Table 1. Main tobacco control measures of FCTC

Increase tobacco price and tax (Article 6)
Protection from exposure to tobacco smoke (Article 8)
Health warnings on tobacco products (Article 11)
Ban tobacco advertising, promotion and sponsorship (Article 13)
Disseminate tobacco dependence treatment (Article 14)
Eliminate illicit trade (Article 15)
Prohibit sales to and by minors (Article 16)

Table 2. Diagnostic criteria of tobacco dependence

The ICD-10 (WHO)
· F17 : Mental and Behavioral Disorders due to use of tobacco
Dependence Syndrome due to use of tobacco (F17.2)
[Diagnostic criteria]
Three or more of the following at some time during the previous year:
· A strong desire to take the drug
· Difficulty controlling use
· Increased tolerance
· A physical withdrawal state
· A higher priority given to drug use than to other activities and obligations
· Persisting in use despite harmful consequences

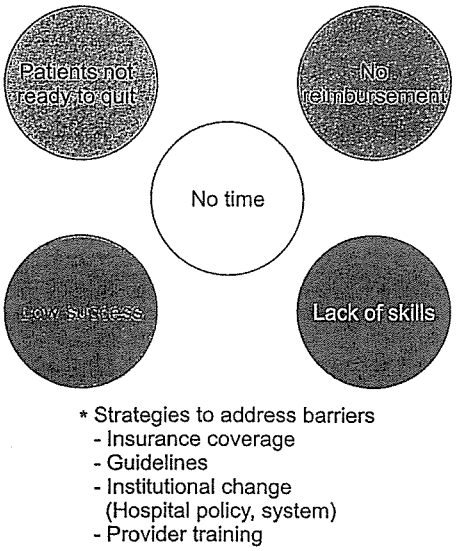

Fig. 2. Common barriers to disseminating nicotine dependence treatment -providers side-.

the future. The burden of tobacco-caused diseases in the first half of the 21st century occurred mainly in those who were current smokers.[5] Thus, comprehensive tobacco control measures to reduce smoking prevalence are urgently needed.

In the Article 14 of the WHO Framework Convention for Tobacco Control (FCTC) (Table 1),[6] countries are requested to "develop and disseminate appropriate, comprehensive and integrated guidelines based on scientific evidence and best practices" and to "take effective measures to promote cessation of tobacco use and adequate treatment for tobacco dependence." Governments are requested to include the "diagnosis and treatment of tobacco dependence and counseling services on cessation of tobacco use in national health and education programs, plans and strategies."

The essence of tobacco use is nicotine dependence (Table 2).[7] Nicotine dependence is a chronic disease that often requires repeated intervention.[8] Environmental change strategies for tobacco control, such as tobacco taxation and smoking restriction in public places, can be effective in reducing tobacco use,[9,10] but smokers often find it difficult to overcome their dependence without help.[11] Effective treatments to promote smoking cessation need to be implemented in various health care settings as part of a comprehensive tobacco control measure.

Lack of insurance coverage and lack of accessibility serve as barriers to use nicotine dependence treatment services (Fig. 2). In countries where publicly funded health insurance exists, consideration should be given to making evidence-based tobacco dependence treatments reimbursable.

In England, nicotine dependence treatment has been provided through the National Health Service since 1999 (Table 3)[12~14]. The treatment is free of charge to all users except for the partial payment for the pharmacotherapy.[15] From April 2004 to March 2005, the sixth year of the services, 529,520 smokers came to the services and set quit date.[14] Of these 297,826 (56%) stopped smoking four weeks later. Around four fifths (80%) of people received Nicotine Replacement Therapy (NRT) only, 6% received bupropion only, and 1% received both NRT and bupropion. In England, smoking costs the health service about 1.5 billion pounds each year. The nicotine dependence treatment services are costing approximately between 21.5 million and 45.8 million pounds per year.

In USA, private sector mainly takes care of health insurance coverage, and 87% of those companies provided smoking cessation programs free of charge or at a cheap price.[16] Eighty-

Table 3. Results of the national smoking cessation services in England

	1999	2000	2001	2002	2003	2004*
Number setting quit date	14,600	132,500	227,300	234,900	361,200	529,520
Self-reported 4-week quitters	5,800	64,600	119,800	124,100	204,900	297,828
(% of those setting quit date)	(39)	(49)	(53)	(53)	(57)	(56)
Percent of number who received						
NRT	39	36	63	75	77	80
Bupropion	–	–	19	11	8	6
Both	–	–	2	1	1	1

*provisional results.

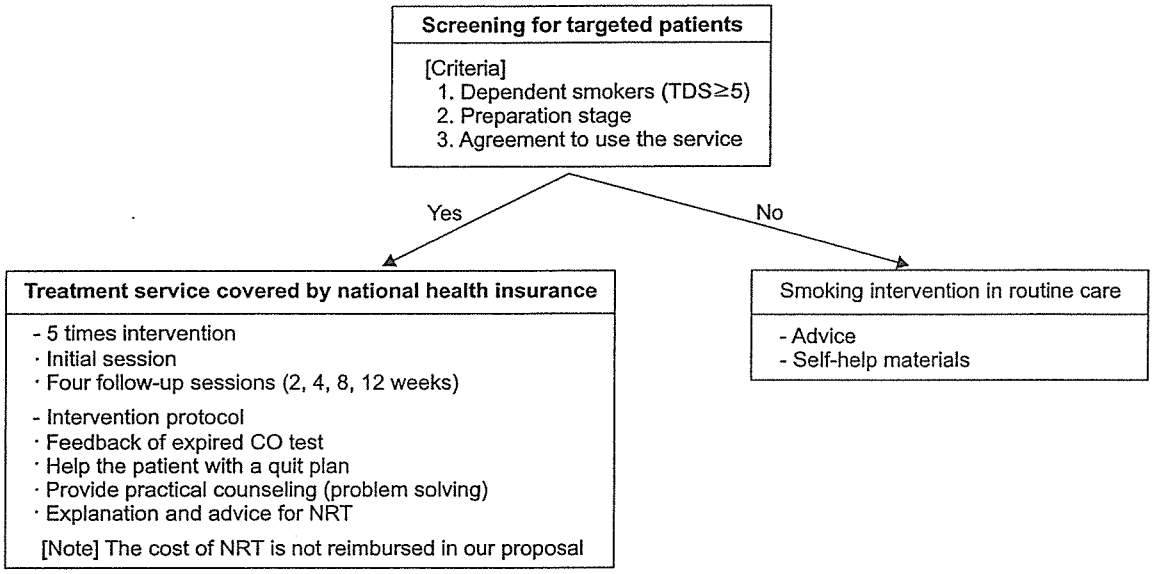

Fig. 3. Flow chart of a proposed nicotine dependence treatment service protocol.

one percent recommended the use of tobacco cessation medical products. There are two types of public medical insurance systems in USA, Medicaid for the poor and disabled, and Medicare for the people older than 65 years. In Medicaid, 36 out of 50 states covered pharmacotherapy treatments and 24 out of 50 states covered smoking cessation counseling in 2002.[17] In Medicare, coverage of smoking cessation counseling have just started in 2005.[18]

As a part of "Third Term Comprehensive Control Research for Cancer" granted by the Japanese Ministry of Health, Labor and Welfare, we have been conducting a research to establish nicotine dependence treatment services in clinical setting in Japan. In this research, we are developing an evidence-based clinical guideline for nicotine dependence treatment. We are also conducting medical economy studies to examine cost-effectiveness and cost-benefit of nicotine dependence treatment based on Japanese data. In July 2005, we had submitted the proposal to the Japanese Ministry of Health, Labor and Welfare for reimbursement of nicotine dependence treatment services. For the proposal, we developed standard protocol for nicotine dependence treatment in routine medical practice (Fig. 3). We estimated the budget impact of the protocol-based nicotine dependence treatment. We assumed percentage of these who utilized the services would gradually increase from 0.1% to 0.5% for the first five years and would be constant. We found out that if we start the nicotine dependence treatment services, the medical cost would be reduced by 0.6 billion Japanese yen after seven years, 7.5 billion yen after ten years and 22.5 billion yen after 15 years (Fig. 4).

In conclusion, to reduce smoking-caused health burdens, it

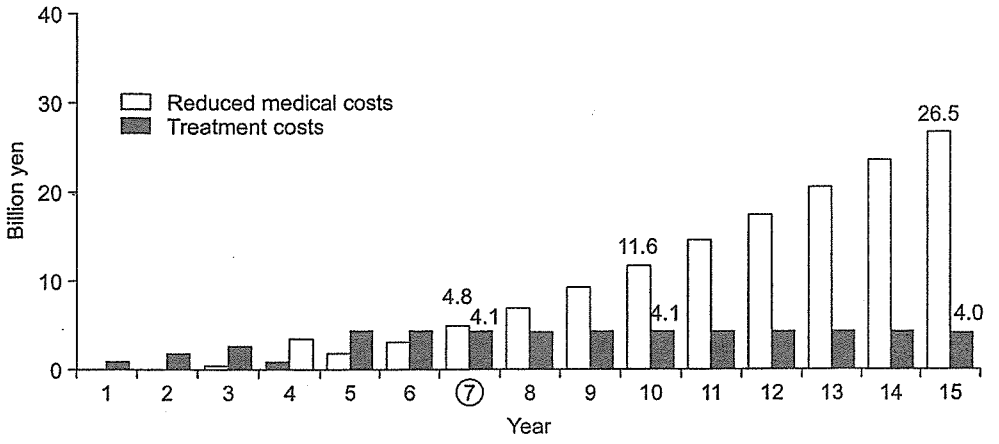

Fig. 4. Estimation of cost savings by nicotine dependence treatment services in Japan. The reduced medical costs would exceed treatment costs after 7 years, by 7.5 billion yen after 10 years and by 22.5 billion yen after 15 years.

is necessary to establish evidence-based nicotine dependence treatment services and disseminate them into routine medical practice under the health insurance coverage as a part of comprehensive tobacco control.

ACKNOWEDGEMENT

This study is granted by the grant of the "Third Term Comprehensive Control Research for Cancer" granted by the Japanese Ministry of Health, Labor and Welfare.

Aco-author, Takako Morita, PhD is an Awardee of Research Resident Fellowship from the Foundation for Promotion of Cancer Research (Japan) for the 3rd Term Comprehensive 10-Year Strategy for Cancer Control.

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scores measuring health perception, and physical and mental well-being also in 2003. The higher the HSQ-12 score, the better the outcome. Duration of smoking cessation was categorized into 3 levels: short (less than 10 years), moderate (10–29 years), and long (≥30 years). **Results:** Mean age was 75.3 for men and 77.3 for women. On average, a higher proportion of men quit smoking for ≥30 years than women (49.8% vs. 37.4%). With adjustment for age, race, education, marital status, living arrangement, alcohol use, body mass index, and number of cigarettes smoking/day in the past, means of HSQ-12 scores of physical, mental, and social functioning were lowest (worse) among older ex-smoker men with shortest cessation duration (< 10 years) and highest (better) among those who had quit smoking for more than 30 years or longer (p-trends <0.001) - see Table. The association remained strong and significant with further adjustment for comorbidities. However, no association was observed in older ex-smoker women. **Conclusions:** Longer duration of smoking cessation in older ex-smoker men is associated with higher HRQOL. A smoking cessation intervention early in life could have a great potential to improve quality of life in older age. More research is needed to determine reasons for the lack of association between length of smoking cessation and quality of life in women.

Adjusted Mean of HSQ-12 Scores for Men Ages 65+ by Duration of Smoking Cessation Categories

	Cessation Duration Levels			
	< 10 years	10–29 years	≥30 years	P-Trend*
(No. of people)	(206)	(857)	(1055)	
Summary Score (0–800)	540.4	583.5¶	610.9¶	<0.001
Physical Component Score (0–400)	249.1	279.5¶	295.7¶	<0.001
Mental Component Score (0–400)	291.3	303.9	315.2¶	<0.001

Adjusted for age, race, education, marital status, living arrangement, alcohol use, BMI, and number of cigarettes smoking/day in the past. §p<0.05; ‖p<0.01; ¶p<0.001 for comparison with the shortest cessation duration group based on GLM models. *P-values for linear trend with cessation duration is a continuous variable based on GLM models

3980

Effect of Smoking Cessation on the Number, Proliferation and Adhesive Properties of Endothelial Progenitor Cells

Miriam Puls, Marco Schroeter, Jasmin Steier, Lena Stijohann, Stefan Andreas, Tobias Raupach, Gerd Hasenfuss, Stavros Konstantinides, Katrin Schaefer; Georg August Univ, Goettingen, Germany

Endothelial progenitor cells (EPC) may participate in vascular repair, and studies reported that cardiovascular risk factors are associated with reduced circulating levels of EPC. In order to examine the effect of smoking cessation (SC) on EPC number and function, we prospectively followed (over 6 months) 124 smokers (50 men; mean age, 47.1±12.2 years) participating in a supervised 5-week SC program. In contrast to previous studies which focused on healthy young adults, additional cardiovascular risk factors or known cardiovascular disease were present in 59 (47.6%) and 9 (7.3%) of our patients, respectively. At the end of the 5-week intervention, participants had decreased smoking from 20.2 to 1.2 cigarettes per day, and 86% completely quit smoking. SC was associated with a significant decrease in plasma LDL cholesterol (P=0.001) and fibrinogen (P=0.0004) levels at 5 weeks, whereas a decrease in hsCRP levels was observed 6 months later (2.2±1.8 vs. 1.4±1.1 mg/L; P=0.025). SC did not significantly alter the number of circulating CD34+, VEGF-R2+ cells (0.19±0.18 vs. 0.17±0.18%; P=0.88), or the number of EPC colony forming units (43±46 vs. 58±46 EPC-CFU; P=0.22). On the other hand, fewer acLDL+, lectin+ cells could be expanded ex vivo after SC (197±166 vs. 124±105 cells; P<0.0001), and this effect persisted 6 months later (112±83 cells). Interestingly, the decrease in acLDL+; lectin+ cells after SC was particularly pronounced in persons with additional cardiovascular risk factors. Further studies revealed that SC was associated with reduced adhesion of acLDL+ cells to fibronectin-coated culture dishes (60±26 vs. 35±16 cells; P=0.001), and to mature endothelial cells (30±14.1 vs. 21±12; P=0.003). As the reduction of EPC adhesion after SC might be related to a reduction in oxidative stress, we determined plasma levels of asymmetric dimethyl arginine (ADMA), a competitive inhibitor of endothelial nitric oxide synthase. ADMA levels significantly decreased after SC (from 0.70±0.13 to 0.66±0.15 μmol/L; P=0.008). The results of this ongoing study were partly unexpected in view of previous reports. They suggest that smoking and smoking cessation may modulate EPC function, particularly adhesion, rather than circulating EPC numbers.

3981

Efficacy and Safety of Varenicline, an α4β2 Acetylcholine Nicotinic Receptor Partial Agonist, for Smoking Cessation in Japanese Smokers

Masakazu Nakamura, Osaka Med Cntr for Health Science and Promotion, Osaka, Japan; Yoko Fujimoto, Nami Maruyama, Taro Ishibashi, Pfizer Global Rsch and Development, Tokyo, Japan; Karen Reeves; Pfizer Global Rsch and Development, Groton, CT

Background: Smoking is the leading preventable cause of illness and premature death by increasing the risk of acute MI, sudden death and cerebrovascular disease. Varenicline, an α4β2 nicotinic acetylcholine receptor (nAChR) partial agonist, was developed specifically for smoking cessation with the potential to relieve nicotine craving and withdrawal symptoms while reducing the reinforcing effects of nicotine. Superior efficacy of varenicline 1 mg BID compared with bupropion 150 mg BID and placebo in achieving smoking cessation at the end of the 12-week treatment and one year was demonstrated in two identically designed, randomized, double-blind, 52-week studies conducted in the United States. The objective of this study was to evaluate the effect of varenicline in conjunction with smoking cessation counseling in Japanese smokers. **Methods and Results:** In a randomized, double-blind placebo-controlled study in Japanese smokers, treatment with three doses of varenicline (0.25 mg BID, 0.5 mg BID, 1 mg BID) for 12 weeks was followed by a 40-week non-drug treatment period. All subjects were given brief counseling at each study visit. A total of 618 smokers from 19 centers in Japan were treated; 515 smokers were diagnosed as nicotine dependent, scoring 5 or greater on the Tobacco Dependence Screener (TDS). The 4-week continuous quit rate (CQR) during weeks 9–12, the primary endpoint, was significantly higher for all doses of varenicline than for placebo (39.5%), and the highest quit rate was achieved in the 1 mg BID group (65.4%, p<0.0001). The continuous abstinence (CA) rate during weeks 9–52 in the 1 mg BID group (34.6%) was also significantly higher than placebo (23.3%, p=0.0355). All doses of varenicline were safe and well-tolerated, with overall discontinuation rates similar to placebo. Nausea occurred more frequently with varenicline and was mild to moderate in intensity. **Conclusions:** This was the first randomized, double-blind, placebo-controlled study that evaluated the effect of varenicline in conjunction with smoking cessation counseling using the 4-week CQR and CA rate in Japan. Results demonstrate that varenicline, the first in a new class of compounds developed for smoking cessation, is efficacious and well tolerated in the Japanese population.

Epidemiology: New Risk Factors for Cardiovascular Disease

Subspecialty: Epidemiology
Monday Afternoon
McCormick Place, S106a
Abstracts 3982–3991

3982

Lipoprotein(a), Hormone Replacement Therapy and the Risk of Future Cardiovascular Disease in Women

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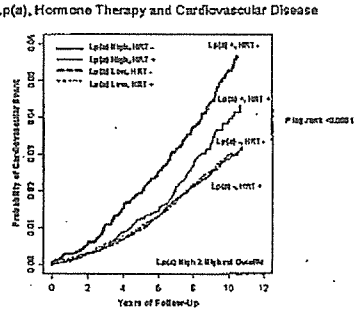
BACKGROUND: While multiple studies indicate that hormone replacement therapy (HRT) decreases plasma levels of lipoprotein (a) (Lp(a)), whether this effect alters the relationship of Lp(a) with cardiovascular risk is unknown. **METHODS:** Lp(a) was measured at baseline among 27,791 initially healthy women of whom 12,075 were on HRT and 15,661 were not. The risk of first-ever major cardiovascular event over a ten-year period (nonfatal myocardial infarction, nonfatal cerebrovascular event, coronary revascularization or cardiovascular deaths) was assessed in Cox-proportional hazard models according to baseline Lp(a) levels and HRT status, and adjusted for confounding variables. **RESULTS:** As anticipated, Lp(a) values were lower among women taking HRT (median 9.4 vs. 11. 6 mg/dL, *P*<0.0001). Furthermore, in women not taking HRT, the hazard ratio of future cardiovascular disease for the highest Lp(a) quintile compared to the lowest was 1.7 (*P*-trend among quintiles <0.0001). In contrast, among women taking HRT, there was no elevation of cardiovascular risk seen [hazard ratio 1.1, *P*-trend =0.20]. Interaction between HRT and Lp(a) quintiles on CVD was significant (*P*-interaction = 0.005). **CONCLUSIONS:** The relationship of high Lp(a) levels and incident cardiovascular events is modified by hormone replacement therapy in women.



3983

Normalization of Coronary Microvascular Function in the Infarct Artery by Bone Marrow-derived Progenitor Cells after Acute Myocardial Infarction: Results from the Double-blind, Placebo-controlled Repair-AMI Trial

Sandra Erbs, Axel Linke, Heart Cntr, Univ of Leipzig, Leipzig, Germany; Birgit Assmus, J.W. Goethe Univ, Frankfurt, Germany; Christina Hoffmann, Heart and Diabetes Cntr NRW, Ruhr Univ of Bochum, Bad Oeynhausen, Germany; Volker Schachinger, Torsten Tonn, Stephanie Dimmeler, J.W. Goethe Univ, Frankfurt, Germany; Gerhard Schuler, Heart Cntr, Univ of Leipzig, Leipzig, Germany; Andreas M Zeiher, J.W. Goethe Univ, Frankfurt, Germany; Rainer Hambrecht; Heart Cntr, Univ of Leipzig, Leipzig, Germany

Recently, intracoronary (i.c.) infusion of bone marrow-derived progenitor cells (BMC) in patients (pts) with reperfused acute myocardial infarction (AMI) has been shown to augment cardiac function and prevent endsystolic volume expansion. This was partially attributed to an improved progenitor cell-mediated neovascularization, but clear evidence from studies in humans is missing so far. Therefore, the "i.c. Doppler substudy" of the randomized, double-blind, and placebo-controlled REPAIR-AMI trial (*R*einfusion of *E*nriched *P*rogenitor cells *A*nd *I*nfarct *R*emodeling in *A*cute *M*yocardial *I*nfarction) aimed to investigate the effects of an i.c. BMC therapy on coronary microcirculation in pts with reperfused AMI. In this substudy, a total of 54 pts were enrolled (BMC: n=28; placebo: n=26). Coronary flow reserve (CFR) in the infarct artery as well as in a reference (ref.) vessel was assessed by i.c. Doppler at the time of study therapy and at 4 months follow-up. Results: At the time of study therapy (3–7 days after AMI),

特集

がん対策・2

がん対策と経済学①
米国における保険者のがん検診サービスの枠組みに関する調査

経営的視点に焦点を当てて

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公　衆　衛　生
第71巻　第2号 別刷
2007年2月15日　発行

医学書院

がん対策と経済学①

米国における保険者のがん検診サービスの枠組みに関する調査
経営的視点に焦点を当てて

大重 賢治[1)] 岡本 直幸[2)] 水嶋 春朔[3)]

わが国においては，早期発見・早期治療を行う目的で，公的な保健事業として各種のがん検診が実施されてきた．公的な事業として行われる以上，その支出に見合うだけの効果が得られているかを評価することは重要なことである．

保健事業の経済的評価の手法としては，費用効果分析，費用便益分析などがあり[1~4]，多くの研究にて活用されている．がん検診の場合，「効果」の指標は，がん検診を行うことによって獲得された余命年数(life-year saved)や質調整生存年数(quality-adjusted life years)であり[5~7]，「便益」の指標は，がん検診に対して住民が支払っても良いと考える(willingness-to-pay)金額の総和となる[8~10]．すなわち，がん検診を経済学的に評価するためには，がん検診の「効果」や「便益」を数値で表すことが基本条件となる．しかしながら，これらを定量的に示すことが難しいこともあって，わが国においては，がん検診の経済的評価はまだ十分になされていないのが現状である．

「効果」や「便益」が，がん検診に投じた費用に見合っているかは，経済的に非常に重要な視点であるが，その他，もう1つ重要な視点(もしかしたら，政府や保険者にとっては最も重要な視点？)として，がん検診事業を行うことによって，将来の医療費が抑制されるか否か，がある．

経済的評価の手法としては費用分析の範疇に入り[2)]，検診事業を行う場合の費用と行わない場合の費用をいわば金銭的損得の観点から検討するものである．保険者が営利企業の場合，検診事業を行わない場合の費用が行う場合の費用を上回ると考えられる場合，保険者に検診事業を行う経済的インセンティブが発生する．逆に言うと，補助金などの制度がない限り，赤字になるような事業には取り組みにくいというのが現実であろう．たとえ保険者が，非営利団体であったとしても，恒常的に赤字を生み出すような事業には積極的にはなれないと考えられる．

われわれは，平成17年度厚生労働科学研究費補助金特別研究「がん検診の経済的効果及び制度の在り方に関する研究(主任研究者：水嶋春朔)」の一環として，医療が市場経済の仕組みの中で動いている米国において，がん検診がどのように提供されているかを調査した．米国の医療制度では，主体が，保険者およびサービス供給者ともに民間であることから，がん検診に対する考え方の中に経営的視点が反映されているのではないかと考えたからである．最も確認したかったのは，米国におけるがん検診が，政府の指導のもとにしぶしぶ行われているのか，それとも事業として積極的に行われているのかという点である．調査結果については，厚生労働科学研究費補助金特別研究報告書にて報告[11)]を行っているが，本稿では，そ

1) おおしげ けんじ：横浜市立大学医学部社会予防医学教室準教授 連絡先：〒236-0004 横浜市金沢区福浦3-9
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表　マネージドケア型組織 HMO と PPO の比較(文献[13]より)

	HMO	PPO
名称	Health Maintenance Organization	Preferred Provider Organization
主目的	医療費のコントロール	医療費のコントロール
特徴	医療機関と財政機関の両方を組織内に併せ持つ．組織外で行われた医療サービスには保険は支払われない．	医療保険者が独立した医療機関と契約を結び医療ネットワークを形作る．契約を行った医療機関は通常よりも安い金額で医療サービスを提供する．患者がネットワーク以外の医療機関を受診した場合，給付水準が減額される．
経済的インセンティブ	費用効果的なサービスを行おうとするインセンティブが働く	費用効果的なサービスを行おうとするインセンティブが働く
ゲートキーパーの存在	医療サービスの提供をコントロールする(ゲートキーパーの役割を担う)医師が存在する．ゲートキーパーである医師を介しない医療サービスには保険が支払われない．	ゲートキーパーの役割は存在しない．
医師の関わり方	組織に直接雇用される形態と，雇用ではなく契約を結ぶ形態がある．	組織と医師・医療機関との間で契約が結ばれる
組織の例	Keiser Parmanente 等	Health Net Inc. 等

註) この表は典型的な組織形態の比較であり，実際にはバリエーションが存在する．

の概要について紹介したい．

米国の医療保険者

米国では，高齢者と障害者を対象とした医療制度(メディケア)と貧困者のための医療制度(メディケイド)を除いては，医療は私的なサービスとして提供されている．医療保険は，主に福利厚生の一環として企業によって購入されてきた．

米国の国民医療費の対 GDP 比は，先進国の中でもずば抜けて高く，医療費の上昇は，医療保険の購入者である企業にとっても大きな負担となっていた．そのため 1980 年代頃より，医療費の抑制(企業側からみれば負担する保険料の抑制)に対して効果の期待できるマネージドケア型の医療システムが発達し，現在では，米国における民間医療保険の大部分が，この型のヘルスプランを採用している[12~15]．

マネージドケア型の医療システムの特徴は，保険者が，供給する医療，利用方法，価格などを一定の管理状態に置くところにある．このシステムの具体的な形態として，健康維持組織(Health Maintenance Organization：HMO)がある．HMO の基本的な形は，保険者と医療提供者(病院/医師)が一体となっているものである．

マネージドケア型の医療システムの形態にはバリエーションがある．例えば PPO(Preferred Provider Organization)のように，保険者が特定の医療サービス機関と契約を交わし，保険加入者にそれらのネットワーク内の医療機関を利用するよう奨励するシステムや，Point of Service(POS) Plan のように，HMO と PPO を併せたようなシステムもある(表)[13]．

調査地

2006 年 3 月，米国カリフォルニア州においてヘルスプランを提供しているマネージドケア型の組織を訪れ，がん検診サービスのあり方に関して聞き取り調査を行った．同州は，マネージドケア型の医療システムが最も発達している州の 1 つである[16]．訪問した機関は，HMO 型の Keiser Parmanente[17](以下，Keiser と略)と，PPO ネットワーク型の Health Net Inc.[18](以下，Health Net と略)である．聞き取り調査の相手は，両組織共に医師であり，Keiser の担当者の職位は，Assistant Medical Director for Quality and Clinical Analysis，Health Net の担当者の職位は，Regional Medical Director であった．

調査結果

1. がん検診の実施状況

両組織とも，がん検診は，United States Preventive Task Force[19]と American Cancer Society[20]のガイドラインに沿って実施していた．実施対象のがんも共通しており，積極的な検診の対象としているのが乳がん，子宮頸がん，大腸がんである．前立腺がん検診に関しては，「50歳以上の男性，ハイリスクの場合には45歳以上の男性に対して，PSA(prostate specific antigen)テストを，益と害を理解してもらった上で，希望があれば提供している(Keiser)」，「50歳以上の男性に対して，直腸診検査を毎年受けることを勧めている．PSA検査に関しては，まだ具体的な方針は立っていない．擬陽性が多いため判断保留中である(Health Net)」との回答であった．肺がん検診と胃がん検診は，有効性に関するエビデンス不足ということで，両組織とも実施を勧めていないとのことであった．

1) 乳がん検診の状況

Keiserでは，50～69歳の女性に対して2年に1度のマンモグラフィーによる検診を推奨している(40～49歳に関しては専門家との相談の上で実施)．受診率は最新の結果で84%とのことである(2年に1度の受診で，“受診者”にカウントされるため，対象者の84%が1年間に受診しているというわけではない．以下同様)．

Health Netでは，20～40歳の女性には3年に1度，40歳以上には毎年，医師による診察を受けるよう推奨している．また，40歳以上の女性にはマンモグラフィーによる検査を，1年もしくは2年に1回受けるよう推奨している．超音波検査は，ルーティンの検査としては行われていない．2005年，カリフォルニアにおける検診受診率(2年間で1回でも受診したもの)は，74.9%であった．

2) 大腸がん検診の状況

Keiserでは，50歳以上に対して，年に1度の便潜血テスト，5年に1度のS状結腸内視鏡検査(Flexible Sigmoidoscopy)による検査，10年に1度の大腸内視鏡(Colonoscopy)による検査を推奨している．受診率は最新の結果で45%である．

Health Netにおける大腸がん検診の取り組みも，Keiserと同様である．既往歴，家族歴があるような人には，より頻回の大腸内視鏡検査を勧めているという．2005年，カリフォルニアにおける検診受診率は45.7%であった．

3) 子宮頸がん検診の状況

Keiserでは，30～64歳までの女性に対して，3年に1度のPAPテストとHPV(human papilloma virus)検査を行うことを推奨している．18～29歳にも3年に1度のPAPテストを実施し，陽性者に対してHPV検査を追加して行うことを勧めている．受診率は最新の結果で79%である．

Health Netでは，21～65歳までの女性に対して，PAPテストを少なくとも3年に1回は行うように勧めている．2005年，カリフォルニアにおける検診受診率は，81.9%であった．

2. がん検診の経済的側面

検診受診料に関しては，「契約している医療保険の内容によって異なっており，無料から多少料金のかかる場合もある(Keiser)」，「どのような契約を行っているかによってバリエーションが多く，一概には言えないが，乳がん，大腸がん，子宮頸がん検診の受診者負担は大きくはない．無料の場合もある(Health Net)」との回答であった．

がん検診の実施に関して国の法律はあるか，という問いに対して，カリフォルニアの州法では「規定がある．また，パブリックリポート(保険契約の際の情報となる．毎年作成し加入者に配布)として出す必要がある(Keiser)」との回答を得た．がん検診の実施にあたっての政府の経済的援助は，「ない．ただし，メディケアの場合は，公的な枠組みの中で行われている(Health Net)」とのことである．がん検診に医療費抑制効果があると思うかという問いには，「ある．進行したがんになった場合，抗がん剤がものすごく高い．乳がんの化学療法の費用は，だいたい25万ドルぐらいかかる．がん検診は，とても費用効果的である

(Keiser)」,「ある．進行がんの場合，抗がん剤治療や集中治療など，医療費は莫大なものとなる．検診のコストのほうがはるかに安い(Health Net)」と，明確な回答が返ってきた．

3. 受診率向上の取り組み

がん検診の受診率を上げるためにはどうしたらよいかという問いに対して，「第一に，検診の重要性を会員ならびに医師に認識してもらうことである．特に現場の医師が検診の有効性に確信を持っていることが重要である．医師の認識を高めるための経済的インセンティブも必要である．第二に，がん検診受診勧奨の宣伝をメディアを利用して積極的に行うことが大切である．特に，有名人のがん罹患や死亡の発表に併せたキャンペーンは効果的である．第三に，がん検診の有効性に関するエビデンスを構築する必要がある．そのためには評価研究が欠かせない(Keiser)」,「教育が最も大事である．新聞，雑誌，TVなどを使って，がん検診の大切さについて教育を行っている．医師への教育も重要である．また，医師に対しては，検診受診率を高めるため，経済的なインセンティブが考えられている(Health Net)」との回答を得た．

患者(加入者)に対する経済的なインセンティブは，「グループ購入の場合など(企業による保険購入などを指す)，そのグループの受診率によって，保険料が変更されることもある．これも契約の内容による(Health Net)」とのことであった．検診を受けないことに対する患者側へのペナルティおよび医師側へのペナルティは「ない(Health Net)」ということである．

考察

今回の調査では，非営利組織と営利組織の両方の情報を得ることができた．若干の相違はあるものの，がん検診の取り組みはほぼ同様であった．有効性が明らかであるがん検診(乳がん検診，子宮頸がん検診，大腸がん検診)は強力に推進するが，有効性が十分に明らかにされていない検診の実施に関しては消極的であることも共通していた．

営利・非営利の違いがあるとはいえ，両組織とも民間の組織であり，米国の自由市場的な医療制度の中で，魅力的な保険料(保険購入者にとっては安いほうが魅力的)と魅力的なサービス提供で競争を行っている．がん検診は，医療費を抑え保険料を安くするという意味でも，消費者の満足度を高めるという意味でも，経営戦略的に重要な事業のようである．

まとめ

米国のマネージドケア型の組織を訪問し，がん検診サービスのあり方について聞き取り調査を行った．がん検診のサービスは，US Preventive Task Force等から出されているガイドラインに基づいて提供されており，乳がん検診，子宮頸がん検診に関しては，高い受診率が達成されていた．訪問した2つの組織の担当者とも，乳がん検診，子宮頸がん検診，大腸がん検診には，医療費抑制効果があるとの認識であった．がん検診の実施は，医師-患者関係の中で決定されており，検診の受診率を高めるための方策として，両組織の担当者とも，教育の重要性を強調していた．また，医師に対する経済的なインセンティブも重視していた．

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J Occup Health 2005; 47: 134–140

Journal of Occupational Health

Field Study

Two New Criteria of the Metabolic Syndrome: Prevalence and the Association with Brachial-Ankle Pulse Wave Velocity in Japanese Male Workers

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Abstract: Two New Criteria of the Metabolic Syndrome: Prevalence and the Association with Brachial-Ankle Pulse Wave Velocity in Japanese Male Workers: Koichi MIYAKI, *et al.* Department of Preventive Medicine and Public Health, School of Medicine, Keio University—In 1998 and 2001, The World Health Organization and the National Cholesterol Education Program Adult Treatment Panel III proposed working criteria for the metabolic syndrome (MS), but they are not perfect for use in diverse ethnicities. In 2005, the International Diabetes Federation (IDF) and eight societies in Japan respectively proposed new criteria. However, there has been no report regarding the application of these new criteria in Japanese workplaces. We conducted a cross-sectional study of 377 healthy Japanese men aged 20–64 yr who worked in a chemical factory in Kanagawa, Japan. Participants completed a self-reported questionnaire, underwent a physical examination including waist measurements and brachial-ankle pulse wave velocity (baPWV), and provided overnight fasting blood samples. The prevalence of MS in Japanese men was 17.0% and 13.5% according to the new IDF and Japanese criteria respectively. In both of the new criteria, baPWV was significantly higher in those with MS than those without MS (1,563 ± 264.2 vs 1,362 ± 204.6 cm/sec, $p<0.001$ in the new IDF criterion; 1,574 ± 265.2 vs 1,368 ± 209.1 cm/sec, $p<0.001$ in the Japanese criterion). In the analysis of the 5 or 6 subgroups stratified according to the number of MS components, baPWV increased significantly with increasing number of MS components (p for trend<0.01 in both criteria). The new IDF and Japanese criterion are both good for diagnosing MS among Japanese because a linear increase in baPWV occurred with increasing MS components after adjustment for potential confounding factors. Further studies are expected using these new criteria.
(J Occup Health 2006; 48: 134–140)

Key words: Metabolic syndrome, baPWV, New criteria, Japan

Metabolic syndrome (MS) is a cluster of metabolic disorders including central obesity, glucose intolerance, hypertension, and dyslipidemia[1, 2]. These traits occur simultaneously to a greater degree than would be expected by chance alone[3, 4]. Although the contribution of an individual trait may be small, multiple traits may act together and exert an even greater influence than any one trait alone[5].

The concept of MS has become well established, and several studies have suggested that subjects with MS are at an increased risk for type 2 diabetes[6, 7] and cardiovascular disease[8–12]. However, there has been no uniform case definition for MS.

In 1998 and 2001, the World Health Organization (WHO)[13] and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)[14] each proposed working criteria for MS. The NCEP ATP III report recommended the use of five variables for diagnosis of MS, including waist circumference, triglyceride level, HDL cholesterol level, blood pressure, and fasting glucose level. Subjects meeting three of these five criteria are classified as having MS. The WHO criteria are more complex because they take account of microalbuminuria and plasma insulin levels.

Received Aug 23, 2005; Accepted Jan 10, 2006
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According to the NCEP ATP III and WHO criteria, several studies of the prevalence and characteristics of MS have been conducted among diverse ethnicities[15-23]. Some studies showed ethnic variation in the prevalence of MS[15, 16, 23] and some studies which conducted in Asia suggested that the definition of central obesity recommended by the NCEP ATP III was inappropriate for Asian populations which are generally of smaller build than Caucasians because the criterion had been based on data from Caucasian cohorts[16, 17, 21].

In consideration of the ethnic differences in prevalence and characteristics of MS, the International Diabetes Federation (IDF) proposed the worldwide MS criteria that includes a criterion for Japanese in April 2005[24]. According to the new IDF criteria, a person defined as having MS must have central obesity plus any two of the following four factors: 1) raised triglyceride level; 2) reduced HDL cholesterol; 3) raised blood pressure; 4) raised fasting plasma glucose. With regard to the definition of central obesity, ethnic specific values for waist circumference are used.

At almost the same time, in April of 2005, eight societies in Japan, the Japan Society for the Study of Obesity, the Japan Atherosclerosis Society, the Japan Diabetes Society, the Japanese Society of Hypertension, the Japanese Circulation Society, the Japanese Society of Nephrology, the Japanese Society on Thrombosis and Hemostasis, and the Japanese Society of Internal Medicine, proposed a new criterion of MS for Japanese[25]. According to the criterion, subjects are defined as having MS if they have central obesity plus any two of the following three factors: 1) dyslipidemia (raised TG level and/or reduced HDL cholesterol); 2) raised blood pressure; 3) raised fasting plasma glucose. To our knowledge no assessment of these new criteria has been performed among Japanese workers.

Pulse wave velocity (PWV) is an index of arterial stiffness[26, 27], and is regarded as a non-invasive marker of vascular damage[28-30]. Previous studies have demonstrated that PWV is a marker of the severity of cardiovascular disease[31] and a predictor of future events[32-34]. As well, it is applicable as a screening tool for cardiovascular risk in a general population[29, 35]. Recently, a simple device for measuring brachial-ankle PWV (baPWV) has been developed and made available[36, 37].

MS is a predictor of cardiovascular mortality[8-10] and many studies have focused on the association of cardiovascular disease and its risk factors with increased PWV[31, 32, 34, 36-38]. However, there are almost no studies relating PWV to MS[5, 39], and no study to our knowledge has investigated the relationship between PWV and MS as defined by the new criteria.

The aims of this study were to assess the prevalence and characteristics of MS using the two new criteria, the new IDF criterion and the Japanese criterion, and to investigate the association between baPWV and MS in middle-aged Japanese men.

Methods

We conducted a cross-sectional study of Japanese male workers who worked in a chemical factory in Kanagawa, Japan. Of the 438 male workers, 377 (86.1%) aged 20–64 yr participated in the study. We divided the subjects into two subgroups according to the kind of occupation, office workers and laborers. Office workers were 176 (46.7%) and laborers were 201 (53.3%).

Of 377 subjects, 43 (11.4%), 4 (1.1%), and 7 (1.9%) were taking medication for hypertension, dyslipidemia, and diabetes, respectively. Although there were the potential effects of medications on metabolic values, we did not exclude the above-mentioned subjects because they should be included in each criterion of MS and for the purpose of reflecting the workplace population as it is without selection bias.

Participants completed a self-reported questionnaire (including medical history, medication use and smoking status), underwent a physical examination (including height, weight, waist circumference, blood pressure, and baPWV measurements), and provided overnight fasting blood samples. Body mass index (BMI) was calculated by kg/m^2. baPWV was measured by well-trained nurses on the left and right sides using the PWV/ABI device (Nippon Colin, Aichi, Japan) which was approved by the US Food and Drug Administration (FDA) as VP-2000/1000. We used the mean value of the right and left baPWV values. Of 377 subjects, 67 (17.8%) showed ≥1,600 cm/sec baPWV and were diagnosed as having abnormally high PWV values. In this study, past smokers and those who had never smoked were combined and compared with current smokers. All subjects in the study gave their informed consent for the use of personal information for analysis. The Ethics Committee of the Keio University School of Medicine, Tokyo, Japan, approved the study protocol.

Definition of metabolic syndrome

According to the new IDF criterion, the characteristics of MS in Japan are defined by the following cutoff limits and the subjects are defined as having MS if they have central obesity plus two or more of the other components: 1) central obesity (waist circumference ≥85 cm in men); 2) raised triglyceride level (triglyceride ≥150 mg/d*l*) or specific treatment for this lipid abnormality; 3) reduced HDL cholesterol (HDL cholesterol<40 mg/d*l*) or specific treatment for this lipid abnormality; 4) raised blood pressure (systolic blood pressure ≥130 mmHg or/and diastolic blood pressure ≥85 mmHg) or treatment of previously diagnosed hypertension; 5) raised fasting plasma glucose (fasting plasma glucose ≥100 mg/d*l*) or previously diagnosed type 2 diabetes.

According to the Japanese criterion, the characteristics of MS are defined by the following cutoff limits and the subjects are defined as having MS if they have central obesity plus two or more of the other components: 1) central obesity (waist circumference ≥85 cm in men); 2) dyslipidemia (triglyceride ≥150 mg/dl or/and HDL cholesterol<40 mg/dl) or medication for dyslipidemia; 3) raised blood pressure (systolic blood pressure ≥130 mmHg or/and diastolic blood pressure ≥85 mmHg) or medication for hypertension; 4) raised fasting plasma glucose (fasting plasma glucose ≥110 mg/dl) or medication for diabetes.

According to the NCEP ATP III criterion[14], the characteristics of MS in men are defined by the following cutoff limits and subjects having three or more of the components are defined as having MS: 1) waist circumference>102 cm; 2) triglyceride ≥150 mg/dl; 3) HDL cholesterol<40 mg/dl; 4) systolic blood pressure ≥130 mmHg or/and diastolic blood pressure ≥85 mmHg or known treatment for hypertension; 5) fasting plasma glucose ≥110 mg/dl or known treatment for diabetes.

Statistical analysis

All log-normally distributed variables (fasting plasma glucose, triglyceride, and HDL cholesterol) were log-transformed before statistical analysis and back-transformed for reporting. Differences in metabolic, anthropometric, and numerical demographic variables between individuals with and without MS were assessed using independent samples *t* testing. The χ^2 test was used to determine whether frequencies for categorical variables differed between these two groups of subjects. Age-, BMI-, systolic blood pressure (SBP)-, and smoking status-adjusted Pearson correlations were calculated to investigate the relationship between baPWV and MS as well as other metabolic and anthropometric variables. Multivariate logistic regression analysis was used to assess the relationship between risk of increased baPWV and each feature of MS. All analyses were performed with the SPSS statistical package for Windows version 12.0. All reported p-values were two-sided, and $p<0.05$ was considered statistically significant.

Table 1. Clinical and biochemical characteristics of all the subjects and the subjects with or without metabolic syndrome by the Japanese criterion and the new IDF criterion

		Metabolic syndrome			
		by the Japanese criterion		by the new IDF criterion	
	All subjects	No	Yes	No	Yes
n	377	326	51	313	64
Age (yr)	45.6 ± 11.6	44.3 ± 11.9	51.8 ± 6.34*	44.6 ± 11.9	50.8 ± 8.21*
Height (cm)	168.6 ± 6.37	168.6 ± 6.44	168.5 ± 5.93	168.6 ± 6.25	168.7 ± 6.97
Weight (kg)	65.8 ± 10.3	64.4 ± 9.69	74.6 ± 9.64*	64.1 ± 9.31	74.1 ± 10.8*
BMI (kg/m^2)	23.1 ± 3.26	22.6 ± 3.06	26.2 ± 2.80*	22.5 ± 3.00	26.0 ± 2.97*
Waist circumference (cm)	83.2 ± 9.20	81.7 ± 8.74	92.8 ± 5.65*	81.3 ± 8.55	92.4 ± 6.32*
Systolic blood pressure (mmHg)	134.0 ± 17.3	131.6 ± 16.3	149.4 ± 15.5*	131.5 ± 16.3	146.4 ± 16.9*
Diastolic blood pressure (mmHg)	81.4 ± 12.4	79.7 ± 11.9	92.2 ± 9.99*	79.5 ± 11.8	90.3 ± 11.5*
Fasting plasma glucose (mg/dL)	96.3[1.24]	93.4[1.20]	116.7[1.37]*	92.7[1.19]	115.7[1.36]*
Total cholesterol (mg/dL)	205.8 ± 37.0	203.0 ± 35.6	223.9 ± 40.5†	202.6 ± 35.8	221.5 ± 38.9†
Triglyceride (mg/dL)	112.9[1.74]	103.7[1.67]	195.0[1.64]*	102.5[1.66]	181.0[1.71]*
HDL cholesterol (mg/dL)	54.1[1.28]	55.4[1.27]	46.6[1.31]*	55.7[1.27]	47.1[1.30]*
baPWV (cm/sec)	1,396 ± 228.3	1,368 ± 209.1	1,574 ± 265.2*	1,362 ± 204.6	1,563 ± 264.2*
Current smoking (%)	58.6	58.9	56.9	58.5	59.4
Waist circumference ≥85 (cm) (%)	43.5	34.7	100*	31.9	100*
SBP ≥130 or DBP ≥85 (mmHg) (%)	38.5	30.7	88.2*	30	79.7*
Fasting plasma glucose ≥100 (mg/dL) (%)	30	–	–	21.7	70.3*
Fasting plasma glucose ≥110 (mg/dL) (%)	18.8	13.5	54.0*	–	–
Dyslipidemia‡ (%)	31.3	23.2	84.0*	–	–
Triglyceride ≥150 (mg/dL) (%)	28.4	–	–	19.5	71.9*
HDL cholesterol<40 (mg/dL) (%)	9.3	–	–	6.4	23.4*

Data are means ± SD and % for normally distributed variables, and geometric means [GSD] for non-normally distributed variables. *$p<0.001$; †$p=0.001$ for the t test of differences in means or the χ^2 test of differences in proportions for continuous and categorical variables, respectively, in comparisons between subjects with or without metabolic syndrome.

‡Triglyceride ≥150 (mg/dL) or/and HDL cholesterol<40 (mg/dL).

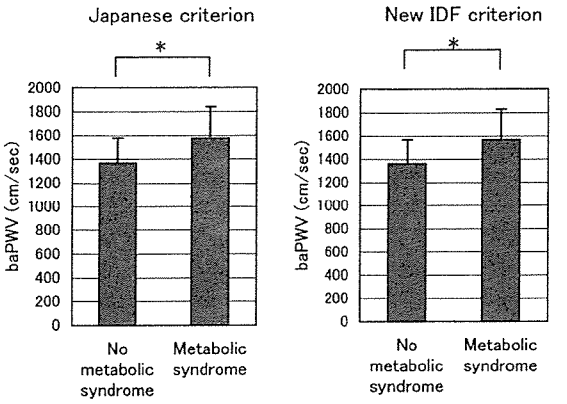

Fig. 1. The relation between baPWV values and metabolic syndrome by the Japanese criterion and the new IDF criterion. *p<0.001 for the t test of differences in means in comparisons between subjects with or without metabolic syndrome.

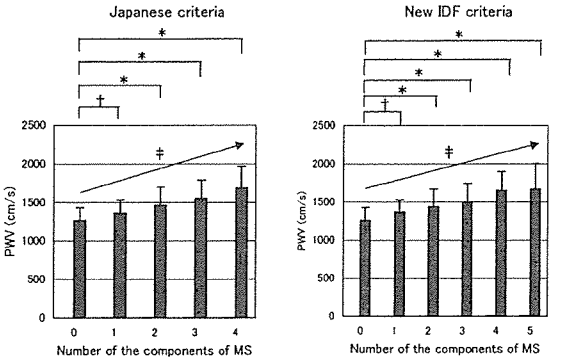

Fig. 2. The relation between baPWV values and the number of components of metabolic syndrome by the Japanese criterion and the new IDF criterion. *p<0.001; †<0.01 for Tukey's multiple comparison test. ‡p<0.01 for linear trend test adjusted for age, BMI, SBP and smoking status.

Table 2. Multivariate logistic regression analysis with baPWV* as a dependent variable and metabolic syndrome as an indepedent variable in the Japanese criterion and the new IDF criterion

	OR (95% CI)†	p
Metabolic syndrome by the Japanese criterion	2.08 (0.90–4.81)	0.087
Metabolic syndrome by the new IDF criterion	2.88 (1.30–6.37)	0.009

*High baPWV was defined as ≥1,600 cm/sec, †Adjusted for age, BMI, Systolic blood pressure (SBP), and smoking status.

Results

Table 1 shows the clinical and biochemical characteristics of all the subjects and the subjects with or without MS by the new IDF criterion and the Japanese criterion. The prevalence of MS was 17.0% (n=64) in the new IDF criterion and 13.5% (n=51) in the Japanese criterion. Using the NCEP ATP III criterion, the prevalence of MS was 5.84% (data not shown).

In both the new criteria, subjects with MS were significantly older, and had higher BMI, waist circumference, SBP, DBP, fasting plasma glucose, triglyceride, and baPWV but smaller HDL cholesterol than the subjects without MS. Height and percentage of current smoking subjects did not differ between the two groups in both the criteria.

In the analysis of two subgroups, laborers and office workers, the prevalences of MS were not significantly different in both the new IDF and Japanese criteria (p=0.083 in the IDF criterion; p=0.111 in the Japanese criterion) (data not shown).

baPWV was significantly higher in those with MS than those without MS in both the criteria (1,563 ± 264.2 vs 1,362 ± 204.6 cm/sec, p<0.001 in the new IDF criterion; 1,574 ± 265.2 vs 1,368 ± 209.1 cm/sec, p<0.001 in the Japanese criterion) (Fig. 1). After adjustment for age, BMI, SBP, and smoking status, baPWV was still significantly higher in those with MS than those without MS (p=0.001 in the new IDF criterion; p=0.045 in the Japanese criterion). In the two subgroups, laborers and office workers, baPWV was also significantly higher in those with MS than those without MS in both the criteria (p<0.001 in both the criteria in both subgroups) (data not shown).

Subjects with different numbers of components of MS were placed in 6 and 5 subgroups, respectively, in the new IDF criterion and the Japanese criterion (graded from 0 through 5 and 4, respectively). Following stratification into the 6 and 5 subgroups, age-, BMI-, SBP-, and smoking status-adjusted baPWV significantly increased with increasing numbers of components of MS (1,257 ± 172.2, 1,371 ± 158.0, 1,438 ± 231.5, 1,648 ± 246.8, 1,669 ± 344.7cm/sec, p for trend<0.01 in the new IDF criterion; 1,264 ± 171.1, 1,364 ± 169.9, 1,465 ± 235.4, 1,553 ± 236.9, 1,689 ± 281.1cm/sec, p for trend<0.01 in the Japanese criterion) (Fig. 2). The subjects with 1, 2, 3,

and 4 components of MS had significantly higher baPWV than those without MS in both of the criteria ($p<0.001$ for all). It was also shown in the two subgroups, laborers and office workers, that baPWV increased with increasing number of components of MS after controlling for age, BMI, SBP, and smoking status (p for trend<0.01 in both criteria for laborers; p for trend<0.05 in both criteria for office workers) (data not shown).

To assess the utility of the two new criteria of MS to identify individuals with increased baPWV, we analyzed the risk of increased baPWV in relation to MS in the two criteria by a multiple logistic regression analysis. After controlling for age, BMI, SBP, and smoking status, the odds ratios for increased baPWV in subjects with MS were 2.07 (95%CI=0.90–4.81) in the Japanese criterion and 2.88 (1.30–6.36) in the new IDF criterion compared with those without MS (Table 2).

Discussion

In the present study, only 1.6% of all subjects were classified as having central obesity using the NCEP ATP III criterion of central obesity (data not shown) and the prevalence of MS by the NCEP ATP III criteria was 5.84% which is a quarter of the prevalence of 24.0% reported in the U.S. using the NCEP ATP III criteria[40]. Because the NCEP ATP III criteria are based on data from Caucasian cohorts, the great difference of the prevalence of MS may reflect not only the prevalence itself but also the build between races and, thus, the NCEP ATP III criteria may not be appropriate for Japanese.

On the other hand, the prevalences of MS by the new IDF and Japanese criteria were 17.0% and 13.5%, respectively, in middle-aged Japanese men. Because the new criteria use ethnic specific values for waist circumference, the difference of MS prevalence between Japan (17.0% by the new IDF criterion; 13.5% by the new IDF criterion) and the U.S. (24.0% by the NECP ATP III criterion) may reflect the true value of the difference of MS prevalence. Thus, the new two criteria may be better for diagnosis of MS than the NCEP ATP III criterion, although we understand that the present data cannot be simply compared with previous data obtained using the other criterion of MS.

The two new criteria are similar in that they regard central obesity as an indispensable item and include the criteria of dyslipidemia, hyperglycemia, and hypertension. However, there are two different points. First, the fasting plasma glucose threshold is higher in the Japanese criterion than in the new IDF criterion. If the cutoff value for the fasting plasma glucose in the Japanese criterion (≥110 mg/dL) is substituted with the cutoff value in the new IDF criterion (≥100 mg/dL), the number of subjects with MS increases by 9 to 60 (15.9%) which is almost the same number as that of the MS subjects by the new IDF criterion. Therefore, the difference in the prevalence of MS between the new IDF criterion (17.0%) and the Japanese criterion (13.5%) was mainly the result of a difference in the fasting plasma glucose threshold. Second, while the new IDF criterion uses two items of dyslipidemia, i.e. HDL cholesterol and triglyceride, for the criteria of MS on equal terms with other criteria, the Japanese criterion put the two items together as dyslipidemia. Weighting each trait equally in the new IDF criterion may overweight the contribution of dyslipidemia to MS, though it is unlikely that each trait confers equivalent disease risk.

Of the 377 subjects, 14 (3.7%) satisfied the IDF criterion of MS but did not satisfy the Japanese criterion of MS. Their mean value of baPWV was 1,482.4 ± 290.1 and it was not significantly different from that of those who satisfied both criteria (baPWV=1,585.8 ± 255.0, p=0.241) or that of those who satisfied neither criteria (baPWV=1,362.1 ± 204.6, p=0.148). Therefore, we could not conclude which of the two criteria was good for Japanese men in terms of a predictor for high baPWV.

The present study demonstrated that MS was significantly associated with a risk of increased baPWV after adjustment for the potential confounding factor of aortic stiffness in both the new criteria. This assures that multiple risk factors act together and exert an even greater influence on future events than expected by each risk factor alone. Our data concurs with a previous study which reported that clustered features of MS are related to increased aortic PWV[5]. However, in the previous study, the characteristics of MS were not defined by any proposed criteria but by their original criterion because the aim of the study was to investigate the association between clusters features of MS and increased aortic PWV.

Although the present study also demonstrated that the new IDF criterion was a better predictor of increased baPWV than the Japanese criterion, further studies are expected to assess the utility of the two new criteria to identify individuals with increased cardiovascular risk, because baPWV is a surrogate marker of cardiovascular disease.

The present study has several limitations. First, the number of subjects was relatively small and the results of this study need to be assessed in larger sample size. However, there was a strong and positive association of MS components with the level of baPWV after adjustment for potential confounding factors in both of the new criteria, and the relationship between baPWV and MS was not associated with the kind of occupation according to the analysis of the subgroups of laborers and office workers. Therefore, we suggest that the two new criteria are good for diagnosing MS among Japanese men in large populations. Second, we used a surrogate measurement of arterial stiffness and therefore may not have identified its prevalence precisely. However, previous studies have

shown that PWV reflects vascular damage[28–30] and severity of cardiovascular disease[31], and predicts future events[32–34]; moreover, PWV is a non-invasive marker. Therefore, PWV may have been an appropriate marker for arterial stiffness in the present study. Finally, our cross-sectional study design lacks information on the time sequence of events and, thus, does not permit identification of causal relationships.

In conclusion, the new IDF criterion and the Japanese criterion are both good for diagnosing MS among Japanese men, because a linear increase in baPWV occurred with increasing MS components after adjustment for potential confounding factors in both the new criteria. Our study was a cross-sectional study, and further prospective studies are expected to follow.

Acknowledgments: This research was supported by the Ministry of Economy, Trade and Industry, Japan (R&D for practical use of university-based technology by matching government and private funds). We thank all the staff and study participants.

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Periodontal disease and atherosclerosis from the viewpoint of the relationship between community periodontal index of treatment needs and brachial-ankle pulse wave velocity

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Published: 14 May 2006

BMC Public Health 2006, **6**:131 doi:10.1186/1471-2458-6-131

Received: 14 November 2005

Accepted: 14 May 2006

This article is available from: http://www.biomedcentral.com/1471-2458/6/131

Abstract

Background: It has been suggested that periodontal disease may be an independent risk factor for the development of atherosclerosis. However, the relationship between periodontal disease and atherosclerosis has not been fully elucidated. This study aimed to assess the effects of periodontal disease on atherosclerosis.

Methods: The study design was a cross-sectional study. Subjects were 291 healthy male workers in Japan. We used the Community Periodontal Index of Treatment Needs (CPITN) score, average probing depth and gingival bleeding index (rate of bleeding gums) to assess the severity of periodontal disease. We also used the Brachial-Ankle Pulse Wave Velocity (baPWV) as the index for the development of atherosclerosis.

Results: The unadjusted odds ratio (OR) of atherosclerosis in relation to the CPITN score was 1.41 [95% CI: 1.16–1.73]. However, after adjustment for age, systolic blood pressure and smoking, the CPITN score had no relationship with atherosclerosis (adjusted OR: 0.91 [0.68–1.20]).

Conclusion: Our results show no relationship between mild periodontal disease and atherosclerosis after appropriate adjustments.

Background

For many people, periodontal disease causes problems in day-to-day life due to loss of teeth. Recently, it has been argued that periodontal disease may be an independent risk factor for the development of atherosclerosis. The potential mechanisms that could explain a role for periodontal disease in atherosclerosis are general inflammatory mechanisms and specific bacterial interactions. One hypothesis is that the cause of atherosclerosis is direct injury to vascular endothelial cells by an infecting organ-

ism; another is that inflammatory cytokines contribute to atherosclerosis [1,2]. It has been reported that the infected or inflamed area in periodontitis is associated with macrophage activation via increased serum lipopolysaccharide concentrations [3]. It has also been reported that subjects with advanced periodontal disease had endothelial dysfunction and evidence of systemic inflammation, possibly placing them at an increased risk for cardiovascular disease [4]. The relationship between periodontal disease and diseases of the blood vessels, such as peripheral vascular disease and coronary heart disease (CHD), has been discussed in several reports [5-9]. For example, a meta-analysis of nine cohort studies (eight prospective and one retrospective) comparing individuals with and without periodontal disease showed that the relative risk (RR) of cardiovascular events was 1.19 [1.08–1.32]. When the outcome was restricted to stroke only, the RR was 2.85 [1.78–4.56] [9].

More than 70% of all people have gum problems [10]. Among Japanese, the prevalence of advanced periodontal disease is 32% in people in their 40 s and 47% in people in their 50 s [11]. Advanced periodontal disease is defined by a Community Periodontal Index score (CPITN score) of 3–4. The CPITN score, which is defined by the World Health Organization (WHO) protocol and provides a standardized means of measurement, makes it easy to compare reports. Periodontal disease is one of the most widespread diseases in the world [12], and if it affects atherosclerosis, it must be considered an important aspect of public health. Therefore, it is essential to clarify the relationship between periodontal disease and atherosclerosis.

We defined atherosclerosis by using Pulse wave velocity (PWV), an index of arterial stiffness [13,14] regarded as a non-invasive marker of vascular damage [15-17]. Previous studies have shown that PWV is a marker of the severity of cardiovascular disease [18] and a predictor of future cardiovascular events [19-21]; moreover, it can be applied as a screening tool for cardiovascular risk in a general population [16,22]. Recently, a simple device for measuring brachial-ankle PWV (baPWV) has been developed and made available [23,24].

In this study, we assessed the effect of periodontal disease on atherosclerosis from the viewpoint of the relationship between CPITN score and Brachial-Ankle Pulse Wave Velocity (baPWV), by which we non-invasively assessed the progress of atherosclerosis.

Methods

Study subjects and design

This was a cross-sectional study. The setting was a Japanese chemical company. After receiving approval from the ethical committee of Keio University School of Medicine, we obtained informed consent from 291 male employees of the chemical company who were selected for participation in the cross-sectional study. In September 2004, we gave the participants questionnaires about their daily life and dental habits. Oral and medical examinations were performed in October 2004, at which time the questionnaires were also collected.

Periodontal measurements

We used the CPITN score, average probing depth and gingival bleeding index (rate of bleeding gums) to determine the severity of periodontal disease. Dental examinations were conducted by two dentists who, according to the WHO protocol, used flat dental mirrors and periodontal probes [25]. Teeth numbers 2, 3, 8, 14, 15, 18, 19, 24, 30 and 31 were studied, and six segments of each tooth were evaluated. Probing depth was measured at two locations per index tooth. Each sextant was designed as either healthy (Score 0), bleeding but no dental calculus detected (Score 1), calculus detected but no pockets (Score 2), a probing depth of more than 4 mm (Score 3) or a probing depth of more than 6 mm (Score 4), according to the highest score recorded at the index teeth. The highest score was recorded as the CPITN score of the participant. The assignment of the two dentists to subjects was carried out at random. Interexaminer agreement between the dentists was tested at baseline and calculated using the Kappa statistics. The same dentists carried out the dental examinations during the entire study period.

Medical measurements

We used baPWV as the index for atherosclerosis. Nurses measured the baPWV and blood pressure of each subject twice using a baPWV/ABI device (Nippon Colin, Aichi, Japan) while the subject was at rest in a supine position. This device, approved by the US Food and Drug Administration as VP-2000/1000, can monitor bilateral brachial and ankle pressure wave forms simultaneously using the volume plethysmographic method, with two optional tonometry sensors for carotid and femoral arterial wave measurements. The nurses practiced baPWV measurements beforehand and made arrangements for standardization.

Age and smoking status were self-reported, and medical history was acquired by interview. We applied pack-years (smoking period [years] × number of packs [/day]) as the cumulative smoking index. Height, weight, systolic and diastolic blood pressures (SBP and DBP), fasting blood glucose level, serum lipid levels [total cholesterol, triglyceride and high-density lipoprotein (HDL) cholesterol] and HbA1c were measured in all subjects.

Statistical analyses

The distributions of triglyceride, HDL cholesterol and HbA1c were skewed and regarded as log-normal. Therefore, these data were logarithmically transformed, and the Student's *t*-test was applied. For age, as the distribution was skewed and not log-normal, the Wilcoxon's rank sum test was applied. The other variables were regarded as normally distributed, and the Student's *t*-test was applied.

We divided the subjects based on CPITN score, average probing depth and gingival bleeding index. Subjects with CPITN scores of 0, ≧1, ≧3 and ≧4 were defined as healthy, having periodontal disease, having advanced periodontal disease and having severe periodontal disease, respectively. Similarly, for average probing depth and gingival bleeding index, we placed the subjects in four groups. The boundary values for average probing depth were 2 mm, 3 mm and 4 mm, and those for gingival bleeding index were 25%, 50% and 75%.

We defined atherosclerosis as baPWV ≧1400 (cm/sec), which is an independent variable for risk stratification by the Framingham score and for the discrimination of patients with atherosclerotic cardiovascular disease. It is the commonly used cut-off value in clinical practice [16].

Odds ratios (ORs) and 95% CIs were calculated using logistic regression analysis. All statistical analyses were performed using SPSS for Windows version 12.0 (Statistical Product and Service Solutions, IL, USA), and statistical significance was accepted at $p < 0.05$.

Results

Mean age and body mass index were 46.6 ± 11.5 years and 23.4 ± 3.66 kg/m^2 (mean ± SD), respectively, which are typical values in healthy male Japanese workers. The maximum and minimum ages were 21 and 63. The biochemical values of blood did not reveal any significantly abnormal characteristics. The distribution of the CPITN score was typical in Japanese people and in people from other countries [10,12,26-28]. The case-control ratio was 0.99 (case: N = 145, control: N = 146). Between the case and control groups, significant differences were found in age, blood pressure, pack-years, periodontal measurements and other variables (Table 1). The periodontal conditions of the case group were worse than those of the control group. For example, in the case group, the prevalence of severe periodontal disease was about one-ninth, but in the control group, it was about one-fourth (Table 1). [Note: I don't quite understand what "one-ninth" and "one-fourth" mean in the above sentence.] The agreement between examiners was fairly high (Kappa statistics = 0.767, p value = 0.029).

Table 1: Characteristics of study participants

	Atherosclerosis (+)** (N = 45)		Atherosclerosis (-)** (N = 146)		p Value
	Mean	± SD	Mean	± SD	
Age	51.9	7.9	40.7	11.9	0.000*
Weight [kg]	65.4	9.3	68.2	11.3	0.027*
BMI† [kg/m^2]	23.5	3.2	23.5	3.3	0.942
Systolic blood pressure [mmHg]	143.6	16.3	127.1	11.5	0.000*
Diastolic blood pressure [mmHg]	89.0	10.6	77.2	9.2	0.000*
Total cholesterol [mg/dl]	201.9	37.7	195.3	35.3	0.139
Triglyceride [mg/dl]	164.9	129.0	132.0	126.1	0.034*
HDL†cholesterol [mg/dl]	53.9	15.6	54.5	13.0	0.728
Fasting plasma glucose concentrations [mg/dl]	107.6	28.8	95.0	17.0	0.000*
HbA1c† [%]	5.22	0.47	5.07	0.54	0.011*
Pack-years	16.6	17.9	10.8	13.6	0.003*
baPWV† [cm/sec]	1609	185.2	1275	84.8	0.000*
CPITN score†	2.72	1.19	2.20	1.24	0.000*
Average probing depth [mm]	3.20	1.00	2.78	0.87	0.000*
Gingival bleeding index [%]	48.8	-	40.0	-	0.042*
Prevalence of periodontal disease***[%]	90.3	-	86.2	-	0.299
Prevalence of advanced periodontal disease***[%]	73.1	-	50.7	-	0.000*
Prevalence of severe periodontal disease***[%]	24.6	-	11.6	-	0.005*
Number of teeth	25.8	5.2	26.0	5.4	0.773

† BMI: body mass index, HDL: high-density lipoprotein, HbA1c: hemoglobin A1c, baPWV: brachial-ankle pulse wave velocity, CPITN: Community Periodontal Index of Treatment Needs

* p value < 0.05

**Atherosclerosis is defined as baPWV ≧ 1400 (cm/sec)

*** Periodontal disease, advanced periodontal disease and severe periodontal disease are defined by CPITN scores of ≧1, ≧3 and ≧4, respectively.