Tobacco, Cardiopulmonary Vascular Disease, and Aging

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Abstract

Smoking causes disease through oxidative stress, which accelerates aging. Recently, chronic obstructive pulmonary disease (COPD), emblematic of tobacco-related diseases, has come to be viewed as a systemic inflammatory disease. COPD is regarded as contributory to cardiovascular events stemming from vascular inflammation. As an independent risk factor for cardiovascular disease, COPD in combination with smoking also raises cardiovascular risk synergistically. Vascular endotheliopathy caused by tobacco is also closely related to decreases in endothelial progenitor cells (EPC) and elevated cardiovascular risk. α1-antitrypsin-LDL (AT-LDL), an oxidized/modified LDL that contributes to development of arteriosclerosis, is also elevated in smokers.

Tobacco-induced cardiopulmonary vascular disease entities are in this way interrelated and deemed to create a vicious circle. The EPC reduced in smokers recovers rapidly after smoking cessation, and increased AT-LDL also decreases after smoking cessation. Smoking cessation is thus essential to breaking this vicious circle. In the interest of arresting and preventing aging and disease, we hope to deepen understanding of smoking cessation among smokers through patient-based awareness.

KEY WORDS: chronic obstructive pulmonary disease (COPD), cardiovascular disease, oxidative stress, vascular endotheliopathy, smoking cessation therapy

Introduction

Smoking is a cause of cancer, stroke, myocardial infarction, and chronic obstructive pulmonary disease (COPD) and is also involved in aspects of aging such as increased wrinkles and gray hair. Oxidative stress is one important mechanism that causes these changes. Smoking causes disease through oxidative stress, which accelerates aging.

Regulatory measures to prevent passive smoke exposure have been enacted recently in Japan; an anti-smoking policy in the form of higher tobacco taxes has also been promoted, and the creation of a standard smoking cessation protocol has broadened use of smoking cessation therapy. At the same time, measures in Japan remain insufficient compared to those in the developed countries of the EU and US, and health care providers still require a deeper understanding and awareness of tobacco-induced health injuries and nicotine dependence.

To deepen understanding of tobacco-induced health injuries, our review first presents an overview of COPD, a representative tobacco-related disease, by Professor Hiroshi Kimura. Dr. Yasuko K Bando then surveys the mechanisms leading from smoking to arteriosclerotic vascular disease. Dr. Hiromichi Wada describes the relation of a new arteriosclerosis marker, α1-antitrypsin-LDL, to cigarette smoking. Finally, to deepen understanding of smoking cessation among smokers based on the idea that smokers are patients, Professor Yuko Takahashi describes smoking cessation support and recent smoking cessation therapy for rejuvenation and disease prevention.
I. Chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease occurs among middle and older aged individuals with a long-term history of smoking and reportedly affects 15-20% of smokers. Various comorbidities are observed frequently in conjunction with smoking and age. The background of these observations suggests that, rather than an elevated incidence of comorbidities due to frequent observation of COPD among elderly individuals, COPD and various comorbidities may share a common etiology and pathalogy.

In a 2006 revision, the Global Initiative for Chronic Obstructive Lung Disease (GOLD), an international guideline on COPD, described a new disease concept of COPD in which “the severity of illness in individual patients also causes extrapulmonary symptoms (extrapulmonary effects)” 1). Subsequently, from a pathophysiological perspective, the 2009 revised 3rd Edition of “Guidelines for Diagnosis and Treatment of COPD” 2) by the Japan Respiratory Society also led to greater emphasis on the systemic effects of COPD.

Comorbidities and Systemic Inflammation in COPD

From 1979 to 2001, the National Hospital Discharge Survey was conducted among retired military personnel in the US. Results from a study of the association between COPD status and incidence of comorbidities at hospital discharge among 47 million individuals showed that the incidence of diseases including hypertension, ischemic heart disease, diabetes, pneumonia, congestive heart failure, and respiratory failure was significantly higher in a cohort diagnosed with COPD than one not diagnosed with COPD (no coexisting COPD). In other words, comorbidities were associated with COPD pathology, represented a primary factor governing the severity of COPD, and may also have been associated with prognosis. Essentially, the results indicated that systemic comorbidities are an important target in disease management of COPD. This paper addresses COPD as a systemic disease and focuses succinctly on corrective measures for nutritional imbalances and systemic inflammation, osteoporosis, cardiovascular disease, and systemic inflammation.

1. Nutritional imbalances and systemic inflammation

In 2008, Japan conducted a national status survey on COPD outpatients (survey research by the Ministry of Health, Labour and Welfare Respiratory Failure Survey Research Group) 3). This survey found that roughly 30% of COPD outpatients had a body mass index (BMI) of less than 20 kg/m². Weight loss of this nature was also associated with severity of COPD, with body weight loss observed among approximately 60% of patients at the highest level of severity (%FEV<30%). Despite the fact that airflow limitation is more severe among COPD patients in the EU and US, the incidence of weight loss is approximately 23%, and overweight status is reportedly observed among 20% or more of such patients. The GOLD 4) also stated that approximately 25% of COPD patients with moderate to severe disease evidenced body weight loss, but weight loss is clearly observed at a higher rate in Japan than in the EU and US. The GOLD 4) also elaborates the fact that body weight loss based on many immunological research results represents an independent prognostic factor with respect to respiratory dysfunction. Besides weight loss, it is important to ascertain fat mass (FM), fat-free mass (FFM) as a quantitative index of muscle protein, and other such changes in body composition; FFM in particular is correlated to basic pathophysiological indices such as respiratory function and respiratory muscle strength, and exercise tolerance. The facts suggest that reduction in FFM is linked directly to decreases in activities of daily living (ADL) and quality of life (QOL) 4). FFM has also been shown to be a more sensitive prognostic factor than body weight 5). In nutritional imbalances, contributory factors include increased energy consumption at rest, systemic inflammation, and abnormalities in food intake-regulating factors such as leptin and ghrelin 4).

Fig. 1A presents resting energy expenditure (REE) data for patients with stable COPD. Predicted REE ratio (%REE) is significantly higher for COPD patients versus controls adjusted for age and sex, indicating that metabolism is accelerated in COPD patients 5). Among COPD patients as well, metabolism is further accelerated in a body weight loss cohort versus a normal body weight cohort. Values for %REE are correlated to forced expiratory volume in one second (FEV1), an index of residual volume and airflow restriction, and factors such as airflow limitation and pulmonary hyperinflation, the essential state of COPD, represent likely factors causing increased REE. Consequently, the absence of an energy supply commensurate with such increased consumption indicates a nutritional imbalance. Even in study results showing good correspondence in BMI between healthy controls and a COPD cohort, fat-free mass index (FFMI), the amount of muscle protein present, is significantly lower in COPD cohort (Fig. 1B). Study of the association between the GOLD severity classification of COPD (severity according to FEV1 by spirometry) and body components also showed that bone mineral mass and fat mass were significantly reduced in Stage III and IV severe disease cohorts versus controls, but there was no difference between Stage I and II non-severe disease cohorts. However, loss of muscle protein mass consistent with severity was observed as data progressed from non-severe disease cohorts to severe disease cohorts. These findings indicate that muscle protein mass is an important endpoint for evaluating the severity of COPD.

Examining the association between systemic inflammation and body weight loss, the elevation observed in blood concentrations of inflammatory cytokines such as TNF-α and IL-6 as weight loss progresses suggests the role of systemic inflammation in nutritional imbalance. Entities such as TNF-α and IL-6, together with leptin, also function as food intake-restricting factors.

2. Osteoporosis

Osteoporosis causes problems such as spinal compression fractures and lumbar pain and is of concern as a factor decreasing ADL and QOL. Spinal compression fractures in turn cause vertebral deformation and have a direct, adverse effect on respiratory function. Sin et al. have studied bone mass in the femoral neck. The risk of osteoporotic complication in COPD versus that in controls free from airflow obstruction is reported as an odds ratio of 1.9. The incidence of osteoporotic complication also increases with increasing severity of airflow obstruction and is reported to rise to an odds ratio of 2.4 in severe disease 7).

Among COPD patients, factors such as smoking, hypoxia, subnutrition, diminished skeletal muscle mass, vitamin D or calcium deficiency, and systemic steroid administration can engender osteoporotic complications. A recent meta-analysis of actual COPD patients reported that the incidence of diminished bone mineral density (BMD) is high, at approximately 35% 8).

Though previous studies have not clarified whether severity
of airflow obstruction presents a risk of osteoporosis, a close association has been demonstrated between decreased BMD and decreased BMI or reduced FFM.

At the same time, the extent of pulmonary emphysema on CT imaging is reported to be a regulating factor for vertebral bone density.

3. Cardiovascular disease

COPD is one of the independent risk factors for ischemic heart disease and has an observed association with elevated incidence of complicating arrhythmia and risk of cerebrovascular event. Evaluation of intimal-medial thickness (IMT) of the carotid arteries has also shown that airflow obstruction in COPD patients is a smoking-independent risk factor for arteriosclerosis. Among COPD patients in the EU and US, cardiovascular disease is the cause of death in 20-30% and this trend is observed notably in slight and moderate disease. In Japan, however, the rate of death from cardiovascular disease is low in comparison to the 65-70% accounted by death from respiratory failure, with deaths from heart disease reported as approximately 6% in a recent study. Though the related mechanism is unknown, extremely high blood concentrations of adiponectin among emphysemic COPD patients in Japan are reported to play a role, given the anti-arteriosclerotic effect and anti-inflammatory effect of this substance. In other words, Japanese COPD patients have higher concentrations of total adiponectin in blood than healthy controls of same body weight. Further study is needed to determine whether and how elevated levels of anti-arteriosclerotic adiponectin in Japanese COPD patients play some role in cardiovascular disease in these patients.

4. Treatment of systemic inflammation in COPD

Inhaled corticosteroids (ICS)

When treating COPD as a systemic disease, a treatment plan must be created to control systemic inflammation. The hypothetical mechanism of onset for systemic inflammation is “spillover” to other body systems of inflammatory cytokines produced by the lungs. Inhalation of 800 µg/day of the inhaled corticosteroid (ICS) budesonide has been reported to significantly inhibit ischemic heart disease events versus placebo controls. Migration of ICS throughout the body cannot be completely discounted, and these results suggest that ICS may inhibit systemic inflammation. However, inflammation in the pulmonary region and throughout the body may be controlled differently, and at present, the mechanism of onset for systemic inflammation is unclear.

Statins

Though there is currently no established treatment for inhibition of systemic inflammation, new therapeutic strategies and various other possibilities are being researched. Statins act to restrict inflammation caused by NF-κB and as an agonist to restrict inflammation caused by peroxisome proliferator-activator receptor (PPAR)-γ or PPAR-α. In COPD patients, administration of statins has been shown to inhibit reduction of FEV₁, and another report states that these agents are otherwise effective in reducing death rates and reducing the incidence of myocardial infarction. In cigarette smoke exposure experiments, administration of statins has also been reported to alleviate elevation of pulmonary arterial systolic blood pressure and to inhibit progression to emphysema.
Anti-TNF-α blockers

The effect of the anti-TNF-α blocker infliximab on improving motor activity and QOL has been studied. Though no distinct efficacy was observed among all patient cohorts combined, a sub-analysis found improvement in a >age 65 years patient cohort and in a nutritional imbalance patient cohort with respect to the primary endpoint of 6-minute walking distance. Further study on topics including infectious disease is now awaited.

PPARs agonists

Expression of PPAR-α mRNA is decreased in the skeletal muscle of COPD patients, and such decrease is reportedly correlated with blood levels of TNF-α. Inflammation or increased oxidative stress of skeletal muscle impairs skeletal muscle function, leading to diminished exercise tolerance. Administration of PPAR agonist may therefore improve these pathological conditions.

Sirtuin (SIRT1) protein

Sirtuin (SIRT1) protein is involved with deacetylation of histone proteins. The amount of SIRT1 protein in pulmonary tissue of COPD patients has been found to be lower than that in healthy individuals. Decreased histone deacetylase (HDAC) activity plays a substantial role in inflammatory cytokine production. Administration of resveratrol and other such sirtuin (SIRT1) activation factors is regarded to be useful as anti-inflammatory treatment. In vitro experiments using monocytes/macrophages has also found that increased acetylation of NFκB accompanies decreased expression of SIRT1 caused by exposure to a tobacco-derived fluid (cigarette smoke extract (CSE)), but when siRNA is used to knock down SIRT1 and CSE exposure is then performed, acetylation of NFκB is reportedly increased further. These findings suggest that maintenance and augmentation of sirtuin activity may prove to be an effective treatment strategy in smokers and COPD patients.

Ghrelin

Ghrelin is a growth hormone secretor factor expressed by gastric tissue as an intrinsic ligand for growth hormone secretagogue receptors. It has anabolic action or food intake-stimulating action as well as anti-inflammatory action. In studies on COPD patients we have demonstrated that plasma ghrelin concentration was elevated significantly in a body weight loss COPD cohort versus a normal body weight COPD cohort and a healthy control cohort. Plasma ghrelin concentration has also been found to have a significant, negative correlation to BMI. In a pilot study wherein ghrelin was administered to COPD patients presenting nutritional imbalances, improvement in QOL was observed, as was improvement in physiological functions including quantitative dietary intake, body weight, fat-free mass index, grip strength, respiratory muscle strength, and 6-minute walking distance, suggesting that administration of ghrelin could be an effective treatment strategy for nutritional imbalance in COPD. In results from a multicenter, double-blind, comparative study using ghrelin administration (2 µg/kg) or placebo administration (physiological saline) in addition to respiratory rehabilitation, the ghrelin administration cohort demonstrated improvement of 6-minute walking distance maintained as a long-term trend. The ghrelin administration cohort also maintained significant improvement of symptoms on the St. George Respiratory Questionnaire (SGRQ).

Fig. 2. Plasma adiponectin levels in COPD
II. Tobacco and Vascular Aging: Molecular Mechanism of Tobacco-Induced Vascular Endotheliopathy

Cigarette smoking is well known to increase the risk for occurrence of cardiovascular events by increasing vascular aging in the form of arteriosclerosis. In the proposed mechanism, one causal factor is increased oxidative stress or inflammation caused by the cigarette smoke components nicotine and tar or by nitric acid or other gaseous components, leading to injury of the vascular endothelium. At the same time, there remains scope for debate as to the best index for measuring this vascular aging effect of cigarette smoke. Endothelial progenitor cells (EPC) contribute to regeneration of vascular endothelium or neovascularization, and their level has been proposed recently as a possible cardiovascular risk factor. Murohara et al. discovered that EPC counts in peripheral blood were decreased in healthy cigarette smokers and also revealed that EPC counts increased in chronic cigarette smokers after just a short duration of smoking cessation. Our paper discusses cigarette smoking and mechanisms concerning EPC and endothelial function and also mentions results from our own inquiry, i.e., the protective effect of statins on endothelial function in cigarette smokers, and the role of EPC as a biomarker for vascular injury.

Self-Imperceptible Vascular Aging: The Importance of Surrogate Markers for Endothelial Injury

According to death rates by primary cause of death, we have now arrived in an era where approximately one in four Japanese individuals dies from arteriosclerotic disease [22]. Cigarette smoking is a primary risk factor for non-LDL arteriosclerosis [23], and the 2010 revised guidelines of the Japanese Circulation Society also cite arteriosclerosis, a “vascular aging” pathology, as an adverse effect of cigarette smoking (Fig. 3) [24]. However, as in human aging, vascular aging proceeds without subjective symptoms and is well known to manifest first in an aggravated form such as myocardial infarction or stroke. This characteristic that “vascular aging is self-imperceptible” suggests the importance of what is termed biomarker-based monitoring of vascular aging and disease at the outpatient level.

Fig. 3. Oxidative stress is essential for progression of vascular aging
Endothelial Injury and Endothelial Progenitor Cells (EPC): The Role of EPC as a Biomarker

Endothelial progenitor cells (EPC) are a type of undifferentiated somatic stem cell endowed with capacity for differentiation and reproduction, the role of which is determined almost entirely by the vascular endothelial system. A 2001 pilot study in the New England Journal of Medicine reported that EPC counts in peripheral blood were decreased among effort angina patients, and a 2003 study published in the same also reported that EPC counts in peripheral blood were inversely proportional to cardiovascular risk. EPC were subsequently acknowledged as an important biomarker for monitoring endothelial injury.

Corrective Measures for Cigarette Smoking-Induced Cardiovascular Injury: Smoking Cessation and Statins

What methods are effective for inhibiting vascular injury caused by cigarette smoking? Cumulative findings to date have shown the usefulness of statin administration in smoking cessation. Smoking cessation has been shown to increase EPC counts and improve function in smokers. Of greater interest, smoking cessation has been reported to improve patient prognosis after myocardial infarction both in Japan and abroad, though the detailed molecular mechanism requires further study.

Apart from smoking cessation, statins, a class of therapeutics for dyslipidemia, have also shown potential for anti-arteriosclerosis as a mitigation strategy for vascular injury. In 1994, articles in the Lancet reported that statins were effective in lowering the total death rate among hypercholesterolemia patients with a history of IHD (4S study, Lancet, 1994), while subsequent research reported a secondary preventive effect on cardiovascular events among IHD patients with complicating mild dyslipidemia (less than 240 mg/dL; CARE, 1996), and a secondary preventive effect on cardiovascular deaths, total deaths, and cerebral stroke among patients with average cholesterol levels (cholesterol less than 213 mg/dL in 42%; LIPID, 1998). Statins were subsequently shown to have a primary and secondary preventive effect for cardiovascular events which is independent of their lipid-lowering action, and these actions are recognized as pleiotropic effects beyond the original therapeutic effect of statins for dyslipidemia.

Statins are reported to increase mobilization of EPCs to peripheral blood by promoting cell differentiation, and to inhibit remodeling of injured blood vessels by promoting recruitment of EPCs to injured endothelium and thus contributing to endothelial repair. Our research group also studied outcomes of pitavastatin administered to 30 male smokers diagnosed with dyslipidemia and found that pitavastatin had an improving effect on vascular endothelial function in smokers mediated by an antioxidative effect.

III. Tobacco and the New Oxidized/Modified LDL Marker α1-Antitrypsin-LDL (AT-LDL)

Cigarette smoking is one principal cause of lipid peroxidation, and oxidized LDL plays an important role in onset and progression of arteriosclerosis. Recently, two novel oxidized/modified LDL markers have been identified: serum amyloid A/LDL complex (SAA-LDL) and α1-antitrypsin-LDL complex (AT-LDL). SAA-LDL is a complex in which low-density lipoprotein (LDL) and serum amyloid A (SAA), an acute phase reactive protein present in bound form with HDL, are bound by reactive oxygen species derived from activated,
inflammatory cells at sites of endovascular inflammation. This complex is regarded as LDL oxidatively altered by oxidation of lipids in the complex and by fragmentation of apoB, and the complex is reported to be associated closely with obesity and inflammation. In contrast, AT-LDL is a complex formed from low-density lipoprotein (LDL) and α1-antitrypsin, and is regarded as a type of oxidized LDL subjected to oxidative alteration by macrophage uptake at atherosclerotic lesions, due to the degree of lipid oxidation involved. Oxidized LDL is present at atherosclerotic lesions and contributes to formation of atheroma by undergoing macrophage uptake and forming foam cells; it also has a variety of arteriosclerosis-promoting effects, such as activation of endovascular cells. In this light, AT-LDL is regarded as a useful marker in arteriosclerosis research. We discovered that SAA-LDL and AT-LDL are both significantly elevated in the serum of cigarette smokers; that 3 months of smoking cessation did not change levels of SAA-LDL but reduced levels of AT-LDL significantly (Fig. 5); and through multivariate analysis, that AT-LDL, together with age and HDL-C, is closely associated with current cigarette smoking. AT-LDL may be useful as an arteriosclerosis marker closely associated with cigarette smoking and aging.

**IV. Rejuvenation From Smoking Cessation**

Smoking cessation has come to be seen as an important strategy and an essential part of treatment and prevention of many diseases [38-49]. In this context, it is apparent from copious data that cigarette smoking promotes aging, and there is now a focus on the importance of smoking cessation therapy to facilitate the transition from smoking to smoking cessation.

Our paper addresses and comments in turn on three recent smoking cessation-related topics: “Passive smoking,” “smoking cessation therapy,” and “social support and treatment for women, children, and smokers with psychiatric disorders.”

**Passive Smoking**

Though active smoking is a major risk factor for cardiovascular disease, ischemic heart disease foremost therein, it has become clear recently that passive smoking, as well as active smoking, is such a risk factor.

The nicotine in tobacco smoke stimulates the sympathetic nerve system, causing contraction of the peripheral vessels, elevation of blood pressure, and increased heart rate. Tobacco smoke contains approximately 4% carbon monoxide, which binds firmly to hemoglobin in the blood, producing a state of chronic hypoxia or promoting alteration of cholesterol and injury of the vascular endothelium, while also diminishing HDL cholesterol levels and thus promoting arteriosclerosis [39-41].

A review encompassing the health effects from passive smoking shows that the rate of death from myocardial infarction among non-smokers is increased by a factor of 1.3 or more by even minor amounts of passive smoking, and that 1-3% of persons subjected to higher levels of passive smoking die of myocardial infarction caused by passive smoking. Passive smoking is also not prevented by smoking outdoors or with ventilation [42-44].

A 2010 study on the effects of smoking outdoors showed that passive smoking can occur even at a location separated [from the source] by 17 meters. It is not surprising then that indoor smoking, from the outset, and outdoor smoking too, have come under more stringent regulation.

**Smoking Cessation Therapy**

For quite some time, smoking has been regarded as a matter of habit, and smoking cessation an act of will power, but nicotine has been shown to create dependence and is the major cause of tobacco dependence. Prochaska encompassed the path of the smoker leading to smoking cessation in the Transtheoretical Model (TTM) theory [45]. At present, smoking cessation in health care facilities typically combines drug treatment with behavioral therapy such as “avoiding smoking materials” or “changing behavior patterns.”

In Japan, health insurance coverage for smoking cessation as a “nicotine dependence control cost” was initiated in April 2006. On notification, health care facilities fulfilling 5 criteria, including prohibition of smoking on the facility property, can provide smoking cessation therapy using health insurance, upon approval from the competent authorities [46]. Patient requirements include a score of 5 points or higher on the “Tobacco Dependence Screener” (TDS), a tobacco dependence screening test. Insurance benefits for smoking cessation therapy (“nicotine dependence control costs”) cover outpatients, and treatment initiated after hospitalization is out-of-pocket care; this and other aspects differ from ordinary insurance care. Note should also be taken that after one session of smoking cessation therapy covered by insurance is provided, the cost cannot be recalculated for a year or more from the initial date of calculation.
There are two smoking cessation aids currently available in Japan: nicotine patches and varenicline. Support for smoking cessation is adjusted individually for the severity (nicotine dependence level) and the living environment of the case, with drug therapy provided as appropriate. When a smoking cessation aid is used, the success rate of smoking cessation is said to increase roughly 2 to 3-fold.

**Nicotine replacement therapy**

Nicotine substitutes include nicotine patches requiring a physician prescription and nicotine patches (small size) and nicotine gum available for purchase without prescription at pharmacies and drugstores.

Nicotine substitutes contain nicotine which is absorbed into the body gradually from contact surfaces of the skin or oral mucosa, the purpose of which is to support smoking cessation by alleviating withdrawal symptoms that occur during smoking cessation. Outside of Japan, aids are sold in a variety of forms, but in Japan, only two types of aids are available for use: nicotine gum and nicotine patches.

Use of such aids during pregnancy is not permitted in Japan. Prudent use is also needed immediately after contraction of a disease increasing the risks imposed by nicotine, such as myocardial infarction or cerebral infarction. The most frequent adverse effect is a rash at the application site or stomatitis. Oral Smoking Cessation Aids

The α4β2 receptor site agonist varenicline can be used as an internal medicine. This agent binds with nicotine receptors to prevent nicotine binding and at the same time releases a low dosage of dopamine. This treatment alleviates the withdrawal symptoms accompanying smoking cessation as well as craving for tobacco. Because it does not contain nicotine, it can be used readily for smoking cessation therapy for ischemic heart disease patients not readily able to use conventional nicotine formulations such as patches. Given its mechanism of action, this agent and a nicotine formulation cannot be used concomitantly. Because the agent is excreted by the kidneys, caution is needed in persons with poor renal function. The agent can also be used during pregnancy or lactation.

The most frequent adverse effect is nausea; headache, constipation, insomnia, and nightmares are also noted. Because the agent can also cause drowsiness, prudent administration to drivers was also deemed necessary in July 2011.

Outcomes of insured treatment for smoking cessation, including drug therapy, have been published as a study by the Central Social Insurance Medical Council, which reported a success rate of approximately 80% when the specified number of treatments ($S$) was completed by the end of the 12-month period of insured treatment.

**Social Support and Smoking Cessation Support for Women**

As smoking cessation therapy becomes more widely practiced, smoking recidivism after the end of the insured treatment period has become a problem. The psychological dependence arising in memory persists long after smoking has ceased and can manifest to trigger recidivist smoking. Many smokers overcome by a temptation for just one taste return in a short time to the smokers they were. For long-term continuation of smoking cessation, it is important to utilize social support from the family, workplace, and other settings to complement smoking cessation support in a health care setting. Even in Japan, the Internet “Quit Smoking Marathon” and other programs that alleviate the work of health care providers have been developed for long-term smoking cessation support, with some indications of a preventive effect on recidivist smoking. The self-help mailing list “Quit Smoking Health Net KK” is also offered free of charge for smoking cessation support (sign up from the Quit Smoking Marathon home page), and we would hope to see active use.

Other non-health smoking cessation benefits such as “my grandchildren started visiting me more” and “my efficiency at work improved” are deemed useful for continuing long-term smoking cessation.

Smoking cessation is reputedly more difficult for women than men. Most women smoke few cigarettes and are reluctant to visit a smoking cessation therapy setting, but smoking even a small number of cigarettes often engenders strong nicotine cravings or depressions of mood. Even if insurance coverage is difficult, the use of smoking cessation aids is recommended. The reason smokers relate most frequently for not quitting smoking is weight gain after quitting. Weight gain after smoking cessation is generally seen within 3 months of cessation, and two-thirds of former smokers who have quit are said to experience weight gain. The following three causes of weight gain have been suggested: 1) Increased appetite or oral fixation as a symptom of nicotine abstention, or increased food intake due to change in flavor, 2) Increased absorption due to recovery of gastrointestinal function accompanying smoking cessation, and 3) Change in metabolic pathways formerly involving nicotine. Of these, items 2) and 3) are causes of weight gain arising without any change in quantitative dietary intake, and body weight gain for these reasons is generally limited to 3 kg or less. Consequently, weight gain on the order of 3 kg after smoking cessation is not regarded as pathological.

Even in a short period, weight gain attenuates the will to cease smoking. There is also a negative effect on biochemical data, such as HbA1c and neutral fats.

Dietary advice and enhanced exercise are essential to counter these phenomena. Use of a nicotine patch during smoking cessation also restricts weight gain after cessation. Though the internally-administered drug varenicline is not recognized to have a weight-restricting effect, based on the observation that nausea as a frequently occurring adverse effect does restrict appetite, smoking cessation drug therapy is also recommended for preventing weight gain after cessation.

**V. Conclusion**

Oxidative stress and inflammation caused by cigarette smoking injure pulmonary alveolus and vascular endothelium and cause cardiopulmonary vascular disease. These effects are sustained systemically, not only in the cardiopulmonary vascular system, and manifestly contribute to aging in individuals. COPD, representative of tobacco-related disease, has recently come to be regarded as a systemic inflammatory disease. As an independent risk factor for cardiovascular disease, COPD is deemed to raise cardiovascular risk synergistically with smoking through vascular inflammation. From the standpoint of inhibiting occurrence of life-threatening cardiovascular events, physicians must keep in mind the need to raise awareness and adoption of smoking cessation, and the fact that smoking cessation therapies are useful for alleviating withdrawal symptoms in nicotine-dependent smokers; their application in treatment and advice for cigarette smokers is essential.
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