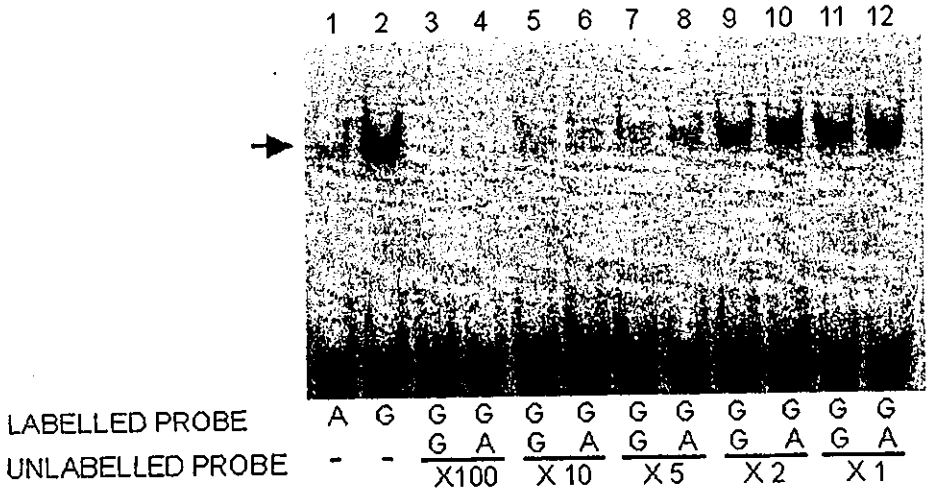

FIG. 3. Differential binding patterns between G- and A-bearing alleles of the *klotho* promoter. Synthetic allele-specific oligonucleotides representing the polymorphic G-395A site were incubated with nuclear extracts from cultured human embryonal kidney 293 cells. Lanes 1 and 2 show the DNA-protein complex formed by labeled probes with A- and G-bearing alleles. Lanes 3–12 show cold competition with various concentrations of unlabeled probes with G- and A-bearing alleles (X1–X100 of the labeled probe) against the complex formation by the labeled probe with G-bearing alleles.

klotho gene is known to be expressed most predominantly in the kidney but not in bone or bone marrow, in mice and humans.[22–24] In fact, we confirmed the expression of the *klotho* in 293 cells. Consequently, it was indicated that some transcription factors, coactivators, or co-repressors bound to the sequence including the polymorphic site in the promoter region (G-395A) and the substitution affected its binding affinity. Sequence analysis of the 5′ flanking region revealed that there was no typical TATA box, but there were five potential binding sites for Sp1 that are known to be found often in TATA-less promoter.[24] DNA sequences around the G-395A site are highly conserved with those of murine *klotho* gene (> 70%), and this site is located close to Sp1. It is interesting to note here that the polymorphism in the collagen Iα1 gene associated with low bone density is also located at the Sp1 binding site.[14,15] However, our functional study using 415 bp of the human *klotho* promoter construct containing the G-395A site ligated to the luciferase reporter gene failed to show a significant difference of the reporter activity by the G/A substitution in transfected 293 cells (data not shown). This discrepancy might be because there are other important elements than the G-395A site in the promoter region that regulate the *klotho* gene transcription. Another possibility might be that the expression of the transcription factors/cofactors in the 293 cells was sufficient for the binding of the *klotho* promoter but might be insufficient for the activation of exogenously transfected promoter construct.

C1818T, the SNP in exon 4 associated with bone density, was a variation that caused no amino acid substitution. Although several reports have suggested the possibility that a silent mutation in an exon may yield an alternative transcript with abnormal function or affect the expression level of the product,[29,30] our preliminary analysis has so far failed to detect splicing variants of the *klotho* transcript by RT-PCR using human kidney samples obtained from 18 renal disease patients (data not shown). Another possibility is that the association of C1818T may be linked physically to an SNP that could influence the function of the *klotho* gene. Because C2298T that is located downstream of C1818T did not exhibit any association with BMD, the functional variant might possibly be located upstream of C1818T.

Among identified SNPs, three of them, one in the white population (G1110C) and two in the Japanese population (A44C and C234G), resulted in amino acid substitutions that might affect the structure of the protein. Recently, the G1110C was identified by another group as a functional variant that contributes to the longevity of humans[31]; however, our association study failed to show significant associations between G1110C and bone density in any subpopulation (all $p > 0.05$, data not shown). In addition, the allelic frequency of the minor *C* allele was not significantly different among subpopulations classified by ages in the white postmenopausal women. This discrepancy might possibly be caused by the difference of races. Neither A44C nor C234G was applicable for the association study because of the shortage of the number of patients with the minor allele in the Japanese population.

Aging is a common and potent risk factor in all age-related disorders in humans, and for the first time this study indicated the involvement of an aging-related gene *klotho* in the pathophysiology of a major age-related disorder, osteoporosis. The SNPs identified in this report will be useful for testing the association between *klotho* and other age-related diseases. We propose that further studies on the function of the *klotho* gene will provide new insight into the understanding of molecular mechanisms of age-related disorders.

ACKNOWLEDGMENTS

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シリーズ
加齢と臓器の変化

各論II 加齢と眼

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人口の高齢化に伴い，視覚障害を有する高齢者も増加している。視覚はヒトが得る情報の9割近くを占める重要な感覚である。加齢に伴う視機能の変化には二つの面がある。ひとつは眼球構造の加齢変化に伴う視機能の生理的な低下である。もうひとつは加齢に伴い生じやすくなる眼疾患による視機能の障害である。本稿ではこの両者につき概要を示す。

眼球構造の加齢変化と視機能の低下

(1) 角膜の変化

若年期における角膜の形状は，眼球の水平軸よりも垂直軸の屈折力が強い「直乱視」がほとんどであるが，加齢に伴い形状が変化し，高齢者では水平軸の屈折力の方が強い「倒乱視」の割合が増加する。この倒乱視化には加齢に伴う眼瞼の眼球に与える圧力の低下が考えられているが不明な点も多い。近視や遠視と異なり，乱視では遠距離でも近距離でも焦点が合わないため裸眼視力の低下をもたらし，Quality of Visionへ影響を及ぼす。

また，加齢と伴にデスメ膜肥厚や角膜内皮細胞の減少が生じて角膜の透明性が低下する。角膜周辺部にリン脂質が沈着する老人環が代表的なものであり，70歳台で90%程度，80歳台でほぼ100%にみとめられる。ただし，老人環が視力に影響を与えることは稀である。

角膜内面を一層に覆っている内皮細胞は，生後から増殖しないと考えられており，年齢とともに徐々に減少する。内皮細胞密度は正常成人では3000/mm^{2}程度であるが，70歳台になると2500/mm^{2}前後となる。加齢その他の原因により内皮細胞が脱落するとその周囲の細胞面積が大きくなることにより代償され，その結果，内皮細胞に大小不同が生じる。一般的には内皮細胞密度が500/mm^{2}以下となると角膜浮腫などが生じるとされるが，単に加齢変化のみで500/mm^{2}以下となることはない。

Key words 加齢／視機能／眼球／眼疾患

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(2) 水晶体

水晶体は水晶体嚢，水晶体上皮細胞，および水晶体線維から構成される。水晶体は発生初期より他組織から隔離されて生育し，生涯にわたって成長するため，年齢に伴って徐々に厚くなり，また質量も増加する。水晶体上皮細胞は前嚢の後面を一層に覆っており，主に赤道部の上皮細胞が分化して水晶体線維が形成される。水晶体線維は水晶体外に排出されることなく順次中心部へ移動し，脱核して水晶体核に誘導される。

水晶体では加齢に伴い，散乱光の増加（透明度の減少），核の硬化，核の着色が生じる。皮質における散乱光増加の本態は分子量 1×10^6～5×10^6程度のhigh molecular weight proteinで，主に水晶体可溶性蛋白質のひとつであるαクリスタリンが凝集したものである。一方，水晶体核ではαクリスタリンが数珠状につながって網状構造を形成し，不溶性蛋白質の増加による核の硬化を引き起こす[1]。また，水晶体は加齢に伴って青色から黄色，褐色に変化するが，近年，トリプトファン由来のキヌレニン誘導体が水晶体の着色と蛍光物質の増加に関与する主要物質であることが明らかにされてきている。

(3) 網膜・硝子体

硝子体はおもにコラーゲン線維，ヒアルロン酸，水から構成されているが，加齢に伴い硝子体のゲル成分が中心部から融解する。また，中高年期では後部硝子体と網膜内境界膜が剥離し，後部硝子体剥離と呼ばれ，飛蚊症が生じる一因となる。

網膜は加齢に伴い中心窩近傍の網膜反射が乏しくなり，色調も暗く，脈絡膜大血管が透見される老人性豹紋状眼底を呈する。組織学的には，網膜神経節細胞が減少し，視細胞にも変形や減少がみられる。代わって網膜における神経膠細胞であるMüller細胞の活性が高まり，その基底膜である内境界膜の肥厚がみられる[2]。一方，網膜における貪食細胞である色素上皮細胞はその全体数が減少するとともに六角形構造が崩れ，核も大小不同となる。また，色素上皮細胞質内のメラニン顆粒が減少し，代わってリポフスチンが増加する。リポフスチンが色素上皮基

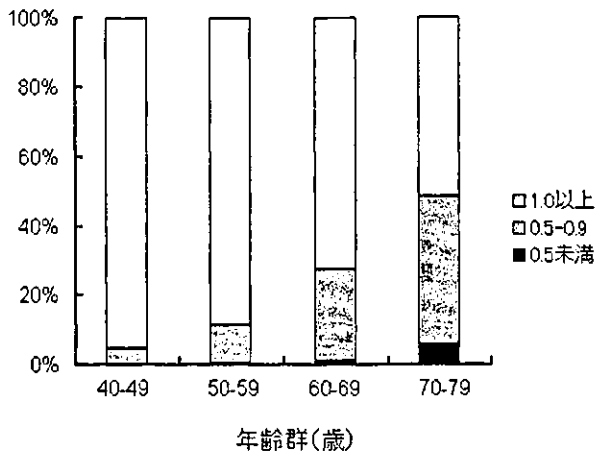

図1　一般地域住民調査（NILS-LSA）における中高年者の視力分布

底膜とブルッフ膜との間に結節状に蓄積されるとドルーゼンと呼ばれる。ドルーゼンは黄斑部に出現しやすく，加齢性黄斑変性症の前駆病変とみなされている。

網膜血管は加齢に伴い動脈硬化所見を示す。我々が実施している一般住民を対象とした疫学調査（National Institute for Longevity Sciences-Longitudinal Study for Aging：NILS-LSA）の結果によると[3,4]，眼底動脈硬化を有する比率は40歳台では3割にも満たないが，70歳台では8割近くに上昇する。この変化は網膜細動脈における中膜の肥厚と平滑筋細胞の減少によるものである[5]。

(4) 視機能

上記のような眼球構造の加齢変化に伴い視機能も徐々に低下する。市川は眼科外来患者のうち視力障害を主訴としない者を対象に視力を測定し，その結果，視力は45歳以降ほぼ直線的に低下することを示した[6]。NILS-LSAの結果では，矯正視力1.0以上の割合は40歳台で95%以上に対し，70歳台では約50%となっている（図1）。加齢に伴う視力低下の原因として，加齢性縮瞳と水晶体透過率低下による網膜照度の低下，および網膜以降の中枢性機能低下が考えられる。

日常生活において見る対象物は視力表のように白黒のコントラストがはっきりしているものばかりではない。対象物の淡い濃淡を見分ける機能はコントラスト感度として評価される。視力と同様にコントラスト感度も加齢に伴い低下がみられる。特に高周波数領域での低下が著しく，白内障に起因するものと考えられる。視力が1.0以上あってもコントラスト感度がかなり低下している場合もあり，視力とは異なる視機能を反映していると考えられる[7]。

(5) 老視

水晶体の硬化に伴う調節障害（近見障害）を老視という。ヒトの眼球における調節力は幼少時には10～15Diopter（D）であるが，加齢とともにほぼ直線的に減弱し，60歳を過ぎると1D以下となる。正視（遠視も近視もない状態）の眼の場合，近見時には3～4Dの調節力が必要であるため，調節力が3～4Dに低下する40歳台で老視を自覚する場合が多い。放置しておくと眼精疲労などを招くため適切な眼鏡処方が必要となる。

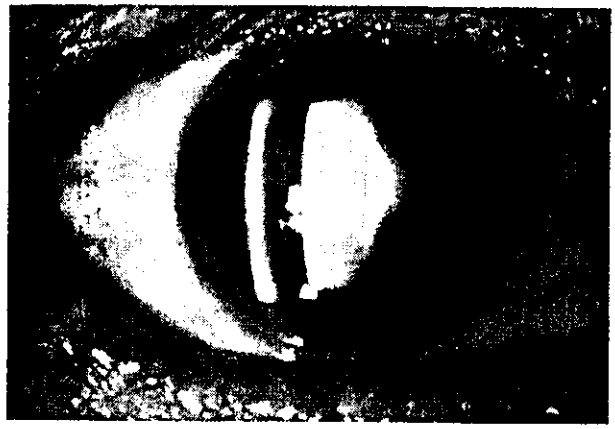

図2　白内障細隙灯写真
水晶体核部に著明な黄色化をみとめる。

加齢に伴い生じやすい眼疾患

(1) 加齢白内障

白内障の原因として，ステロイド投与や糖尿病・アトピー性皮膚炎の存在などがあるが，他に明らかな原因がなく加齢に伴って生じてくるのが加齢白内障である（図2）。白内障は水晶体の混濁の部位により，皮質白内障，核白内障，嚢下白内障に大別される。皮質白内障では水晶体赤道部より楔状の混濁が徐々に始まり，混濁が瞳孔領にまで及ぶと視力に影響を与える。前嚢下白内障はアトピー性皮膚炎などで，また後嚢下白内障は糖尿病やステロイド投与などで生じやすい病型である。それぞれ中央部から混濁が始まることが多いため，軽症例でも視力障害が生じやすく，特に明所で羞明や昼盲を訴える頻度が高い。一方，核白内障は一般的な水晶体の加齢変化が進行したタイプと考えられ，水晶体核における硬化・着色が年齢とともに著明になった状態である。ただし核白内障では水晶体線維の構造が比較的保たれるため，視力障害の進行は一般に緩徐である。

白内障の治療には薬物療法と手術療法とがある。薬物療法としてピレノキシンやグルタチオンが点眼として使用される場合が多い。しかし，現時点では薬物療法による水晶体混濁の低減は得られず，混濁の進行を予防する程度である。一方，手術療法は近年の手術法や手術器機の改良に伴い劇的に進歩した。以前には白内障核をそのまま娩出する嚢外摘出法が主流であったが，現在では3mm程度の強角膜創から水晶体核を破砕吸引する超音波乳化吸引術が

図3 増殖性糖尿病網膜症：レーザー光凝固術が施行されているが，視神経乳頭部新生血管からの網膜前出血が生じている。

普及している。眼内レンズにも改良が加えられ，より小さな切開創で移植できるよう折りたたみ眼内レンズが導入されている。手術時間も15～20分程度と大幅に短縮され，日帰り手術も可能となってきた。白内障手術はいわゆる開眼手術からQuality of Visionを求める手術へ変貌してきている。

(2) 糖尿病網膜症

現在，わが国における中途視覚障害の原因第一位は糖尿病網膜症である[8]。糖尿病網膜症の発症と進展には，血糖コントロールに加え，その罹病期間が大きく関与しているため，高齢者糖尿病患者において網膜症を合併する割合が高くなる。Satoら[9]によるとHbA1cが8.6%以上で罹病期間が10年の場合では増殖性糖尿病網膜症発症の可能性は60%に達する。

糖尿病網膜症は大きく単純網膜症，前増殖性網膜症および増殖性網膜症とに分類される。単純網膜症では毛細血管瘤，出血，硬性白斑などを生じるが，自覚症状に乏しい。この時期の治療は内科治療が中心である。前増殖期になると網膜に軟性白斑が生じ，蛍光眼底造影検査で無灌流域および網膜血管の透過性亢進がみとめられる。前増殖期には黄斑部浮腫が起こり視力の低下を招く場合があるが，それ以外では自覚症状が少ないため，定期検査が重要となる。一般的にこの前増殖期に網膜レーザー凝固治療を開始する。増殖期になると網膜新生血管が発生し，硝子体出血，線維増殖組織形成，牽引性網膜剥離などにより視力障害が生じてくる（図3）。この時期には汎網膜レーザー凝固および硝子体手術が適応となる。硝子体手術は牽引性網膜剥離の原因となる増殖組織や新生血管を取り除く手術で，近年の手術法の進歩により，手術の成功率も向上している。

網膜症未発症の場合も含めてすべての時期で最も重要なのは食事療法を中心にした内科的な全身的管理である。網膜症に対する薬物療法には，末梢循環改善剤，血管強化剤，脂質代謝改善剤などが用いられているが，補助的な意味合いが強い。

図4 加齢黄斑変性（滲出型）：黄斑部に脈絡膜新生血管盤があり，硬性白斑を伴う黄斑浮腫がみられる。

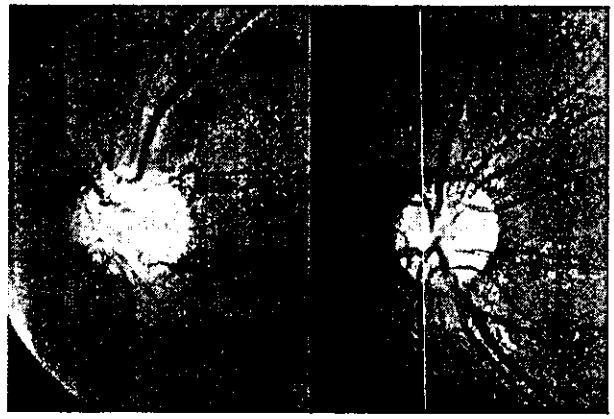

図5 緑内障眼と正常眼との視神経乳頭比較（左：緑内障，右：正常）：緑内障眼では視神経乳頭陥凹拡大が著明にみとめられる。また，乳頭上縁にnotchがみとめられ，それに対応して楔形の網膜神経線維欠損が生じている。

(3) 加齢黄斑変性

加齢に伴い網膜の中心である黄斑部に変性を生じる病態の総称を加齢黄斑変性という（図4）。加齢黄斑変性は大きく滲出型と非滲出型とに分類される。脈絡膜新生血管による網膜下出血や浮腫をきたしやすい滲出型は，重篤な視力障害を招き，欧米において中途失明の主要原因となっている。初期症状は変視症や中心暗点であるが，病態の進行に伴い視力低下を生じる。

脈絡膜新生血管発生のメカニズムは十分に解明されていないが，網膜色素上皮とブルッフ膜との間にリポフスチンなどが沈着し，これらの蓄積によって生じる慢性の炎症反応の結果として新生血管が発生すると考えられている。

発症の危険要因として最も重要なのは年齢であるが，遺伝要因や環境要因も関与している。環境要因のなかでは喫煙と高血圧が重要なリスクファクターとして報告されている[10]。一方，ビタミンC，Eなど抗酸化ビタミンと亜鉛に加齢黄斑変性の発症・進行を予防する効果が報告されている[11]。

加齢黄斑変性の非観血的治療として，網膜中心窩外の新生血管に対するレーザー光凝固がおこなわれる。中心窩に達する新生血管に対しては低線量放射線療法，経瞳孔的温熱療法などが試みられているが，その評価は定まっていない[12]。外科的治療も積極的に試みられており，傍中心窩新生血管に対する新生血管抜去術の有効性が確立されている[13]。しかし，中心窩新生血管に対する網膜中心窩移動術など先駆的な手術法には克服すべき課題も多い[14]。

(4) 緑内障

緑内障は単一の疾患ではなく，何らかの原因で網膜神経節細胞軸索の萎縮が生じて視野障害を来す疾患群である。緑内障は閉塞隅角緑内障，開放隅角緑内障，および正常圧緑内障に大別される。角膜と虹彩根部よりなる隅角は房水流出路であり，そこが閉塞し眼圧が上昇する閉塞隅角緑内障は中年期以降の女性に多い。急性タイプの場合は眼痛，視力低下，頭痛，嘔吐などの症状を呈する。閉塞隅角緑内障の場合，抗コリン剤やマイナートランキライザーなどの薬剤は禁忌である。

1988～89年の疫学調査の結果[15]，日本人では正常圧緑内障が緑内障の過半数を占めることが明らかとなった。正常圧緑内障とは眼圧が正常域（21mmHg以下）であるにも関わらず緑内障性視神経障害が生じるタイプで，視神経乳頭篩板の脆弱性に問題があると考えられている。開放隅角緑内障と同様に，末期に至るまで自覚症状はほとんどなく，視野異常が進行して気付くことが多い。視野異常のほかには視神経乳頭の陥凹拡大が唯一の所見である場合が多く，不可逆性の疾患であることから，眼圧検査とともに眼底検査による早期発見・治療が重要である（図5）。

現時点での緑内障治療は眼圧下降療法が中心である。眼圧が高いタイプの緑内障の場合はもちろんであるが，正常圧緑内障でも眼圧下降が唯一確立された治療法となっている[16]。眼圧下降点眼薬として房水流出抵抗軽減に作用する縮瞳薬，房水産生抑制に作用するβ受容体遮断薬が使用されてきた。近年，ぶどう膜強膜流出の促進に作用するプロスタグランジン関連化合薬や房水産生を抑制する炭酸脱水酵素阻害点眼薬などが開発され効果をあげている。手術療法では従来，線維柱帯切除術や線維柱帯切開術が用いられてきた。最近では，術後合併症を抑え眼圧を低くコントロールするための非穿孔線維柱帯切除術など新しい術式が試みられている。

(5) その他

加齢に伴って上記疾患のほかに，網膜静脈閉塞症，黄斑円孔，黄斑上膜などが生じやすくなり，重篤な視覚障害を招く可能性がある。また，涙液分泌の減少に伴うドライアイや，鼻涙管狭窄による流涙症，眼瞼下垂などの頻度も高くなる。

おわりに

本稿では加齢に伴い生じる眼の変化と主な疾患につき概略を述べた。一般に，高齢者では視機能が低下しているため，印刷物や案内表示など公共性の高い場合には，大きな文字を使用したりコントラストを高めるなど，日常生活における視環境への配慮が望まれる。また，高齢者の眼疾患は不可逆性の場合が多く，視機能に重篤な障害を生じるため，疾病の予防が重要であろう。一方，日常生活上では不適切な屈折矯正が視力障害の原因である場合も多い[17]。高齢者では定期的な視力検査の機会も減少するため，住民検診での視力検査や眼底検査などのシステムを整備し，中高年者の眼疾患の早期発見・早期治療に役立てていくことが望まれる。

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ELSEVIER

Refractive Errors and Factors Associated with Myopia in an Adult Japanese Population

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Purpose: To investigate the refractive status and factors associated with myopia by a population-based survey of Japanese adults.

Methods: A total of 2168 subjects aged 40 to 79 years, randomly selected from a local community, were assessed in a cross-sectional study. The spherical equivalent of the refractive error was calculated and used in a multiple logistic regression analysis to evaluate the relationships between myopia and possible related factors.

Results: The mean (± SD) of the spherical equivalent was −0.70 ± 1.40 diopters (D) in men, and −0.50 ± 1.44 D in women. Based on ± 0.5 D cutoff points, the prevalence of myopia, emmetropia, and hypermetropia were 45.7%, 40.8%, and 13.5% in men, and 38.3%, 43.1%, and 18.6% in women, respectively. A 10-year increase in age was associated with reduced risk of myopia [men: odds ratio (OR) = 0.53, 95% confidence interval (CI): 0.44–0.62; women: OR = 0.65, 95% CI: 0.54–0.78]. In men, myopia was significantly associated with higher education (high school: OR = 1.6, 95% CI: 1.1–2.3; college: OR = 2.0, 95% CI: 1.3–3.1) and management occupations (OR = 1.6, 95% CI: 1.0–2.4). For women, high income (OR = 1.5, 95% CI: 1.1–2.2), and clerical (OR = 1.5, 95% CI: 1.0–2.4) and sales/service occupations (OR = 1.7, 95% CI: 1.1–2.6) were also associated with myopia.

Conclusions: The prevalence of myopia in a Japanese population was similar to that in other Asian surveys but higher than in black or white populations. Our study confirmed a higher prevalence of myopia among younger vs. older populations, and a significant association with education levels and socioeconomic factors. **Jpn J Ophthalmol 2003;47:6–12** © 2003 Japanese Ophthalmological Society

Key Words: Age, education level, myopia, refractive error, socioeconomic factors.

Introduction

Earlier studies have shown that the prevalence of myopia is higher in the Asian population than in black and white populations,[1] and several epidemiological studies have shown that both genetic factors, such as race[2] and family history,[2–5] and environmental factors, such as education level[6–8] and socioeconomic status,[9–11] are important risk factors for myopia. The prevalence of myopia seems to be increasing worldwide.[1,12] In particular, the incidence of myopia has increased rapidly in younger generations over the past few decades,[13–15] and the concurrent increase in formal education and white-collar occupations may be a reason for this increase.[1]

In Japan, however, there has been no population-based survey investigating the refractive status in an adult population. Although a nationwide glaucoma survey[16] showed the prevalence of refractive errors by age, other factors related to myopia have not yet been analyzed.

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In the present study, we investigated the refractive status of middle-aged to elderly populations living in two communities in Aichi prefecture, Japan. In addition, the relationships between myopia and several other factors, such as age, physique, education level, and socioeconomic status, were examined.

Materials and Methods

Data for the present report were obtained from a population-based survey of aging conducted in Obushi and Higashiura-cho, Aichi prefecture, Japan, by the National Institute for Longevity Sciences—the Longitudinal Study of Aging (NILS-LSA). Random sampling from the municipal register, which was stratified by age and sex, identified eligible subjects of the same racial and ethnic origin, aged from 40 to 79 years.

A detailed description of this study design has been reported elsewhere.[17] In brief, the NILS-LSA consists of clinical evaluations, body composition and anthropometry, physical functions, nutritional analysis, and psychological tests. Participants were interviewed at the research center on demographic characteristics, medical and ophthalmologic history, and self-reported vision problems. The Ethical Committee of the Chubu National Hospital reviewed and approved all procedures for the study, and a written informed consent was obtained from all subjects.

We analyzed the baseline data of NILS-LSA obtained between March 1997 and April 2000. During this period, 2267 people (1136 men and 1131 women)

Table 1. Characteristics of Participants

	Men (n = 1087)		Women (n = 1081)	
Characteristics	Mean	SD*	Mean	SD*
Age (years)	58.7	10.8	58.7	10.8
Height (cm)	164.7	6.3	151.5	6.0
Weight (kg)	62.3	9.1	52.6	8.3
Smoking (pack-years)	24.6	22.5	1.6	6.6
Refractive error of the right eye (spherical equivalent)				
40–49 years	−1.35	1.37	−1.22	1.37
50–59 years	−1.03	1.43	−0.67	1.33
60–69 years	−0.22	1.17	−0.09	1.37
70–79 years	−0.09	1.20	0.04	1.31
Total	−0.70	1.40	−0.50	1.44
	n	%	n	%
History of				
Hypertension	262	24.1	284	26.3
Diabetes	106	9.8	58	5.4
Household income (Yen)				
<6.5 million	412	37.9	448	41.4
6.5–10 million	376	34.6	290	26.8
>10 million	291	26.8	275	25.4
Education level				
Elementary school or junior high school	314	28.9	393	36.4
High school	438	40.3	430	39.8
College or university or higher	332	30.5	253	23.4
Occupation				
Expert	135	12.4	89	8.2
Management	204	18.8	6	0.6
Clerical	127	11.7	245	22.7
Sales, service	51	4.7	171	15.8
Physical labor	358	32.9	227	21.0
Security guard	24	2.2	0	0.0
Agriculture, forestry, fishery	47	4.3	62	5.7
Business on one's own	78	7.2	57	5.3
Housework	0	0.0	108	10.0
Unclassified	40	3.7	80	7.4

*SD: standard deviation.

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participated in the NILS-LSA. We excluded participants with a previous history of cataract surgery and those without refractive error data, so that 2168 people (1087 men and 1081 women) were included in the present study.

As part of our standardized examination, an automated objective refraction test was performed on each participant with an AutoRefractor & Keratometer (ARK700A, NIDEK, Gamagori). Visual acuity was then measured with Landolt broken rings at 5 meters under standard lighting conditions, and measured initially using any corrective devices the participants were currently using. If the participant was unable to read the 1.0 equivalent line, refraction was performed using the results of the objective refraction as a starting point. The best-corrected visual acuity was found, and both the derived refractive data and the visual acuity were recorded. When the presenting acuity of the participant was 1.0 or better, the initial objective refraction was recorded as the subject's refractive data. The spherical equivalent (sphere + 1/2 cylinder) was used to calculate the refractive error. Because of the age of our study population, cycloplegia was not used.

Information on smoking habits, household income, education level, and lifetime occupation was obtained from the questionnaires filled out by the participants. Total pack-years smoked was defined as the number of cigarettes smoked per day divided by 20, multiplied by the number of years smoked. Any history of hypertension and diabetes was also recorded.

Myopia was defined as the spherical equivalent of ≤ -0.5 diopters (D). We further categorized the myopia as mild myopia (>-0.5 D to -3.0 D), moderate myopia (>-3.0 D to -6.0 D) and high myopia (≥ -6.0 D). Hypermetropia was defined as the spherical equivalent of more than +0.5 D, and emmetropia was defined as the spherical equivalent of +0.5 D or less but >-0.5 D. Because the spherical equivalents in the right and left eyes were highly correlated (Pearson's correlation: $r = 0.91$, $P < .0001$ in men; $r = 0.88$, $P < .0001$ in women), we present the data for only the right eye.

To estimate how other factors may be associated with refractive errors, we grouped household income and education level into three categories each, and occupation into 10 categories (Table 1).

For analysis, the values for the spherical equivalent of refractive errors, age, height, weight, and pack-years smoked were entered as continuous variables. The relationships among these variables were assessed using the Spearman correlation analysis. We used the Student t-test, analysis of variance, the Cochran-Mantel-Haenszel χ^2, and general linear regression (including trend tests) to assess the relationships between the spherical equivalent and other potential risk factors. Multiple logistic regression was used to determine whether these variables affected the risk of myopia. All statistical analyses were performed by sex because there were large differences between the sexes in several factors (eg, smoking habit or occupation). Data were analyzed using the Statistical Analysis System (SAS) release 6.12.[18]

Results

The characteristics of the study population are presented in Table 1. The mean age was 58.7 years for each sex. The mean ($\pm$ SD) spherical equivalent of the refractive error was -0.70 ± 1.40 D in men and -0.50 ± 1.44 D in women. This constituted a significant difference between the sexes (t-test, $P = .001$). The older age groups had more hypermetropic refractive errors in both sexes ($P < .0001$ for trend).

The mean value for pack-years smoked was significantly greater for men than for women (t-test, $P < .0001$), and there were also significant differences in occupations between sexes ($\chi^2 = 478.3$, $P < .0001$). In particular, men did not list housework and women did not list guard work as lifetime occupations.

The distribution of the spherical equivalent of refractive error is shown in Figure 1. Based on the $\pm$ 0.5 D cutoff points, the prevalence of myopia, emmetropia, and hypermetropia were 45.7%, 40.8%, and 13.5% in men, and 38.3%, 43.1%, and 18.6% in women, respectively. This difference in distribution between sexes was also highly significant ($\chi^2 = 16.5$, $P = .0003$). The incidence of mild myopia was 37.9% in men and 30.5% in women, moderate myopia was

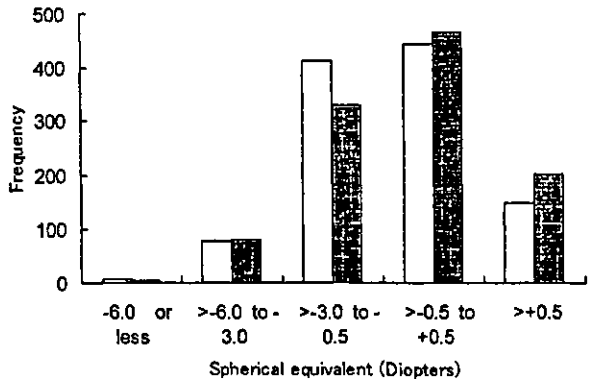

Figure 1. Distribution of refractive errors by sex. □ men women, ■.

7.2% and 7.3%, respectively, and high myopia was 0.6% and 0.5%, respectively.

The distribution of spherical equivalent by age groups and sex is shown in Figure 2. The prevalence of hypermetropia increased with age in both men (Cochran-Mantel-Haenszel $\chi^2 = 108.6$, $P < .001$) and women (Cochran-Mantel-Haenszel $\chi^2 = 149.0$, $P < .001$). For participants in their 40s, 1.4% of men and 1.1% of women showed hypermetropia, while the figures were 27.8% and 38.1% when they reached their 70s. Although the prevalence of hypermetropia was higher in women than in men in all age groups except for the 40–49-year group, the differences in data were not significant between sexes. The prevalence of myopia (spherical equivalent ≤ -0.5 D) decreased with advancing age in both men (Cochran-Mantel-Haenszel $\chi^2 = 118.3$, $P < .001$) and women (Cochran-Mantel-Haenszel $\chi^2 = 87.6$, $P < .001$). In the 40–49-year age group, 69.4% of the men and 60.2% of the women were myopic, while in the 70–79-year age group, only 28.6% of the men and 25.4% of the women were myopic.

A simple correlation analysis showed a significant positive association between age and the spherical equivalent of refractive errors for both sexes ($P < .0001$). Conversely, height and weight had a significant inverse association with the spherical equivalent for both sexes ($P < .0001$), and pack-years smoked

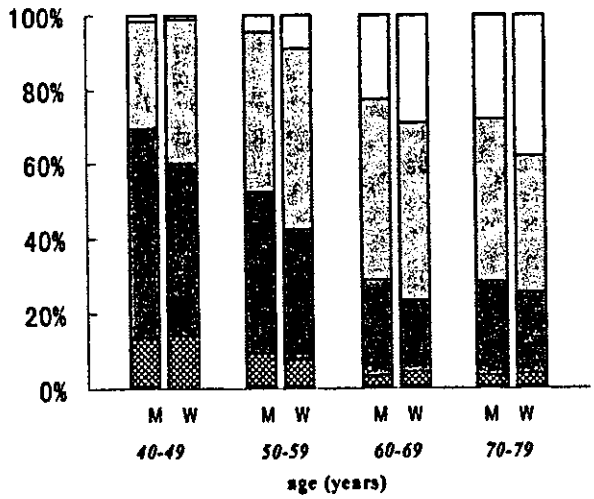

Figure 2. Refractive status, stratified by age and sex. Refractive status, spherical equivalent, are defined as: hypermetropia (> +0.5 diopters [D]), emmetropia (> −0.5 to +0.5 D), mild myopia (> −3.0 to −0.5 D), moderate myopia (> −6.0 to −3.0 D), high myopia (≤ −6.0 D). M: men, W: women. □: hypermetropia, □: emmetropia, □: mild myopia, ▩: moderate myopia, ■: high myopia, in descending order from top to bottom of each column.

was positively correlated with the spherical equivalent in men ($P = .004$), but inversely in women ($P = .001$). However, these significant associations, except for height in women, were not found when adjustments were made for age.

In the categorical variables, the participants with a history of hypertension had a lower mean spherical equivalent value than those without a history of hypertension (t-test, men: $P = .017$, women: $P = .001$). However, a history of diabetes had no significant influence on the mean spherical equivalent in either sex. A significant relationship between the spherical equivalent and household income was found (men: $F = 29.0$, $P < .0001$, women: $F = 21.5$, $P < .0001$), with the spherical equivalent decreasing as the household income increased ($P < .0001$ for trend). Similarly, a higher education level was associated with greater myopia in both sexes (men: $F = 45.4$, $P < .0001$, $P < .0001$ for trend; women: $F = 22.3$, $P < .0001$, $P < .0001$ for trend). There were also significant associations between the spherical equivalent and lifetime occupations (men: $F = 7.7$, $P < .0001$, women: $F = 4.7$, $P < .0001$).

Finally, multiple logistic regression analysis for the risk of myopia (spherical equivalent ≤ -0.5 D) using all variables was performed (Table 2). An increase in age of 10 years was associated with a 0.53 [95% confidence interval (CI): 0.44–0.62] and 0.65 (95% CI: 0.54–0.78) lower probability of having myopia in men and women, respectively. Men with a higher education were at higher risk for myopia: high school, odds ratio (OR) = 1.59, 95% CI: 1.10–2.29; college or higher, OR = 2.05, 95% CI: 1.33–3.14. In women, the highest income group was associated with a higher incidence of myopia (OR = 1.52, 95% CI: 1.05–2.18) compared with the lowest income group.

To assess the effect of occupation, we considered persons in the physical labor category as a reference group because this was the most frequent occupation in the present study (27.0% of the participants). The presence of myopia was associated with management occupations (OR = 1.55, 95% CI: 1.01–2.39) in men, and with clerical (OR = 1.54, 95% CI: 1.01–2.36) and sales/service (OR = 1.66, 95% CI: 1.06–2.61) occupations in women. No association was found in either sex between pack-years smoked, hypertension, or diabetes and the presence of myopia.

Discussion

The main findings of this investigation in a large Japanese population are that the prevalence of myopia was 45.7% in men and 38.3% in women, and that there are significant independent associations be-

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Table 2. Results of Multiple Logistic Regression for Risk of Myopia

Variables	Men		Women	
	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
Age (10 years)	0.53	0.44–0.62	0.65	0.54–0.78
Height (10 cm)	1.24	0.93–1.65	1.14	0.85–1.53
Weight (10 kg)	0.82	0.68–0.98	0.98	0.81–1.18
Education level				
Elementary school or junior high school (reference)	1		1	
High school	1.59	1.10–2.29	1.21	0.85–1.71
College or university or higher	2.05	1.33–3.14	1.27	0.84–1.93
Household income (Yen)				
<6.5 million (reference)	1		1	
6.5–10 million	0.89	0.62–1.26	1.12	0.79–1.60
>10 million	1.04	0.72–1.51	1.52	1.05–2.18
Occupation				
Expert	1.48	0.91–2.41	0.68	0.38–1.22
Management	1.55	1.01–2.39	1.12	0.17–7.40
Clerical	1.52	0.95–2.42	1.54	1.01–2.36
Sales, service	1.56	0.81–3.01	1.66	1.06–2.61
Physical labor (reference)	1		1	
Security guard	1.08	0.42–2.81	N/A*	
Agriculture, forestry, fishery	1.70	0.83–3.45	1.07	0.52–2.17
Business on one's own	0.58	0.32–1.05	1.12	0.57–2.18
Housework	N/A*		0.78	0.45–1.38
Unclassified	1.78	0.84–3.77	1.00	0.56–1.79
Smoking (per 10-pack-years)	1.00	0.94–1.06	1.07	0.87–1.31
History of				
Hypertension	1.15	0.82–1.61	0.88	0.62–1.26
Diabetes	1.15	0.72–1.84	1.63	0.83–3.18

*N/A: not applicable

tween the presence of myopia and several socioeconomic factors.

There are many studies examining the distribution of refractive error and the risk factors for the refractive errors. In an adult population, it has been reported that there is a significant association between myopia and several different factors such as age,[6,7,9–11,16,19–24] family history,[2–5] education level,[6–8] socioeconomic status,[9–11] and cataracts.[9,11] The relationships between refractive error and height or weight are unconvincing, although eye size may be linked to body stature.[25] Other factors such as nutrition, ultraviolet exposure, use of drugs, cigarette smoking, hypertension, and diabetes might be associated with myopia, because they are associated with the prevalence of age-related cataracts.[26]

Previous population-based surveys reported a racial difference in the prevalence of myopia. The proportion of myopia is 17–26.2% in white populations[3,6,7,9,19,20] and 13–21.9% in black populations.[7,11,20] In contrast, the prevalence of myopia in East Asian countries is much higher. Wong et al[10] showed that the prevalence of myopia in Singapore Chinese people between 40 and 79 years of age was 38.7%, and Van Newkirk measured the prevalence in Hong Kong at approximately 40%.[27] In Japan, it was reported that 47.6% of people 40–69 years old were myopic.[16] The Visual Impairment Project study in Australia[9] concluded that people born in Southeast Asia had significantly higher rates of myopia than in any other geographical area, even after adjusting for age and education level. Our results showed that the prevalence of myopia in Japan is as high as in other Southeast Asian countries.

It has been suggested that genetic variations among races influence the prevalence of myopia in the groups studied.[1] Studies in twins also suggest the importance of genetic factors in myopia. In particular, a recent twin study in the United Kingdom by Hammond et al[5] indicated that the heritability for myopia was 84% to 86%, with the remaining 16% to 14% of the variance due to environmental factors.

Cross-sectional studies have shown that the prevalence of myopia is higher in recent years than in former times.[13–15] In particular, among East Asian countries, the prevalence of myopia has increased remarkably over the last few decades.[13,28]

Because it is highly unlikely that this rapid change could be explained by genetic factors alone, environmental factors are probably also important in the etiology of myopia. A possible reason for the rapid increase in myopia rates in Asian countries is the greater close work demands on the younger generation, such as increased formal education or the shift to white-collar occupations.[1] In fact, several longitudinal studies have revealed that reading or close work could cause refractive myopic shifts from childhood through adolescence.[29–31]

Similarly, we found a significant independent association between education level and the prevalence of myopia in men. The relationship between myopia and certain occupations was demonstrated by data on professionals and clerks in the Visual Impairment Project study,[9] professional and office workers among Singapore Chinese,[10] and with near-work–related occupations (professional, managerial, clerical, technical, electrical) in the Barbados Eye Study.[11] Our study showed similar results in people who stated they were in management or clerical occupations. Sales/service occupations in women also showed a significant relationship to myopia in the present study, which may be due to the indistinct boundary between clerical and sales/service occupations for women. These results seem consistent with the use-abuse theory.[1,32]

Our findings confirmed the age-related increase in hypermetropia with an associated age-related decrease in myopia, which has been reported in previous studies.[6,7,9–11,16,19–24] It was suggested that this trend toward hypermetropia was due to decreasing lens power with aging,[33] or an increasing optical density of the lens cortex making the lens more uniformly refractive.[34] Another possible explanation is that the relationship between age and refraction reflects a worldwide trend. Bengtsson et al[12] showed that a true hypermetropic shift did exist between 55 and 70 years of age; however, there was also a persistent worldwide trend toward myopia using a meta-analysis method. It was assumed that this worldwide trend for myopia is 0.01 D per year.

The relationship between refraction and stature is inconsistent. It was reported in one study that myopic subjects were taller than nonmyopic subjects.[35] In contrast, there was no significant association between height and refractive error after adjustment for sex in the Blue Mountains Eye Study.[19] Wong et al[25] showed that the refraction between tall and short people appeared to be similar, although taller persons tended to have longer globes. Similarly, the relationship that myopia was prevalent in taller and heavier persons in our univariate analysis seems to be apparent in our results. This may be due to the cohort phenomenon that younger persons are larger in physique and more myopic in refraction than elderly persons in Japan.

To the best of our knowledge, there are no available population-based studies on the association of refractive errors with hypertension or cigarette smoking. However, because a significant relationship between cataracts and myopia has been detected in several studies,[9–11] and cataracts appear to be associated with hypertension and smoking,[36] we assume that a history of hypertension or smoking has some influence on refractive errors. However, in our study, they were not significant independent factors affecting the prevalence of myopia. There was also no significant difference in refractive error between people with or without diabetes, which is consistent with the Beaver Dam Eye Study.[6] In contrast, a significantly higher prevalence of myopia in diabetics as compared to nondiabetics was found in two Danish studies.[37,38] Up to the present, longitudinal prospective studies investigating the influence of smoking, hypertension, and diabetes on refractive error have not been conducted.

There are some important limitations in the present study. First, these data were cross-sectional, with all parameters measured simultaneously. Therefore, it is difficult to make conclusive statements about a cause–effect relationship between refractive errors and the educational level or socioeconomic factors. A high education level may not only cause a myopic shift in refraction, but it also seems likely that those with myopia are more likely to choose a higher education level or close work. Second, although we did not have data on cataract status or family history of refractive errors, several studies have indicated the independent effect of family history[1,2] and cataract status[9–11] on refractive errors. Third, there was a selection bias in our population. Because the examinations of the NILS-LSA participants were performed at the National Institute for Longevity Science, those participants with limited activity level or living in an institution may not have been able to travel and participate in our survey, which may have influenced our findings.

In conclusion, we showed the prevalence of refractive errors in a middle-aged and elderly Japanese population. The frequency of myopia was 45.7% in men and 38.3% in women, which are findings similar to those in other Asian surveys and higher than those found in black or white populations. As previously reported, our study confirmed a higher prevalence of my-

opia among the younger population than the elderly. It was also found that myopia was independently associated with education level and socioeconomic factors. Changing environmental factors, such as an increase in close work, may be one of the reasons for the higher prevalence of myopia in the younger generation. Unfortunately, the cross-sectional approach in the present study limits our conclusions. However, prospective research by the NILS-LSA should provide further information on myopia and its risk factors.

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Relationships of the Systolic Blood Pressure Response During Exercise With Insulin Resistance, Obesity, and Endurance Fitness in Men With Type 2 Diabetes Mellitus

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The purpose of the present study was to investigate the relationships among the resting systolic (SBP) and diastolic blood pressure (DBP) or SBP response during exercise with insulin resistance evaluated by a homeostasis model (HOMA-IR), abdominal fat accumulation (visceral fat area [VFA], subcutaneous fat area [SFA]) by computed tomography (CT), and an estimation of the maximal oxygen uptake ($\dot{V}o_2max$) in 63 Japanese middle-aged male patients with type 2 diabetes mellitus (type 2 DM). Body mass index (BMI) and waist-to-hip ratio (WHR) in type 2 DM subjects were significantly higher than in age-matched healthy male control subjects (n = 135) with normal glucose tolerance. Resting SBP (127.7 ± 16.2 mm Hg *v* 119.4 ± 13.0 mm Hg) and DBP (82.2 ± 11.9mmHg *v* 76.8 ± 9.4 mm Hg) levels, and the percentage of hypertension (20.6% *v* 1.5%) in type 2 DM subjects were significantly higher than in the control subjects ($P < .05$). According to a multiple regression analysis for resting blood pressure in type 2 DM, VFA was found to be an independent predictor of SBP, while $\dot{V}o_2max$ and HOMA-IR were independent predictors of DBP. In the controls, however, HOMA-IR was not found to be a significantly independent predictor for either resting SBP or resting DBP. Measurement of the SBP response during graded exercise using a ramp test was performed by an electrical braked cycle ergometer in 54 patients with type 2 DM only. The SBP was measured at 15-second intervals during exercise. The exercise intensity at the double product breaking point (DPBP), which strongly correlated with the exercise intensity at the lactate threshold, was used as an index for the SBP response to standardized exercise intensity. The SBP corresponding to exercise intensity at DPBP (SBP@DPBP) was evaluated as an index of the SBP response to standardized exercise intensity. The change in SBP (ΔSBP = SBP@DPBP − resting SBP) was significantly and positively associated with log area under the curve for glucose (log AUCPG) during a 75-g oral glucose tolerance test (OGTT). In addition, ΔSBP significantly and negatively correlated with the log area under the curve for insulin (log AUCIRI) and log AUCIRI/log AUCPG. Based on these results, insulin resistance was suggested to be independently associated with the resting DBP and SBP response to standardized exercise intensity in type 2 DM patients.

IT HAS BEEN postulated that insulin resistance or hyperinsulinemia might be an etiologic cause of hypertension.[1,2] Obese patients, especially those with visceral fat obesity, and patients with type 2 diabetes mellitus (type 2 DM) frequently demonstrate hypertension.[3] In animal studies, spontaneously hypertensive rats have been reported to have more insulin resistance and/or hyperinsulinemia.[4] However, a few reports have suggested that such insulin action as an etiologic cause of hypertension may be independent of factors such as obesity and glucose intolerance. For example, Modan et al[5] demonstrated significantly higher glucose and insulin responses to a 75-g oral glucose tolerance test (OGTT) in obese hypertensives compared with obese normotensives. In addition, DeFronzo and Ferrannini[6] reported that insulin sensitivity, as evaluated by a hyperinsulinemic eugycemic clamp, in essential hypertension patients was significantly lower than in normotensive controls after matching for age and sex, and independent of obesity and glucose intolerance.

Several cross-sectional studies observed a good correlation between physical activity or endurance fitness (ie, maximal oxygen uptake [$\dot{V}o_2max$]) and resting blood pressure in healthy men and women.[7] In addition, several prospective epidemiologic studies in normotensive subjects have demonstrated that an exaggerated blood pressure response to a given and relative exercise intensity[8-11] and a lower quintile of the $\dot{V}o_2max$ or endurance capacity[12] are good predictors for developing hypertension. Aerobic exercise is recommended to be a useful antihypertensive treatment for hypertensive patients with and without obesity,[13] and aerobic exercise training results in a reduction of the blood pressure response to a given and relative exercise intensity.[14] The resting blood pressure level in hypertensive patients has also been shown to be significantly reduced by exercise therapy, independent of weight loss.[15]

However, there have been few reports concerning the contribution of insulin resistance or hyperinsulinemia on blood pressure at rest and during exercise in type 2 DM subjects, who have insulin resistance as a pathophysiologic condition. Based on the aforementioned evidence, we investigated the relationships between resting blood pressure or blood pressure response during exercise to insulin resistance, obesity indices, and endurance fitness in Japanese male patients with type 2 DM who had not yet been treated with any intervention therapy for diabetes mellitus.

MATERIALS AND METHODS

Subjects

Age-matched Japanese male patients with type 2 DM (n = 63; 49.3 ± 8.6 years) and control subjects with normal glucose tolerance (n = 135; 48.4 ± 5.4 years) were selected for this study. Type 2 DM was classified based on the criteria of the Japan Diabetes Society

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(1999) and was defined as a fasting glucose level ≥ 126 mg/dL and/or 2-hour glucose level ≥ 200 mg/dL. None of the patients had been taking any medication or receiving any intervention therapy such as exercise or diet before participating in the present study. No subject had a history of microalbuminuria. The duration of diabetes mellitus was relatively short, ranging from 2 months to 2 years. The control subjects were apparently healthy male employees working at a food company located in southwestern Japan. Among this group, any subjects taking medications that might affect their lipid and glucose metabolism or resting blood pressure, as well as subjects with a fasting blood glucose greater than 120 mg/dL, were excluded.[16] All experiments and procedures were approved by the Ethics Committee in the Institute of Health Science, Kyushu University. We obtained informed consent from all participants.

Obesity Indices

The anthropometric parameters of shoeless subjects wearing light clothing in an upright position were measured by the same researcher. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Skinfold thickness was measured by Harpenden caliper to calculate the percentage of body fat (%Fat) using the formula described by Brozek and Henschel[17] after estimating body density according to Nagamine and Suzuki.[18] The waist-to-hip ratio (WHR) was used as an index of abdominal fat distribution. Waist circumference was measured at the narrowest point between the rib cage and the iliac crest, and hip circumference was measured at the level of the greater trochanter. In addition to these obesity indices, abdominal fat accumulation at the level of umblicus was measured by computed tomography (CT) scan, and visceral fat area (VFA) and subcutaneous fat area (SFA) were calculated in the type 2 DM patients only. Ordinary CT parameters were used, specifically 120 kV and 200 mA, and a slice thickness of 5 mm, scanning time of 2 seconds, and field of view of 400 mm. Briefly, a region of interest of the subcutaneous fat layer was defined by tracing its contour on each scan, and the attenuation range of the CT numbers (in Hounsfiled units) for fat tissue was calculated. A histogram for fat tissue was computed based on the mean attenuation ± 2 SD. Total and intraperitoneal tissue with attenuation within the mean ± 2 SD were considered to be the total fat area and VFA. The SFA was calculated by subtracting the VFA from the total fat area.

Estimated Maximal Oxygen Uptake

To evaluate the level of endurance fitness, $\dot{V}o_2max$ was calculated by an indirect method using a cycle ergometer.[19]

Blood Pressure Measurement at Rest and During Exercise

The resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured indirectly using a mercury sphygmomanometer placed on the right arm of the seated participant after at least 30 minutes of rest in both the type 2 DM and the control groups. The SBP response to a linear-graded exercise test using a ramp test was measured by an electrical braked cycle ergometer (Examiner Type 400, Lode Co, Groningen, Netherlands) in the type 2 DM group only (n = 54). The work rate was initially set a 0 W and then was increased every 1 minute by 15 W, while cycling at 60 rpm. The test was stopped when the subject reached a relative perceived exertion score of 15 (hard). Inspired and expired gases were analyzed by a computerized on-line breath-by-breath system (System RM-300i, Minato Medical Science, Osaka, Japan). Oxygen uptake ($\dot{V}o_2$) was automatically and continuously measured every 30 seconds using a mass spectrometer (WSMR-1400, Westron, Chiba, Japan) for O_2 and CO_2 fractions. Inspiratory and expiratory flow rates were measured by a hot-wire flowmeter. SBP and heart rate (HR) were measured using a modified automated blood pressure and HR monitor (CM-4001, Kyokko Bussan, Tokyo, Japan) during exercise. The cuff-pressure decreased to 0 mm Hg immediately after determining the SBP and began to increase at 5-second intervals. The double product, which is defined as an indirect indicator of the myocardial oxygen demand, was calculated almost every 15 seconds from the SBP and the HR corresponding to the time when the SBP was measured. These measurements were done automatically and the data were displayed on the monitor during exercise using a personal computer (NEC PC9801, Tokyo, Japan). The exercise intensity at the double product breaking point (DPBP), which was strongly correlated with the exercise intensity at the lactate threshold,[20] was used as an index for the SBP response to standardized exercise intensity. Tanaka et al[20] reported that the test-retest mean difference in DPBP with CM-4001 was not statistically significant, and that the correlation coefficient between 2 tests was 0.95 ($P < .05$). The SBP corresponding to the exercise intensity at BPDP (SBP@DPBP) was evaluated. The change in SBP (ΔSBP) was calculated as SBP@DPBP − resting SBP. The test was continued until DPBP was detected by 2 researchers. This exercise test was not performed on the control subjects.

Oral Glucose Tolerance Test

Blood samples were drawn from an antecubital vein after a 12-hour fast to determine the fasting plasma glucose (FPG) and fasting insulin (FIRI). Thereafter, a 75-g OGTT was conducted in type 2 DM patients only and analyzed for plasma glucose and insulin. Blood samples were taken at 0, 30, 60, 90, and 120 minutes. Plasma glucose and insulin were measured by an enzymatic method and by radioimmunoassay using an IRI Kit (Pharmacia, Uppsala, Sweden), respectively. The plasma glucose area under the curve (AUCPG) and insulin area under the curve (AUCIRI) were calculated by the trapezoidal rule using absolute values. Insulin resistance (HOMA-IR) was evaluated using a homeostasis model (HOMA)[21] based on the following formula: FIRI(μU/mL) × FPG (mmol/mL)/22.5. A significant correlation has been reported between HOMA-IR and insulin sensitivity evaluated by hyperinsulinemic euglycemic glucose clamp in Japanese patients with type 2 DM with fasting blood glucose levels ranging from 80 to 170 mg/dL.[22] These results have also been reproduced by another group of Japanese researchers using similar samples of Japanese patients with type 2 DM.[23,24]

Statistical Analysis

Results were expressed as the mean ± SD. Linear correlation and stepwise multiple regression analyses were used for statistical analysis using the StatView software package. Because FIRI, AUCPG, and AUCIRI were not normally distributed, log-transformed values were used. After log transformation, FIRI, AUCPG, and AUCIRI were normally distributed. A probability value of less than .05 was considered to indicate statistical significance.

RESULTS

Table 1 shows the physical characteristics in both groups. Both the BMI and WHR were significantly higher in the type 2 DM group than in the control group. Resting SBP (127.7 ± 16.2 mm Hg *v* 119.4 ± 13.0 mm Hg) and DBP (82.2 ± 11.9 mm Hg *v* 76.8 ±9.4 mm Hg) were significantly higher in the type 2 DM group than in the control group. The percentages of hypertension evaluated by World Health Organization (WHO) criteria in the type 2 DM and control groups were 20.6% (n = 13) and 1.5% (n = 2), respectively ($P < .05$). No difference between the groups was observed in $\dot{V}o_2max$.

Table 2 shows the simple correlation coefficients in the control and type 2 DM groups. In the type 2 DM group, the

Table 1. Physical Characteristics of the Control and Type 2 DM Groups

	Control (n = 135)	Type 2 DM (n = 63)
Age (yr)	48.4 ± 5.4	49.3 ± 8.6
BMI (kg/m^2)	23.0 ± 2.3	25.3 ± 3.9*
WHR	0.87 ± 0.05	0.95 ± 0.05*
%Fat (%)	19.0 ± 6.3	20.3 ± 5.7
SFA (cm^2)	—	137.2 ± 66.6
VFA (cm^2)	—	167.3 ± 61.0
$\dot{V}o_2$max (mL/kg/min)	34.5 ± 4.2	34.1 ± 4.9
SBP (mm Hg)	119.4 ± 13.0	127.7 ± 16.2*
DBP (mm Hg)	76.8 ± 9.4	82.2 ± 11.9*
Hypertension (%)	1.5% (n = 2)	20.6% (n = 13)*
FPG (mg/dL)	89.1 ± 7.6	156.4 ± 36.6*
FIRI (μU/mL)	4.9 ± 2.5	7.6 ± 6.2*
HOMA-IR†	1.1 ± 0.6	3.0 ± 2.8*
Insulinogenic index‡	—	0.13 ± 0.14
AUCPG(mg/dL/h)	—	748.7 ± 163.9
AUCIRI (μU/mL/h)	—	79.5 ± 57.3

Abbreviations: BMI, body mass index; WHR, waist-to-hip ratio; % Fat, percentage of body fat; SFA, subcutaneous fat area; VFA, visceral fat area; $\dot{V}o_2$max, maximal oxygen uptake; SBP, systolic blood pressure; DBP, diastolic blood pressure, FPG; fasting plasma glucose, FIRI; fasting insulin level, AUCPG; area under the curve for plasma glucose; AUCIRI, area under the curve for plasma insulin.

*$P < .05$.

†HOMA-IR = FIRI (μU/mL) × FPG (mmol)/22.5.

‡Insulinogenic index = (IRI at 30 min - FIRI)/(PG at 30 min - FPG).

resting SBP level was significantly and positively associated with BMI, VFA, and log FIRI, and negatively with $\dot{V}o_2$max. Resting DBP was significantly and positively associated with BMI, %fat, VFA, SFA, log FIRI, log AUCIRI, and HOMA-IR, and negatively with $\dot{V}o_2$max. In the control group, resting SBP was significantly and positively correlated with age, BMI, WHR, log FIRI, and HOMA-IR, and negatively with $\dot{V}o_2$max. Resting DBP was significantly and positively correlated with BMI and WHR, and negatively with $\dot{V}o_2$max.

Table 3 shows the results of stepwise multiple linear regression analyses with resting SBP and DBP as dependent variables. All regression models included the following factors as potential independent variables; BMI, %fat, VFA, SFA, $\dot{V}o_2$max, HOMA-IR, and AUCIRI in the type 2 DM group, and age, BMI, WHR, $\dot{V}o_2$max, and HOMA-IR in the control group. In addition to these independent variables, model A included FIRI and model B included HOMA-IR. In the type 2 DM group, VFA was a significant independent variable of resting

Table 3. Results of Stepwise Multiple Regression Analysis for the Resting SBP and DBP as Dependent Variables in the Control and Type 2 DM Groups

Dependent Variables	Independent Variables	β†	R^2 for the Model
Control (n = 135)			
SBP	Age	0.22	0.08*
	BMI	0.22	
DBP	BMI	0.28	0.07*
Type 2 DM (n = 63)			
SBP	VFA	0.46	0.19*
DBP	$\dot{V}o_2$max	−0.41	0.31*
	HOMA-IR	0.27	

*$P < .05$.

*β: Regression coefficient. In the control group, the regression models included the following variables as potential independent variables : age, BMI, WHR, $\dot{V}o_2$max, and HOMA-IR. In type 2 DM group, the regression models included the following variables as potential independent variables: BMI, %fat, VFA, SFA, $\dot{V}o_2$max, HOMA-IR, and AUCIRI.

SBP in both models. Resting DBP was independently associated with $\dot{V}o_2$max and HOMA-IR. In the control group, however, insulin resistance was not associated with resting DBP. Age and BMI were independent predictors of resting SBP, and BMI was an independent predictor of resting DBP.

Table 4 lists some physical characteristics and physiologic parameters corresponding to the exercise intensity at DPBP in the type 2 DM group (n = 54). SBP corresponding to the exercise intensity at DPBP was 148.4 ± 22.8 mm Hg.

Table 5 shows the ΔSBP to be significantly and positively associated with log AUCPG and negatively with log AUCIRI and log AUCIRI/AUCPG (Fig 1). On the other hand, age, obesity indices, $\dot{V}o_2$max, and resting SBP were not associated with ΔSBP.

DISCUSSION

We demonstrated a significant correlation between insulin resistance and resting DBP in the type 2 DM group only. In addition, ΔSBP was significantly and positively associated with log AUCPG as an index for glucose intolerance, while it was negatively associated with log AUCIRI and log AUCIRI/AUCPG as an indirect index for insulin sensitivity in the type 2 DM group.

Recently, several studies[25] reported the contribution of insulin resistance or hyperinsulinemia to be one of the etiologic

Table 2. Simple Correlation Coefficients in the Control and Type 2 DM Groups

	Age	BMI	%Fat	WHR	$\dot{V}o_2$max	Log FIRI†	HOMA-IR	VFA	SFA	Insulinogenic Index	Log AUCIRI
Control (n = 135)											
SBP	0.22*	0.22*	0.10	0.21*	−0.18*	0.18*	0.19*				
DBP	0.12	0.28*	0.17	0.22*	−0.20*	0.13	0.14				
Type 2 DM (n = 63)											
SBP	0.18	0.34*	0.24	0.12	−0.33*	0.28*	0.24	0.46*	0.22	0.10	0.22
DBP	−0.09	0.49*	0.41*	0.21	−0.51*	0.42*	0.44*	0.51*	0.40*	0.18	0.26*

*$P < .05$.

†Log-transformed for statistical testing.

Table 4. Physical Characteristics of the Type 2 DM Group (n = 54)

	Type 2 DM Group (n = 54)
Age (yr)	50.7 ± 10.6
Weight (kg)	70.5 ± 13.4
Height (cm)	166.8 ± 6.9
BMI (kg/m^2)	25.3 ± 4.2
WHR	0.9 ± 0.5
%Fat	19.7 ± 5.8
SFA (cm^2)	138.6 ± 70.7
VFA (cm^2)	167.8 ± 65.9
$\dot{V}o_2$max (mL/kg/min)	34.1 ± 5.2
SBD (mm Hg)	127.3 ± 16.6
DBP (mm Hg)	81.5 ± 11.9
$\dot{V}o_2$ at DPBP (mL/kg/min)	11.7 ± 3.3
SBP at DPPP (mm Hg)	148.4 ± 22.8
Hypertension (%)	18.9% (n = 10)
Δ SBP (mm Hg)	26.9 ± 18.0
FPG (mg/dL)	152.6 ± 36.8
FIRI (μU/ml)	7.8 ± 6.6
HOMA-IR	3.0 ± 2.9
Insulinogenic index	0.15 ± 0.17
AUCPG (mg/dL/h)	1122.2 ± 708.5
AUCIRI (μU/mL/h)	85.9 ± 62.8
AUCIRI/AUCPG	0.11 ± 0.12

Abbreviation: Δ SBP, changes from resting SBP to SBP at DPBP.

causes of resting hypertension. However, cause and effect between both variables is still unknown. There have been conflicting findings concerning the resting blood pressure and fasting insulin level or insulin sensitivity.[26-30] The fasting insulin level was more closely correlated with the resting DBP than with the resting SBP.[26,27] Other studies[28-30] did not show any correlation between the fasting insulin level and either resting SBP or resting DBP. We demonstrated that resting DBP in the type 2 DM group was significantly and negatively associated with $\dot{V}o_2$max, while it was positively associated with the index of insulin resistance.

The mechanism for the underlying link between resting DBP and insulin resistance or hyperinsulinemia has been proposed and partially demonstrated in several studies.[25] However, the mechanism mediating the vosodilator action of insulin remains obscure at present. There is evidence for and against both systematic and local mechanisms.[25] The systematic mechanism includes sympathetic neural vasodilation and a humoral vasodilator substance such as epinephrine and insulin in the absence of increased circulating epinephrine levels. The potential local mechanism included a β-adrenergic mechanism, endothelium-dependent relaxation, stimulation of the sodium/potassium pump with hyperpolarization of vascular muscle, increased calcium-adenosine triphosphatase (Ca-ATPase) activity, and metabolic vasodilation secondary to increased skeletal muscle oxygen consumption.[6,25] However, the evidence for both vasodilator mechanisms of insulin is conflicting.

Aoyama et al[31] reported that hyperinsulinemia as evaluated by the insulin level 2 hours after a 75-g OGTT was one of the independent predictors of resting SBP in Japanese middle-aged men including normal healthy controls as well as subjects with impaired glucose tolerance or type 2 DM. In contrast, we found that the HOMA-IR was one of the independent predictors of resting DBP. On the other hand, resting SBP in the type 2 DM group was independently associated with VFA, but not with insulin resistance or hyperinsulinemia.

In this study, we demonstrated that resting DBP in the type 2 DM group was significantly and negatively associated with $\dot{V}o_2$max and positively with insulin resistance. In this context, Dengel et al[32] reported the independent and combined effects of weight loss and aerobic exercise on resting blood pressure and oral glucose tolerance in older men with obesity. They demonstrated that aerobic exercise and weight loss were affective nonpharmacologic therapies to lower blood pressure and alter glucose and insulin responses to an oral glucose challenge. In addition, they found that the best predictor of changes in SBP, DBP, and mean blood pressure after treatment is the change in fasting blood glucose. Several studies[7,13,15,33] have reported an improvement in insulin resistance or glucose intolerance, and in resting blood pressure after exercise therapy in healthy subjects and patients with hypertension and diabetes mellitus with and without obesity. However, few studies have reported a link between the changes in insulin resistance and resting blood pressure. Although our research design was a cross-sectional study, our findings suggested that insulin resistance and endurance fitness were good predictors of resting DBP in type 2 DM. Further study is needed to clarify the effect of insulin resistance on the improvement of resting blood pressure in type 2 DM.

In addition to the correlation between resting DBP and insulin resistance, a significant correlation was observed between ΔSBP and insulin resistance in type 2 DM. A few studies[34,35] were reported concerning the link between blood pressure response during exercise and some risk factors for atherosclerosis. Prud'homme et al[34] demonstrated for the first time in premenopausal obese women that the SBP response to exercise intensity at 55% of an individual's $\dot{V}o_2$max was independently associated with total cholesterol, low-density lipoprotein apoprotein B, and apoprotein B, but not with fasting insulin. Recently, Brett et al[35] demonstrated that changes in DBP during gentle exercise are strongly associated with total

Table 5. Simple Correlation Coefficients in Type 2 DM Group (n = 54)

	Age	BMI	%Fat	WHR	VFA	SFA	$\dot{V}o_2$max
Δ SBP	0.007	−0.205	−0.171	0.025	0.160	−0.232	0.271
	SBP	FPG	Log FIRI	HOMA-IR	Log AUCPG	Log AUCIRI	Log AUCIRI/AUCPG
Δ SBP	−0.147	0.157	−0.241	−0.193	0.303*	−0.296*	−0.380*

*$P < .05$

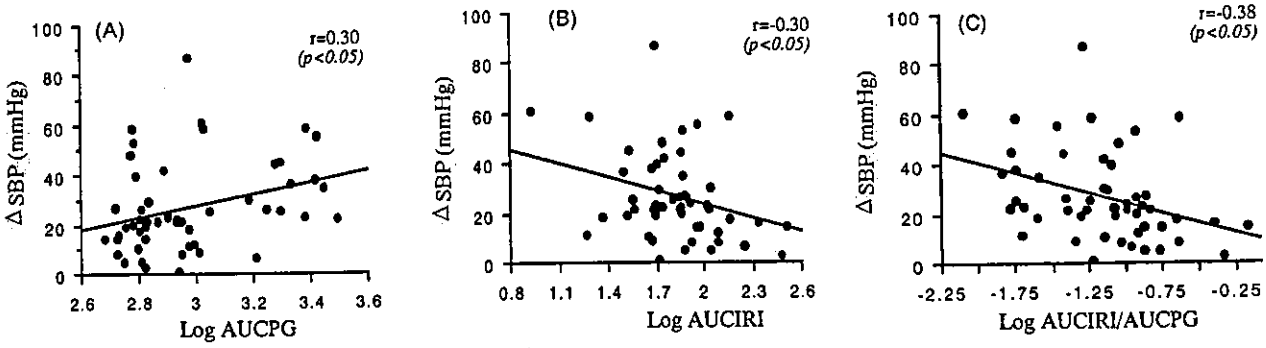

Fig 1. Relationship of SBP response to standardized exercise intensity (ΔSBP) with (A) log AUCPG, (B) log AUCIRI, and (C) log AURPG/AUCIRI.

cholesterol and insulin resistance estimated by homeostasis model assessment in healthy active men. In addition, they reported that the type 2 DM group had a significantly greater DBP response to a given exercise intensity than the healthy controls. However, they did not use the standard exercise intensity for evaluating the blood pressure response during exercise.

Our results indicate the possibility of the increased exercise SBP in type 2 DM patients who have insulin resistance. The SBP response to standardized exercise intensity (ΔSBP) was significantly and positively associated with log AUCPG and negatively with log AUCIRI and log AUCIRI/AUCPG. This phenomenon suggested a significant association between insulin resistance and the blood pressure response to exercise. However, data concerning the contribution of insulin resistance to the blood pressure response to exercise are still limited.

The mechanism underlying the significant correlation between exercising SBP and insulin resistance is still unknown. As mentioned earlier, however, aerobic exercise training induced a reduction in the resting blood pressure and the blood pressure response to a given and relative exercise intensity.[13] Several prospective epidemiologic studies in normotensive subjects have demonstrated that an exaggerated blood pressure response to a given and relative exercise intensity[8-11] and a lower quintile of $\dot{V}o_2max$ or endurance capacity[12] are good predictors for developing hypertension in the future. There are numerous reports[33] on the effect of exercise training for improving insulin resistance. However, there have been no studies on the relationship between an improvement in insulin resistance and the blood pressure response to exercise. Therefore, further research is needed to investigate the effect of exercise training on the relationship between the improvement in blood pressure upon exercise and the change in either insulin resistance or insulin action in patients with type 2 DM.

In summary, our findings suggest that insulin resistance was independently and significantly associated with the resting blood pressure and SBP response to standardized exercise intensity in type 2 DM patients.

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