cholesterol (mg/dl)	Mean	68.5	70.1	67.8	71.6	66.5	69.1	65.6	67.5	63.9	66.1	60.4	65.7	66.4	68.9
	S.D.	(12.5)	(12.8)	(12.9)*	(14.9)*	(13.8)*	(15.8)*	(14.1)*	(16.4)*	(15.3)	(17.2)	(12.9)	(20.8)	(13.8)*	(15.9)*
Triglyceride (mg/dl)	Mean	65.4	68.0	75.4	75.6	87.2	90.4	110.7	109.5	123.9	116.8	125.0	110.1	92.8	94.6
	S.D.	(28.5)	(34.4)	(40.0)	(38.0)	(48.5)*	(59.1)*	(60.3)	(63.7)	(72.5)	(49.3)	(57.4)	(43.4)	(53.9)	(57.7)

S.D., standard deviation. *$P < 0.05$.

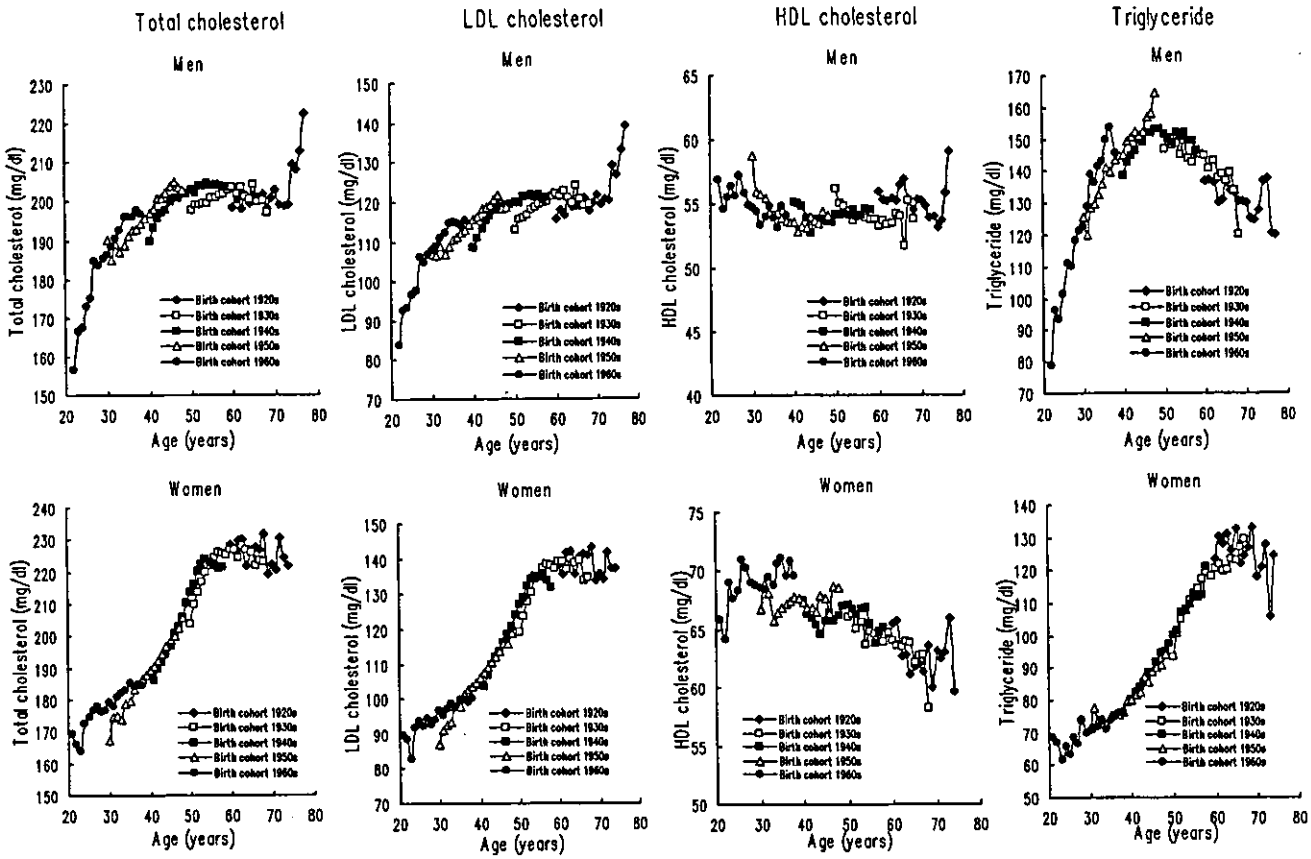

Fig. 2. Longitudinal changes in serum lipid levels. Mean serum lipid levels are shown by age in five birth cohorts.

the cohorts between 1940s and 1960s. In women from the birth cohorts between 1930s and 1960s, total and LDL cholesterol as well as triglyceride levels increased significantly with age. While HDL cholesterol levels decreased in women from the birth cohort of the 1930s, they increased from the cohorts between 1940s and 1960s.

As the tendency of serum lipid levels based on the longitudinal analysis was inconsistent with the results from the cross-sectional analysis, we examined the differences in age-adjusted serum lipid levels in each birth cohort (cohort effect). The serum lipid levels at 50 years of age in men and women were estimated for each birth cohort using the least-square means methods in the

Table 3
Rate of changes in serum lipid levels in longitudinal analysis (mg/dl per year)

Birth cohort	1920–1929	1930–1939	1940–1949	1950–1959	1960–1969
Men					
Number of subjects	1432	9400	17458	16116	5179
Age (years) at initial determination	64.0 (0.08)	55.8 (0.04)	46.5 (0.03)	38.3 (0.03)	31.8 (0.05)
Total cholesterol (mg/dl)	0.25 (0.18)	0.51 (0.07)*	0.92 (0.04)*	1.48 (0.05)*	1.85 (0.11)*
LDL cholesterol (mg/dl)	0.51 (0.16)*	0.71 (0.06)*	0.84 (0.04)*	1.20 (0.04)*	1.37 (0.10)*
HDL cholesterol (mg/dl)	−0.11 (0.07)	−0.15 (0.02)*	−0.03 (0.02)*	−0.10 (0.02)*	−0.13 (0.04)*
Triglyceride (mg/dl)	−0.85 (0.55)	−0.52 (0.21)*	0.48 (0.13)*	2.05 (0.16)*	3.75 (0.35)*
Women					
Number of subjects	683	5036	10064	10070	3868
Age (years) at initial determination	64.5 (0.12)	55.5 (0.05)	46.8 (0.04)	38.7 (0.03)	31.5 (0.06)
Total cholesterol (mg/dl)	−0.43 (0.26)	1.19 (0.09)*	2.92 (0.06)*	1.94 (0.06)*	1.18 (0.12)*
LDL cholesterol (mg/dl)	−0.35 (0.24)	1.07 (0.09)*	2.39 (0.05)*	1.54 (0.06)*	0.73 (0.11)*
HDL cholesterol (mg/dl)	−0.02 (0.11)	−0.21 (0.04)*	0.11 (0.02)*	0.13 (0.03)*	0.30 (0.05)*
Triglyceride (mg/dl)	−0.48 (0.41)	1.70 (0.15)*	2.18 (0.09)*	1.36 (0.10)*	0.78 (0.19)*

Mean ± standard error.
* Significant change ($P < 0.05$).

mixed effects model. Tukey multiple comparison showed significant differences in the estimated serum lipid levels among the birth cohorts except for triglyceride levels in women (Table 4). In men, the younger cohort showed the higher total cholesterol, LDL cholesterol, and triglyceride values, and lower HDL cholesterol at 50 years of age (trend $P < 0.001$). In women, the younger cohort showed higher total, LDL, and HDL cholesterol (trend $P < 0.001$).

4. Discussion

Cross-sectional trends in serum total cholesterol levels in samples of the 20 to 70-year-old Japanese population revealed that, overall, total cholesterol levels increased significantly between 1989 and 1998 in men and women from 193.9 to 201.5 and from 197.6 to 203.8 mg/dl, respectively. LDL cholesterol and triglyceride levels also significantly increased in men, whereas HDL cholesterol decreased between 1989 and 1998 for men. On the other hand, for women, mean values of LDL as well as HDL cholesterol levels significantly increased between 1989 and 1998, but triglyceride level showed no significant changes during this 10 years. The cross-sectional results by age groups suggested that total cholesterol, LDL cholesterol, and triglyceride levels increased, and that HDL cholesterol decreased in middle-aged adults (from 30 to 60 years of age) from 1989 to 1998 in the Japanese male population. In addition, women of 30, 40, and 50 years of age showed increased total, LDL, and HDL cholesterol levels during this 10-year period.

Although the information on nutritional intake was not available for our study, it has been reported that fat intake (especially animal fat) has continued to increase, and carbohydrate intake has been decreasing in the general Japanese population from 1989 to 1997 (fat, 58.9 g/day; animal fat 28.3 g/day in 1989 and fat, 59.3 g/day; animal fat, 29.7 g/day in 1997) (data in 1998 are not available) [23,24]. This may be the one of the reasons that total and LDL cholesterol levels are still increasing in the Japanese population. It has been known that obesity and body mass index (BMI) are significantly related to triglyceride levels [25,26]. In our cohort, BMI has increased in men during the past 10 years, although no change in BMI has been observed in women (data not shown). These tendencies with regard to BMI changes agree with the report showing that BMI and the rates of excess weight and obesity have been increasing during past 10 years in men, but that no increase in BMI has been observed in women of the general Japanese population [24]. This contrast in BMI between men and women may explain the different changes in triglyceride levels between men and women during the past 10 years.

The decrease of HDL cholesterol in men for the past 10 years is consistent with the concept that HDL cholesterol level has an inverse relationship to triglyceride level and BMI [27–29]. However, the reason for the increase of HDL cholesterol level in women in this 10-year period is not clear, since no obvious changes in triglyceride level and BMI were observed in women. It should be noted that the HDL cholesterol levels of our cohort were relatively higher than those reported in other Japanese populations. The National Nutritional Survey conducted by the Japanese Ministry of Health and Welfare in 1989 reported that the average HDL cholesterol level in a random Japanese population was 50.4 ± 14.92 mg/dl (mean $\pm$ S.D.) and 56.0 ± 15.27 mg/dl in men and women between 30 and 70 years of age and more in men, respectively [23]. Based on the data from a survey of serum lipid levels in the general Japanese population conducted by the Japan Atherosclerosis Society in 1990, the mean HDL cholesterol level of the Japanese population from 20 to 79 years of age is 51.1 mg/dl for men and 57.4 mg/dl for women, 4 and 9 mg/dl less than those levels of our study in 1989 [16]. These different HDL cholesterol levels may be due to the difference in survey populations between general and local populations.

Table 4
Estimated serum lipid levels in subjects 50 years of age

Birth cohort	1920–1929	1930–1939	1940–1949	1950–1959	1960–1969
Men					
Total cholesterol (mg/dl)	200.7 (1.31)	203.0 (0.65)	209.2 (0.43)	215.3 (0.57)	222.0 (0.95)
LDL cholesterol (mg/dl)	115.0 (1.20)	118.3 (0.60)	124.0 (0.39)	129.5 (0.52)	135.6 (0.87)
HDL cholesterol (mg/dl)	55.3 (0.50)	53.9 (0.25)	53.5 (0.16)	52.5 (0.22)	52.1 (0.36)
Triglyceride (mg/dl)	160.5 (4.04)	162.5 (2.04)	168.4 (1.34)	175.0 (1.79)	181.3 (3.01)
Women					
Total cholesterol (mg/dl)	198.3 (1.91)	210.8 (0.96)	212.6 (0.66)	212.4 (0.79)	221.4 (1.28)
LDL cholesterol (mg/dl)	114.9 (1.75)	125.2 (0.88)	125.5 (0.61)	123.8 (0.73)	129.0 (1.17)
HDL cholesterol (mg/dl)	65.0 (0.84)	65.9 (0.42)	68.1 (0.29)	70.0 (0.35)	73.4 (0.56)
Triglyceride (mg/dl)	92.9 (2.97)	99.4 (1.52)	96.1 (1.04)	94.0 (1.25)	96.7 (2.02)

Mean $\pm$ standard error. There were significant trends in the estimated serum lipid levels by the birth cohorts except for triglyceride levels in female (trend $P < 0.001$).

Cross-sectional analyses revealed a progressive increase in total and LDL cholesterol to age 50–59 years in men and to 60–69 years in women, after which the levels of cholesterol in women appeared to fall. HDL cholesterol decreased to age 40–49 years in men and to 70–79 years in women followed by the unchanged levels. Triglyceride level increased to 40–49 years in men and to 60–69 years in women, followed by a decline. These cross-sectional age-related distributions of serum lipid levels are in close agreement with the results reported in other population-based samples in Japan [16].

However, longitudinal studies are required to examine age-related changes in serum lipids. Our longitudinal analyses suggested that total and LDL cholesterol tended to increase up to 1920–1929 birth cohort (60–69 years, average 64.0-year-old) and up to 1930–1939 birth cohort (50–59 years, average 55.5-year-old) in men and women, respectively. These results seem to be inconsistent with the few published reports based on longitudinal data. During an 8-year follow-up period, total cholesterol in the Framingham Study was seen to increase in the 35–49-year-old cohort but declined in men aged 50–64 and 65–79 years when follow-up began [30]. Investigators from the Rancho Bernardo Study suggested that total and LDL cholesterol decreased during 8 years of follow-up in both men and women in all age groups above 50 [31]. These inconsistent observations are not due to the racial difference, since total cholesterol declined longitudinally with age after the subjects reached 50s, in the Honolulu Heart Program, which enrolled Japanese–American men [32]. Some ethnic differences including dietary habits, physical activities, or life style as well as differences in public health awareness may contribute these inconsistent observations between other cohorts and ours. However, some selection bias may also exist in our cohort, since most of our subjects were healthy office workers.

At present, very limited data are available regarding the longitudinal changes in triglyceride levels in the mid-aged population and in the elderly. Garry et al. reported that no significant longitudinal changes in triglyceride were observed in either men or women over 60 years of age (median age, 72 years) during 9 years of follow-up [33]. However, in our cohort, triglyceride level increased in the 1940–1949 birth cohort (average 46.5-year-old) and younger, and decreased in the 1930–1939 birth cohort and older cohort for men. For women, triglyceride level increased in the 1930–1939 birth cohort and younger cohorts. These longitudinal changes in total and LDL cholesterol and triglyceride levels were similar to the results of cross-sectional analysis, whereas a significant difference was observed in the longitudinal analysis of HDL cholesterol level. The effect of age on HDL cholesterol is controversial. In our longitudinal analysis, HDL cholesterol tended to decrease in all birth cohorts in men, but increased in the 1940–1949 birth cohort (average 46.8-year-old) and younger cohorts in women. The report from the Honolulu Heart Program demonstrated that HDL cholesterol increased during 8 years of follow-up in men even aged 70–79 [32]. However, HDL cholesterol level declined with age in both men and women in the longitudinal analysis of the Framingham Study [32] and the Rancho Bernardo Study [31].

Our longitudinal analysis indicated a birth cohort effect except for the triglyceride levels in women. Higher estimated total and LDL cholesterol levels were observed in younger birth cohorts than in older cohorts. This may suggest that younger birth cohorts tended to pursue a more westernized lifestyle than do older birth cohorts. Cohort effects seem to contribute to the appearance of the increase in cholesterol levels seen in 1998 in the cross-sectional analysis.

It should be noted that our results may not be indicative of the Japanese population as a whole because the subjects in this study represent an urban population. Some selection bias such as healthy worker bias may exist in our study, since most of the subjects were healthy office workers. In addition, the subjects may be aware of their lipid levels, since they had received annual examinations at a health examination center. Nevertheless, their lipid levels increased during the last 10 years. In this study, subjects who are receiving lipid-lowering medication were excluded. Therefore, the degrees of increase in serum lipid levels may be underestimated.

The main findings in this study include an observed increase in total and LDL cholesterol as well as triglyceride levels in a middle-aged Japanese population during the period of 1989–1998. Birth cohort effects were observed regarding serum lipid levels in the Japanese population. Public health programs to alter the plasma lipid concentrations in the Japanese population will be required to prevent further increases in serum lipid levels as well as in coronary heart disease.

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References

[1] Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heat disease continuous and graded? Finding in 356222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). J Am Med Assoc 1986;256:2823–8.

[2] Anderson KM, Castelli WP, Lvy D. Cholesterol and mortality: 30 years of follow-up from the Framingham study. J Am Med Assoc 1987;257:2176–82.
[3] Rossen G, Shipley M. Plasma cholesterol concentration and death from coronary heart diseases: 10 years results of the Whitehall Study. Br Med J 1986;293:306–7.
[4] Report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of the high blood cholesterol in adults. Arch Intern Med 1988;148:36–69.
[5] Harlan WR, Stross JK. An educational view of national initiative to lower plasma lipid levels. J Am Med Assoc 1985;253:2087–90.
[6] Burke GL, Sprafka JM, Folsom AR, Hahn LP, Luepker RV, Blackburn H. Trends in serum cholesterol levels from to 1987. The Minnesota Heart Survey. New Engl J Med 1991;324:941–6.
[7] Johnson CL, Rifkind BM, Sempos CT, Carroll MD, Bachorik PS, Briefel RR, Gordon DJ, Burt VL, Brown CD, Lippel K, Cleeman JI. Declining serum total cholesterol levels among US adults. J Am Med Assoc 1993;269:3002–8.
[8] Menotti A, Scanga M. Trends in coronary risk factors in Italy. Responsible investigators of the RF2, OB43 and MICOL Research Groups. Int J Epidemiol 1992;21:883–92.
[9] Kannel WB, Thom TJ. Declining cardiovascular disease mortality. Circulation 1984;70:331–6.
[10] Feinleib M. The magnitude and nature of the decrease in coronary heart disease mortality rate. Am J Cardiol 1984;54:2C–6C.
[11] Sigfussion N, Sigvaldason H, Steingrimsdottir L, Gudmundsdottir II, Stefansdottir I, Thorsteinsson T, Sigurdsson G. Decline in ischaemic heart disease in Iceland and change in risk factor levels. Br Med J 1991;302:1371–5.
[12] Research Committee on Familial Hyperlipidemia in Japan. Changes of serum total cholesterol and triglyceride levels in normal subjects in Japan in the past twenty years. Jpn Circ J 1983;47:1351–8.
[13] Research Committee on Atherosclerosis in Japan. Total serum cholesterol and triglyceride levels in normal subjects in Japan. J Jpn Atheroscler Soc 1973;1:101–8 (in Japanese).
[14] Yamada M, Wong FL, Kodama K, Sasaki H, Shimaoka K, Yamakido M. Longitudinal trends in total serum cholesterol levels in a Japanese cohort, 1968–1986. J Clin Epidemiol 1997;50:425–34.
[15] Shimamoto T, Komachi Y, Inada H, Doi M, Iso H, Sato S, Kitamura A, Iida M, Konishi M, Nakanishi N, Terao A, Naito Y, Kojima S. Trends for coronary heart disease and stroke and their risk factors in Japan. Circulation 1989;79:503–15.
[16] Research Committee on Serum Lipid Level Survey 1990 in Japan. Current state of and recent trends in serum lipid levels in the general Japanese population. J Arterioscler Thromb 1995;2:122–32.
[17] Ministry of Health and Welfare (Koseisho), Department of Public Health. National Surveys of Circulatory Disorders 1980. Japanese Heart Foundation, Tokyo, 1982 (in Japanese).
[18] Ministry of Health and Welfare (Koseisho), Disease Control Division. National Surveys of Circulatory Disorders. Japanese Heart Foundation, Tokyo, 1990 (in Japanese).
[19] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.
[20] SAS language guide for personal computers, version 6.03 edition. Cary, NC: SAS Institute, 1988.
[21] Ward MM, Leigh JP. Pooled time series regression analysis in longitudinal studies. J Clin Epidemiol 1993;46:645–59.
[22] Littell RC, Milliken GA, Stroup WW, Wolfinger RD. SAS system for mixed models (1989 printing; chapter 3). Cary, NC: SAS Institute Inc, 1996.
[23] Nutrition Section, Ministry of Health and Welfare: National Nutrition Survey, 1989. Tokyo, Daiichi Shuppan Publishers 1989 (in Japanese).
[24] Nutrition Section, Ministry of Health and Welfare: National Nutrition Survey, 1997. Tokyo, Daiichi Shuppan Publishers 1997 (in Japanese).
[25] Despres J-P, Moorjani S, Lupien PJ, Tremblay A, Nadeau A, Bouchard C. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. Arteriosclerosis 1990;10:497–511.
[26] Lamon-Fava S, Wilson PW, Schaefer EJ. Impact of body mass index on coronary heart disease risk factors in men and women. The Framingham Offspring Study. Arterioscler Thromb Vasc Biol 1996;16:1509–15.
[27] Schaefer EJ, Lamon-Fava S, Ordovas JM, Cohn SD, Schaefer MM, Castelli WP, Wilson PW. Factors associated with low and elevated plasma high density lipoprotein cholesterol and apolipoprotein A-I levels in the Framingham Offspring Study. J Lipid Res 1994;35:871–82.
[28] Lamon-Fava S, Wilson PW, Schaefer EJ. Impact of body mass index on coronary heart disease risk factors in men and women. The Framingham Offspring Study. Arterioscler Thromb Vasc Biol 1996;16:1509–15.
[29] Anderson KM, Wilson PWF, Garrison RJ, Castelli WP. Longitudinal and secular trends in lipoprotein cholesterol measurements in a general population sample. The Framingham offspring study. Atherosclerosis 1987;68:59–66.
[30] Wilson PWF, Anderson KM, Harris T, Kannel WB, Castelli WP. Determinants of change in total cholesterol and HDL-C with age: The Framingham Study. J Gerontol 1994;49:M252–7.
[31] Ferrara A, Barrett-Connor E, Shan J. Total, LDL, and HDL cholesterol decrease with age in older men and women. The Rancho Bernardo Study 1984–1994. Circulation 1997;96:37–43.
[32] Abbott RD, Sharp DS, Burchfiel CM, Curb JD, Rodriguez BL, Hakim AA, Yano K. Cross-sectional and longitudinal changes in total and high-density-lipoprotein cholesterol levels over a 20-year period in elderly men: The Honolulu Heart Program. Ann Epidemiol 1997;7:417–24.
[33] Garry PJ, Hunt WC, Koehler KM, VandeJagt DJ, Vellas BJ. Longitudinal study of dietary intakes and plasma lipids in healthy elderly men and women. Am J Clin Nutr 1992;55:682–8.

□ORIGINAL ARTICLE□

Prevalence of Hyperesthesia Detected by Current Perception Threshold Test in Subjects with Glucose Metabolic Impairments in a Community

Kiyoshi TAKEKUMA, Fujiko ANDO*, Naoakira NIINO* and Hiroshi SHIMOKATA*

Abstract

Objective **Recent studies reported that hyperesthesia may be an indicator of early diabetic polyneuropathy. Using the current perception threshold (CPT) test, which stimulates peripheral sensory nerve fibers by three different frequencies (2,000, 250, and 5 Hz), we investigated the relationship between hyperesthesia and glucose metabolic impairment in a community.**

Methods **The number of subjects, aged 40 to 79 years, was 2,074. The CPT values at each frequency were classified into three categories (hyperesthesia, normal, and hypoesthesia). Subjects were also subgrouped into three groups (normal, insulin resistance, and diabetes) according to glucose metabolic status, and those with hypoesthesia at each frequency were excluded in the analyses.**

Results **The prevalence of hyperesthesia at 2,000, 250, and 5 Hz in male diabetic subjects were 14.1, 15.6, and 7.7%, respectively, and 22.2, 24.5, and 16.4% respectively in female diabetic subjects. In logistic regression analysis adjusted for age, females with diabetes showed a significantly high odds ratio (OR) for hyperesthesia at 2,000 Hz (OR, 2.42; 95% confidence interval (95%CI), 1.18 to 4.97) and 250 Hz (OR, 2.65; 95%CI, 1.31 to 5.37). In male diabetic subjects, a significantly high odds ratio for hyperesthesia was seen at 250 Hz (OR, 2.09; 95%CI, 1.07 to 4.05).**

Conclusion **Our results suggested that hyperesthesia may emerge coupled with developing diabetes, supporting the precedent hypothesis.**

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Key words: CPT, gender difference, diabetic neuropathy, diabetes

Introduction

Quantitative sensation testing methods are recommended for characterizing cutaneous sensation alteration in patients with diabetic polyneuropathy (1). These methods can detect hyperesthesia (1), which is thought to be a marker of injured nerve fibers (2). Recently, Dyck and coworkers reported a higher prevalence of hyperesthesia in patients with a milder spectrum of diabetic polyneuropathy with these methods (3), suggesting it may be worthwhile to assess for hyperesthesia as an indicator of diabetic polyneuropathy.

At present, there is little information on the natural history of diabetic neuropathy. However, some previous studies have reported the occurrence of diabetic polyneuropathy early in the course of diabetes (4, 5). These reports suggested the possibility of hyperesthesia in diabetic patients before the development of overt polyneuropathy.

This study was aimed to examine the possibility whether hyperesthesia may develop early in the course of diabetes in people living in a community. To clarify this issue, we investigated the association between hyperesthesia and glucose metabolic status in subjects subdivided into three groups according to glucose metabolic status (normal, insulin resistance, and diabetes) in a community using current perception threshold (CPT) test, which is used to evaluate peripheral sensory nerve fibers quantitatively (6).

For editorial comment, see p 1079.

Subjects and Methods

This study was a part of a large longitudinal study on aging (National Institute for Longevity Sciences — Longitudinal Study on Aging; NILS-LSA). The design of the study and its objectives have been published previously (7). In brief, participants of this study were recruited from stratified random

From the Department of Public Health, Nagoya City University Medical School, Nagoya and *the Department of Epidemiology, National Institute for Longevity Sciences, Obu

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Reprint requests should be addressed to Dr. Kiyoshi Takekuma, the Department of Public Health, Nagoya City University Medical School, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601