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Japan Medical Association
2-28-16, Honkomagome, Bunkyo-ku, Tokyo 113-8621, Japan
Tel: +81-(0)3-3946-2121
Fax: +81-(0)3-3946-6295
E-mail: jmaintl@po.med.or.jp
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OBESITY AND LIFESTYLE

Sanae FUKUDA, Tatsuya TAKESHITA and Kanehisa MORIMOTO

Department of Social and Environmental Medicine, Course of Social Medicine, Osaka University Graduate School of Medicine

1. Introduction

The Japanese lifestyle has undergone remarkable changes as Japan achieved enormous economic growth. Westernization of the diet is an example of such changes. Another recent concern has been the decrease of physical activity.[1)] One more important change that cannot be overlooked is that people have become exposed to various stresses at school, work, and/or home. These changes have given rise to various diseases, particularly those that are considered to be closely related to lifestyle. The increasing prevalence and mortality due to these diseases have become a matter of concern.

"Obesity," as discussed in this article, is a lifestyle-related disease and is also a risk factor for the development of other lifestyle-related diseases, including diabetes, cardiovascular disease, and cancer. In Japan, the prevalence of obesity and the BMI* have been increasing steadily in all populations, except for women in their 20s to 30s (Fig. 1).[2)] Prevention of obesity through modification of lifestyle is an important goal because it would also assist in the prevention of other lifestyle-related diseases. In this article, risk factors for the development of obesity, particularly those related to lifestyle, are discussed.

2. Obesity and Lifestyle

2-1. Diet

The diet has considered as an important risk factor for obesity. Large-scale

* The body mass index (BMI) is widely used to assess the degree of obesity. In the "National Nutrition Survey" performed by the Ministry of Health and Welfare, the degree of obesity was initially rated from the thickness of subcutaneous fat at two sites (the 1994 National Nutrition Survey Report, 1996). This method was replaced by the BMI (BMI = weight (kg) / height $(m)^2$) since 1995. The WHO has proposed a classification that divides obesity into three grades depending on the BMI: grade 1 (BMI 25.0–29.9), grade 2 (30.0–39.9), and grade 3 (40.0–). According to the classification currently used by the Japan Society for the Study of Obesity, the standard BMI is 22. A BMI exceeding 26.4 is defined as "obesity," a BMI between 24.2 and 26.4 is "overweight," a BMI between 19.8 and 24.2 is "normal," and a BMI of less than 19.8 is "lean". This classification is used in the "National Nutrition Survey" performed by the Ministry of Health and Welfare.

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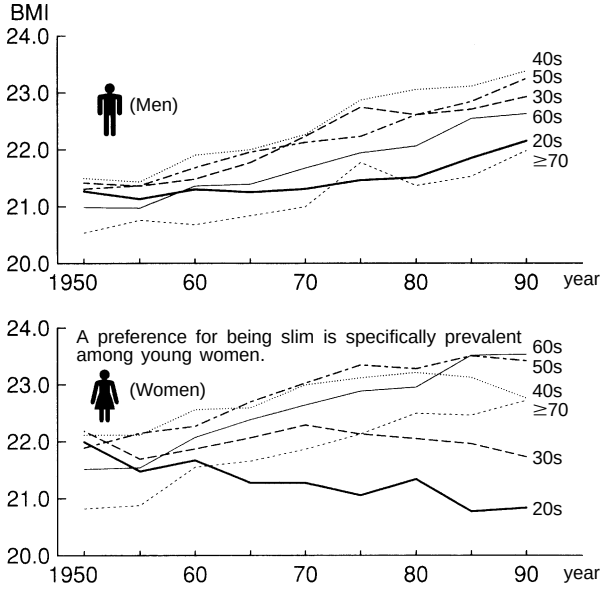

Fig. 1 Annual changes of BMI
Source: National Institute of Health and Nutrition Research
(The 1997 edition of the Health and Welfare White Book)

epidemiological studies on diet and obesity have been performed in many countries.

With respect to the frequency of meals, it has been reported that the prevalence of obesity rises as the frequency of meals decreases.[3] However, this issue does not yet seem to have been settled because some other studies have come to the opposite conclusion.

In large-scale surveys performed in various parts of Europe and the United States, it has been demonstrated that the body weight increases as the total dietary calorie intake increases.[4]

In large-scale surveys such as the National Health and Nutrition Examination Survey (NHANES) performed in the United States and other surveys performed in Germany, Scotland, and Denmark, the BMI or the amount of subcutaneous fat was higher in the high-fat diet group than in the low-fat diet group.[5] In regional surveys performed in Tennessee and North California in the United States and in Finland (Odds ratio (OR) = 1.7), the weight gain of the high-fat diet group was significantly greater than that of the low fat diet group.[4]

According to several large-scale surveys, including the European prospective investigation and the American Cancer Prevention Study (ACPS) II, the consumption of a large amount of meat results in weight gain.[6,7] An investigation by Kahn *et al.* showed that the risk of obesity in relation to increased consumption of meat was estimated by an OR of 1.46.[7] In contrast, the mean BMI of vegetarians is low. A survey performed on 10,000 subjects in Norway and the ACPS II (OR = 0.81) have suggested that it is possible to reduce the BMI by eating a large amount of fruit and vegetables.[6,7]

Table 1 Smoking and Obesity (Including Weight Loss and Gain)
Odds ratios (ORs) calculated by taking the OR for non-smokers as 1.

Survey	OR			Parameter	Reference
Ontario	Smokers	0.8		BMI	16)
	Ex-smokers	1.10			
NHANES III	Men	Smokers	0.52	BMI	17)
		Ex-smokers	2.42		
	Women	Smokers	0.50		
		Ex-smokers	2.02		
CARDIA	Smokers	1.56		Weight loss	18)
Survey in monozygotic twins	Smokers	0.67		BMI	21)
	Ex-smokers	1.20			

2-2. Exercise

A beneficial effect of physical activity on obesity has been demonstrated in many studies.

A study performed on 3,132 individuals at seven health centers delineated the association between exercise and obesity in the Japanese. This study showed that the prevalence of obesity was lower among individuals who were in the habit of performing exercise, and the risk of obesity in this group was low (OR = 0.48).[8)]

Many studies have shown that the prevalence of obesity, the mean BMI, or the body weight decrease as the amount of exercise increases.[4,9,10)] Among persons in their 20s from the Coronary Artery Risk Development in Young Adults (CARDIA) study, there was a significant association between an increase of exercise over 2 years and weight loss. The risk of weight gain was decreased by jogging (OR = 0.57 in men) and aerobics (OR = 0.59 in men), but was not significantly reduced by playing a team sport or tennis.[7,10,11)]

2-3. Stress

The direct association between stress and obesity is not so strong,[12)] but some reports have supported a direct influence of mental stress on the development of obesity.[13–15)] The CARDIA study, a higher Cook-Medley hostility score was significantly correlated with a higher waist-to-hip ratio.[13)] In the NHANES I study, people who gained weight were less happy than those who neither gained nor lost weight (OR for unhappiness: 1.54 for obese vs. 2.03 for non-obese).[14)] In many reports, however, stress was concluded to have no influence on the degree of obesity.[12)] Because the methods used to assess stress have varied among studies, direct comparison is difficult. In addition, the influence of other relevant factors, such as dietary habits, cannot be ignored.

2-4. Smoking

Many epidemiological studies performed in Europe and the United States appear to indicate that smoking reduces obesity (Table 1). In all of these surveys,

including a health survey performed in Ontario on 20,306 subjects, NHANES I and III, the CARDIA study, and a study on 1,911 pairs of monozygotic twins, current smokers were the leanest whereas ex-smokers the most obese.[16–21] However, a 10-year follow-up study performed in the United States showed that the OR of smokers for an increase of BMI was 0.8, indicating no significant difference between smokers and ex-smokers.[7] In Australia, the recent increase of BMI has been reported as not being attributable to the decreasing prevalence of smoking.[22]

Body weight appears to increase for several years after ceasing to smoke. Despite this, anti-smoking campaigns are still useful if the risk of smoking with respect to the development of cardiovascular disease and cancer is considered. It appears necessary to provide appropriate measures for the prevention of weight gain when smokers are trying to quit the habit.

2-5. Alcohol

With respect to the association between alcohol intake and obesity, many large-scale studies have been performed, including the health study in Ontario, NHANES I, the study on monozygotic twins, and the ACPS. In NHANES I,[23] the OR for weight gain by heavy drinkers (defined as intake of alcohol twice daily or more) was 0.9 when the risk for those who did not drink was set at 1 and there was no significant difference. In the study on monozygotic twins cited above (see "Smoking"), when the risk of obesity in subjects who did not drink was set at 1, the OR for heavy drinkers (alcohol intake of 0.99 ounces or more per day) was 1.43 and the OR for non-drinkers was 2.14, showing no significant difference.[21]

2-6. Childhood obesity

There have been many reports that obese children are at high risk of becoming obese adults.[24] The risk has been estimated as very high, with OR values of 2.0 to 6.7. Thus, prevention and management of childhood obesity is considered to be one of the mainstays for primary prevention of adult obesity. To prevent adult obesity, children should be encouraged to lead a healthy lifestyle. Obesity and hyperlipidemia are likely to be the two major risk factors for lifestyle-related diseases at school age.

3. Summary

The relationship between lifestyle and obesity is summarized in Table 2.

Genetic factors and social factors, such as inadequate availability of facilities for exercise and recreation, development of transport that reduces the distance that people have to walk, and instant availability of food over 24 hours whatever people want to eat, are other causes of obesity that are not discussed in this article.

The value of preventing obesity can be considered in relation to the following three factors. First, it can prevent the development of so-called lifestyle-related diseases. Second, a reduction of medical costs can be achieved by such prevention. Third, improvement in the quality of life can be achieved, both for individuals and at the population level.

To prevent obesity, individual and population-based health education needs to

Table 2 Summary of the Relationship between Lifestyle and Obesity

Lifestyle	Effects on obesity: ↓ Tendency to decrease ↑ Tendency to increase ↓↓ Significant decrease ↑↑ Significant increase
Regular exercise, Adequate physical activity	↓↓
Stress	↑ Indirect influence
High-fat diet, consumption of meat	↑↑
Vegetable-rich diet	↓↓
Smoking	↓↓
Cessation of smoking	↑↑
Drinking	↓
Childhood obesity	↑↑

be provided so that people can obtain the basic knowledge necessary to establish a healthy lifestyle that does not lead to obesity.

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PEPTIC ULCERS AND LIFESTYLE

Madoka NAKAJIMA, M.D., Tatsuya TAKESHITA, M.D.
and Kanehisa MORIMOTO, M.D.

Department of Social and Environmental Medicine, Course of Social Medicine, Osaka University Graduate School of Medicine

1. Introduction—Which causes peptic ulcers, *Helicobacter pylori* (HP) or lifestyle?

Table 1 shows changes in the number of articles on relations of lifestyle factors to the occurrence of peptic ulcers. It should be noted that the number of articles on stress rapidly decreased during the period from 1988 to 1997. In peptic ulcer research, the articles including HP appeared from about 1990 onward, showing that the development of the diagnostic and therapeutic methods in relation to mainly HP is progressing.

On the other hand, the results of the survey of the number of articles suggested that the number of articles on lifestyle tended to decrease in concert with the time when HP was debated intensely. This point is a serious situation from the aspect of preventive medicine; i.e., HP infection is certainly an important factor for the occurrence of ulcers, and a critical factor for suppression of the occurrence from the viewpoint of the secondarily preventive approach. However, HP infection can not be the only factor to the occurrence of peptic ulcer. Some attacking factors

Table 1 Changes in the Number of Articles on the Relations of the Occurrence of Peptic Ulcers to Lifestyle (From the Medical Literature Database "MEDLINE")

	1968–1977	1978–1987	1988–1997 (In relation to HP)
Total number of peptic ulcer cases	9,969	9,481	9,840 (1,937)
Smoking	153	228	382 (107)
Stress	226	219	91 (10)
Nutrition, Diet	545	503	505 (80)
Alcohol drinking	47	40	63 (16)
Exercise	17	12	11 (0)
Socioeconomic factors	48	31	60 (30)

Table 2 Relations of Lifestyle and Occurrence of Peptic Ulcers (Outline)

	Risk of peptic ulcers (Risk level)		Risk of HP infection (Risk level)	
Smoking	↑↑↑	2.2–3.4	↑	1.20–1.57
Stress	↑↑	1.4–2.9	—	
Salty food intake	↑	1.2–1.5	↑	1.19–1.92
Alcohol drinking	→	0.6–1.2	↓↓	0.33–0.85
Exercise	→	1.1	—	

and enhancing factors must be involved with the occurrence. It has also become apparent that HP infection itself is influenced by lifestyle and environmental factors.

In this study, the influence of lifestyle-related factors on the onset of peptic ulcer or HP infection is surveyed on the basis of the data of literature search from a viewpoint of primary prevention.

2. Relations of the Occurrence of Peptic Ulcer to Lifestyle

Gastric ulcer tends to occur more markedly in the Japanese than in Western people.[1)] The reason for the difference in the incidence between the Japanese and Western people is estimated to lie on lifestyle from the comparative studies between the Japanese and emigrants of Japanese descent. The high rate of smoking and stress of working environment in the Japanese are enumerated as risk factors for gastric ulcer. The difference between the Japanese and Western people is characteristic of gastric ulcer, but is not of duodenal ulcer. From these features, the eating habit specific to the Japanese, i.e., overintake of salty foods, is also believed to be one of the risk factors for gastric ulcer.

2-1. Smoking

Of lifestyle, smoking is the highest risk factor for peptic ulcer.[2,3)] As shown in Table 2, the risk of the onset in smokers is twice or higher, showing that there is a dose-response relationship between the number of cigarettes smoked and the onset of peptic ulcer.[2)] Some reports have shown that the risk of HP infection is high in smokers [relative risk (RR) = 1.20–1.57], while smoking plays a role in enhancing the risk of ulcer in the situation where ulcer may occur.[4,9)] Smoking acts on the mucosa to induce the condition in which the mucosa is easily infected with HP, thereby weakening the defence mechanism of the mucosa.

2-2. Stress

As described above, the involvement of factors like stress, which are hardly determined, with the onset mechanism of peptic ulcer has tended to be neglected, since attention was paid to HP as the cause of peptic ulcer.[5)] Indeed, any direct causal relationship between stress and HP infection has not been known. However,

Table 3 Risk Level* of Peptic Ulcers Due to Subjective Stress

The amount of subjective stress	Relative risk level** (95% confidence interval)
Absent	1.0
Slightly present	1.4 (1.0–2.1)
Present (routinely)	1.9 (1.3–2.8)
Present (frequently)	2.3 (1.4–3.7)
Considerably present	2.4 (1.5–3.9)
Almost intolerably present	2.9 (1.2–7.5)

*Modified from Ref. 6)
**The values obtained by correction of other factors, Trend test ($p<0.0001$)

Table 4 Relations of the Frequency of Consumption of Salted Vegetables and *Miso* Soup to the Risk of HP Infection

Frequency of consumption	Risk level (OR) (95% confidence interval)
Salted vegetables	
<one day/week	1.00
1–2 days/week	1.19 (0.65–2.19)
3–4 days/week	1.92 (0.98–3.79)
5–7 days/week	1.90 (1.10–3.30)
	Trend test $p=0.015$
Miso soup	
<5 days/week	1.00
5–7 days/week	1.60 (1.03–2.49)

*Modified from Ref. 8)

effects of stress as an enhancing factor in ulcer has been clarified by many experimental studies and from epidemiological findings.

According to Anda *et al.*,[6] the risk of peptic ulcer due to subjective stress is increased with the extent of stress perceived (Table 3). Levenstein *et al.*[7] have presented interesting data showing that even concrete stress items in women in U.S.A., which included "fear of losing employment [odds ratio (OR)=2.4]", and "worries about problems with their children (OR=2.7)", showed higher risks than other items.

2-3. Diet and nutrition

2-3-1. **Salty foods intake**

The risk of peptic ulcer due to salty foods is not so high as that of the onset due to smoking or stress (RR=1.2–1.5),[2] but Tsugane *et al.*[8] have shown that the risk of HP infection is increased when the frequency of consumption of salted vegetables and *miso* soup is high (Table 4). As a factor for the decrease in the ability to defend, salty foods intake becomes a factor for the facilitated ulcer formation in the coexistence with enhancing factors such as smoking and stress. In this regard, specific attention should be paid to the dietary habit including salty foods intake as a potent risk factor, because the habit is essential to daily living.

2-3-2. **Other food products**

Kato *et al.*[2] have investigated relations of gastric ulcer and duodenal ulcer to intake of various food products. There are no food products other than salty foods, which show significantly high risk.

According to Kato *et al.* coffee has no influence on the occurrence of peptic ulcer, but Brenner *et al.*,[4] have shown that the risk of HP infection is significantly increased (OR = 2.49) by the daily intake of three or more cups of coffee.

2-4. Alcohol drinking

Some reports have shown that alcohol drinking is not a risk factor for the occurrence of peptic ulcer, rather a factor for the decrease in the risk of HP infection. According to Brenner *et al.*,[4] the risk of HP infection is decreased (OR = 0.33–0.85) with the amount of alcohol consumption, and this tendency is observed regardless of the type of alcohols (beer, wine, etc.).

2-5. Influence of other environmental factors on the onset of peptic ulcer

With regard to HP infection, its relation to socioeconomic factors has been widely investigated from the aspect of sanitary problems.

Many reports have also shown that the frequency of HP infection is high in the elderly people. In their 50s to 60s, the frequency is particularly high. This tendency is believed to be attributable to the environmental factors specific to these age groups, rather than aging. Details of this regard have been assessed by the EUROGAST Study Group which has dealt with the residents in 17 areas in Western countries and Japan.[9]

The results have shown that among the factors investigated educational level is a factor, which significantly increases the risk of HP infection, even after the age is adjusted. The Study Group has indicated that the influence of smoking and obesity is also derived from the educational level. This is proved by the results of the survey, which showed that the educational level does not become a factor for the increase in the risk of HP infection in the Japanese areas where educational environments have been completed.

Educational environment has been investigated by studies in twins.[10,11] According to these studies, the influence of environments, which have been held in common in childhood, was observed in only about 20%, showing that the influence of the subsequent living environment of an individual was more marked than that of the common environment.

These findings may be observed for diseases other than peptic ulcer, indicating a new problem about relations of the lifestyle after grown-up to the domestic and educational environment in childhood which determines it.

3. Conclusion

The influence of lifestyle-related factors on the onset of peptic ulcers is surveyed. Only little has been known on the health-promoting activities, as compared to risk enhancing factors, probably because the diagnostic and therapeutic methods for the disease have been clinically established.

In recent years, the preventive effect of green tea on diseases is drawing attention, and its suppressive effect on HP infection has become apparent with regard to peptic ulcers. It is hoped that details of the relations of lifestyle to HP infection will be elucidated by longitudinal studies, which will comprehend all three points including the onset of peptic ulcers, HP infection, and lifestyle, and that the findings will contribute to the primary prevention of the peptic ulcer.

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ALLERGIC DISEASES AND LIFESTYLE

Satoshi TSUJITA, Tatsuya TAKESHITA and Kanehisa MORIMOTO

Department of Social and Environmental Medicine, Course of Social Medicine, Osaka University Graduate School of Medicine

1. Introduction

Increases in the morbidity rates of allergic diseases in Japan have been revealed by a variety of epidemiological surveys in recent years.[1–5] The morbidity rate of adult bronchial asthma has increased from approximately 1% to 3% over the past 30 years, and the childhood asthma rate stands at approximately 5%. Although allergic rhinitis, which is mostly caused by Japanese cedar (*Cryptomeria japonica*) pollen, was hardly ever encountered before World War II, it is now said to affect about 10% of the population, and atopic dermatitis is said to have been increasing not only among children but adults as well.[1]

According to a survey conducted by the Epidemiology Group of the Comprehensive Research Project of the Japanese Ministry of Health and Welfare, the current prevalence rate of allergic diseases in Japan is approximately 30%, and approximately 1 out of every 3 persons in the country has contracted some form of allergic disease.[6] Increases in allergic diseases have not just been observed in Japan, but similar increases have also been noted in advanced Western countries,[7–11] and they are even being observed in the urban areas of developing nations.[11]

2. Genetic Factors and Environmental Factors

Bronchial asthma, atopic dermatitis, and allergic rhinitis, the allergic diseases whose increases have become a problem, correspond to class I of classes I–IV in Gell and Cooms' classification of allergic diseases,[12] and IgE antibodies are involved in their development. Many of the patients have a predisposition to tend to produce IgE antibodies to allergens that are normally present in the environment, such as dust, mites, molds, and pollen. This predisposition is called "atopy",[13] and these diseases are referred to as "atopic diseases".

Atopic diseases exhibit family clustering, and the risk of morbidity increases when parents or siblings have atopic diseases (odds ratio: 2.1–7.0).[14–28] Based on gene linkage analyses, etc., a number of candidate genes that support this genetic predisposition have been reported,[29–33] and they consist of genes associated with IgE production or the allergic response (Table 1).

In summarizing the process that occurs in an allergic reaction,[30] first, an allergen is incorporated and broken down by an antigen-presenting cell (APC), such as

Table 1 Candidates for Genes Associated with Atopic Diseases (References 29–33)

Chromosome region	Candidate gene	Functional association
5q31	IL-3, IL-4, IL-5, IL-9, IL-13, GM-CSF	Th2 cytokine functions (induction of class switch to IgE, activation of mast cells, eosinophils, and basophils)
5q32	β2-adrenoceptor	Bronchodilation
6p21	HLA	Antigen presentation
	TNFα	Inflammatory cytokines
7q35	TCRβ	T-cell activation
	Thromboxane A2 synthase	Thromboxane A2 synthesis
11q13	FcεRI	Signal transmission to mast cells, etc.
12q14.3–q24.1	IFNγ	Th2 cell suppression
	Mast cell growth factor	Mast cell activation
14q11.2–13	TCRα/δ	T-cell activation
16p12.1–11.2	IL-4R	IL-4 signal transmission

the Langerhans cells that are present in mucous membranes. The antigenic peptides generated are then presented to the T-cell antigen receptors (TCRs) of $CD4^+$ T cells by the APC class II major histocompatibility complex (MHC), and as a result, naive T cells differentiate into helper T cells (Th2) and mature. The Th2 cells secrete various cytokines that are intimately associated with allergic reactions, namely, interleukin 3 (IL-3), IL-4, IL-5, IL9, and IL-13, and GM-CSF (granulocyte-macrophage colony stimulating factor). IL-4 and IL-13 induce a B-cell isotype switch, and IgE is produced. IgE binds to cells that express high-affinity IgE receptors (FcεRI), such as mast cells. When the IgE on the receptors is bridged by a multivalent antigen, receptor aggregation occurs. The mast cells release active amines, such as histamine, leukotrienes, prostaglandins, proteases, heparin, etc., and then secrete IL-4, IL-5, IL-9, IL-13, etc. Eosinophils are mobilized, and allergic inflammation is induced.

Candidates for genes linked to atopic diseases are the genes for the cytokines, such as IL-4, IL-5, IL-9, and IL-13, involved in the process of this allergic reaction and their receptors, MHC, TCR, and FcεRI, and mutations in them are thought to increase susceptibility to atopic diseases.

However, the development of disease, including atopic diseases, is generally governed by genetic predisposition and environmental factors. Since it seems hard to believe that the gene pools of Japanese and Western populations have changed much over the past 30 years, the increase in atopic disease in recent years appears to be attributable to changes in environmental factors.[8–11)]

3. Westernization of Lifestyle

Urban living and Westernization of lifestyle have been pointed as causes of the increase in atopic diseases.[1–5,9–11)] The basis for these claims is said to be the high asthma morbidity rate among socio-economically affluent people with high medi-

cal care and sanitation standards,[34] the higher atopic disease morbidity rate among urban children than rural children,[35,36] and the children of families that have immigrated to advanced, industrialized countries from developing countries with low atopic disease morbidity rates having atopic disease morbidity rates as high as those of children in advanced countries.[37,38]

Another plausible basis for this comes from surveys of atopic diseases in Germany, which was reunited in 1990. It was shown that the residents of the cities of the former East Germany, both adults[39–41] and children,[42–44] have lower atopic disease morbidity rates, prick-test positivity rates, and blood IgE concentrations than the urban residents of the former West Germany. Their lower levels of atopic disease appear to be attributable to the fact that Germany was divided into East and West in 1949 and that for approximately 40 years, until they were reunited in 1990, the residents of the former East Germany had been in a living environment that differed from the Western lifestyle of the advanced Western countries.

The following can be cited as results of surveys that support this line of reasoning. The atopic disease morbidity rates in East and West Germany were similar among persons who were born between 1946 and 1961, when there is not thought to have been much difference in lifestyle between East and West Germany, but differences were observed between people who were born between 1962 and 1971, a period when the lifestyle in West Germany underwent considerable changes as a result of economic development,[4] and an increase in atopic diseases was observed in children in former East German cities who were born around the time of reunification and reared in a Westernized lifestyle.[44]

How changes in which environmental factors as a result of this urbanization and Westernization of the lifestyle might interact with hereditary factors to increase the atopic disease morbidity rate have been investigated from a variety of different angles, but the factors that are associated, far from being simple, are quite complex.[9–11,15,45]

4. Increases in Allergen Load

Because of the trend toward reinforced concrete/steel-frame construction and conversion to high-rise buildings in cities, as well as aluminum sashes being used to increase the efficiency of indoor heating and cooling, residential structures have become more airtight. The result, however, has been to turn the indoors into a favorable environment for mites and molds, and that has increased the indoor allergen load.[46–51] Moreover, the boom in pet popularity in recent years has continued, and because of housing conditions, dogs and cats and other pets are now being cared for indoors. Not only is that said to have increased the indoor dog and cat allergen load, but to have created conditions that favor the proliferation of mites and molds as well.[48] The increase in the indoor load of these allergens may increase the opportunities for sensitization of persons who have an allergic predisposition. Another problem is unique to Japan: the increase in Japanese cedar pollen allergens associated with cedar afforestation.[51]

5. Air Pollution

In addition to the air pollution associated with the growth of industrial activity in cities, the concentrations of DEPs (diesel exhaust particles), SO_2, NOx, and ozone in the air have risen as a result of increases in motor vehicle traffic. These air pollutants are said to not only irritate the airway mucosa directly and trigger bronchial asthma, but because of their adjuvant action, to promote sensitization to allergens, such as pollen and mites, and the production of IgE.[9,45,50,52)]

Smoking also increased the atopic disease morbidity rate (odds ratio: 1.1–4.9),[17–27)] and there are even reports that parental smoking increases the bronchial asthma morbidity rate of their children.[26,53)] This pollution of indoor and outdoor air appears to increase atopic disease hand-in-hand with the increase in environmental allergen load.

6. Westernization of the Diet

The diet is not only the cause of food allergies because it contains allergens, but an unbalanced diet alters the pathogenesis of allergic diseases. Allergic reactions generally tend to be frequent in regions with high nutrition levels. Economic growth in Japan has been associated with an increase in fat, animal protein, and sugar as a proportion of total energy intake, while the proportion of starches and plant proteins, which contain large amounts of vitamins and dietary fiber, has decreased instead.[54)]

Fat intake, in particular, has increased sharply, and the intake of n-6 fatty acids, as typified by linoleic acid, has risen to 6 times the required amount. The n-6 fatty acids are said to increase the production of arachidonic acid, and to in turn increase the production of leukotrienes and prostaglandins, which are associated with inflammation, and to be associated not only with increases in allergic diseases but with increases in cancer.[55,56)]

By contrast, the n-3 fatty acids, such as α-linoleic acid, EPA (eicosapentaenoic acid), and DHA (docosahexaenoic acid), decrease the production of leukotrienes and inhibit the development of allergies, however, there is said to have been a relative decrease in their intake.[54)] Another study examined the blood lipid composition of atopic disease patients and showed a decrease in the n-3/n-6 ratio.[57)] Sodium intake is also said to be associated with bronchial asthma.[58,59)] However, the data supporting the above findings are still insufficient.[9)]

7. Stress

Stress is an unavoidable problem in modern society. The ways in which psychological stress contributes to the development and course of allergic diseases can be divided into three sets of factors: inducing factors, which contribute directly to the development of the disease, preliminary factors, which facilitate the occurrence of allergy, and persistence-aggravating factors, to which the patient's psychological state after developing the disease is related.[60)] Asthma attacks sometimes occur in response to suggestion or conditioning, and cholinergic neurons are claimed to be

involved because these phenomena are suppressed when atropine is administered advance.[60)]

Bronchial asthma is also associated with different stresses according to life stage. In early childhood, problems such as inappropriate parent-child relations, e.g., overprotection, excessive interference, etc., doing poorly in school, being bullied, etc., in adolescence, problems such as trouble with the family (parents), and maladjustment at school, difficulty getting a job, and in adulthood, problems such as overadaptation to the workplace, depression etc., are said to aggravate the symptoms of bronchial asthma.[61–66)] Psychological stress acts as an aggravating factor in allergic rhinitis and atopic dermatitis as well,[60)] and there is even a report that when strong aggressiveness was managed, intractable urticaria was relieved and serum IgE decreased.[66)]

8. Exercise

Exercise-induced asthma, in which dyspnea associated with wheezing occurs transiently after exercise, is the best known problem in the relationship between exercise and asthma. However, it is claimed that when exercise is avoided because of this, more time is spent indoors, and that as a result the duration of contact with allergens, such as mites and molds, increases. This causes allergic inflammation, asthma attacks are induced, and airway hypersensitivity also increases.[67)] In addition to a decrease in exercise capacity, other problems, such as reduced opportunities to socialize with friends, also arise. Actively engaging in an appropriate level of exercise, on the other hand, has the effect of alleviating bronchial asthma, and this is known as physical training therapy.[67,68)]

9. Infection Reduction

Thanks to improvements in sanitation and improved medical standards in advanced industrialized countries, infectious diseases caused by microorganisms and parasites have decreased. On the contrary, this has shifted the T-lymphocyte Th1-Th2 balance in the direction of increased Th2 cells and IgE production has been facilitated, probably leading to the increase in atopic diseases.[9–11)] This has been explained by the fact that the prevalence rate of atopic diseases is low among people who have contracted measles, hepatitis A, or tuberculosis during the childhood.[9–10)] The fact that there were few siblings among atopic disease patients is also said to suggest that there were few opportunities for infection by microorganisms or parasites.[9)]

10. Maternal Diet During Pregnancy

There is no direct communication between the blood of the fetus, which circulates within the placental villi, and the blood of the mother in the spaces between the villi. However, in the final stage of pregnancy, the placenta undergoes aging, and allergens in the blood of the mother pass through the placenta relatively easily and sensitize the fetus.[69-71)] It has been pointed out that antigenic peptides

bound to maternal IgG antibodies may pass through the placenta and sensitize the fetus.[70)]

Actually, T cells that react with food allergens and environmental allergens have been detected in umbilical cord blood, regardless of whether there is any atopic predisposition or not.[70,71)] However, while there are studies that consider dietary restrictions in the final stage of pregnancy, e.g., not eating eggs, to be effective, the incidence of allergy in children due to transplacental sensitization is less than 1% of newborn infants, and there is research claiming that it is impossible to hope to prevent childhood allergies by dietary restriction in the final stage of pregnancy.[69,70)]

11. Diet of Mother and Child during Breast-feeding

Because the digestive organs of infants are anatomically and functionally immature, they readily absorb food allergens, causing food allergies. By contrast, the proteins in breast milk, even if they are absorbed, never sensitize infants. It is therefore considered preferable to feed infants nothing but breast milk during the first six months after birth as a means of preventing sensitization during infancy, and there is a report that strictly feeding infants breast milk for the first six months actually cut the atopic disease morbidity rate of children with an atopic predisposition in half.[73)]

Nevertheless, there is also a report that the results of an epidemiologic survey showed that while children fed breast milk had a significantly lower prevalence of bronchial asthma than children fed an artificial diet, they tended to have a higher prevalence of atopic dermatitis.[74)] Another report states that the facial eczema of children with an atopic predisposition who were fed breast milk was sometimes aggravated when their mothers ate eggs, and that when the mothers eliminated eggs from their diet, their children's symptoms resolved, as well as that when the mother-child egg-free diet was started before 6 months after birth a significantly smaller proportion of children subsequently developed mite allergy or wheezing than when it was started between 6 and 12 months after birth.[75)]

On the other hand, although the breast milk of mothers who drank cow milk contained a minute amount of cow milk β-lactoglobulin, it is said to induce tolerance more than sensitization.[76)] There is also a report that consumption of a large volume of cow milk during infancy inhibits the production of IgE.[77)]

12. Conclusion

The major effects of lifestyle on the relative risk of atopic diseases are shown in Table 2.

Measures that reduce the amounts of allergens in the environment and in food would seem to be the most easy to comprehend and practical approaches to the prevention of atopic diseases.[75,78,79)] The fact that sensitization of small children is linked to later atopic diseases[70)] makes measures to prevent allergen exposure in early childhood particularly important. Atopic diseases can be significantly prevented in small children who are predisposed to atopy if dietary restrictions are

Table 2 Lifestyle and Changes in Relative Risk of Developing Atopic Diseases (References 14–28)

Lifestyle	Bronchial asthma	Atopic dermatitis	Allergic rhinitis
Smoking	↑ ↑ (OR2.0–3.1)	↑? (OR1.1)	↑ ↑ (OR4.9)
Exercise	insufficient ↑, appropriate ↓	↓?	↓?
Food	n-6 fatty acids ↑, salt ↑ n-3 fatty acids ↓	n-6 fatty acids ↑ n-3 fatty acids ↓	n-6 fatty acids ↑ n-3 fatty acids ↓
Stress	↑	↑	↑

implemented by feeding them appropriate allergen-free foods,[75,79] the use of rugs and stuffed animals, which become a habitat for mites, is abandoned, no pets are kept, and indoor mite allergens are reduced by thorough cleaning.[78,79] Carrying out these measures should be even more effective if air pollution by smoking were prevented. While controversy still exists in regard to maternal dietary restrictions during pregnancy and breast-feeding, it is preferable to refrain from consuming large quantities of eggs or milk, which often become allergens, and to strive to eat a balanced diet.[69,72]

Nevertheless, since the maximal effect desired can never be achieved, even by making great efforts to eliminate allergens, some are of the opinion that other strategies are needed.[80] For example, it has been advocated that, more than focusing on the factors that promote sensitization, a search should be made for factors that induce tolerance, and that by adjusting the intestinal microflora, the immune system should be shifted to a predominantly Th1 reaction.[80]

In regard to adults, Shirakawa and Morimoto investigated associations between various lifestyle parameters and serum IgE concentrations[82–84] and discovered both factors that increased IgE (subjective stress level, amount of exercise, working hours, having hobbies or not) and factors that decreased IgE (drinking alcoholic beverages, smoking, a feeling of being too busy). They advocated an HPIA (health practice index for allergic reactions) that combines their effects. This index makes it possible to conduct a comprehensive comparative assessment of the advantages and disadvantages of the lifestyles of various individuals on an individual basis, and it seems possible to utilize it to design individual lifestyle improvement measures aimed at preventing allergic diseases.

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(9)

NON-INSULIN-DEPENDENT DIABETES MELLITUS AND LIFESTYLE

Ichiro NAKAMOTO, Tatsuya TAKESHITA, M.D.
and Kanehisa MORIMOTO, D.M.Sc

Department of Social and Environmental Medicine, Course of Social Medicine, Osaka University Graduate School of Medicine

1. The Present Status of Non-insulin-dependent Diabetes Mellitus in Japan

The incidence of diabetes mellitus (DM) varies considerably with nations; the incidence of DM in the total population of Japan is approximately 2%. The proportion of the patients with non-insulin-dependent DM (NIDDM) in DM patients in Japan accounts for approximately 95%.[1)] According to the investigation of the actual condition of DM sponsored by the Japanese Ministry of Health and Welfare,[2)] 6,900,000 people were strongly suspected of having DM, and the number of the people, in whom DM was strongly suspected or the possibility of DM developing was not ruled out, was estimated to be 13,700,000 people. The morbidity rate is approximately 10% in the population 40 years of age or older. The number of the population, who have no DM at present and whose condition may progress to DM several years later unless they receive appropriate preventive therapy, is about twice as large as the current number of DM patients. Taking rapid aging into consideration, the number of DM patients is predicted to increase in the future.

The current medical examination of DM mainly includes the tertiary prophylaxis aiming at prevention of progression of DM. Considering the present state of DM, however, much attention should be paid to the primary prophylaxis (the onset-preventing activity) of DM and the secondary prophylaxis (remission and the inhibition of progression by early detection and treatment of DM).

2. The Onset Mechanisms and Prevention of NIDDM

The onset mechanisms of NIDDM include hereditary factors and the acquirement of resistance to insulin via obesity due to various lifestyles. The acquirement is followed by hyperinsulinemia and impaired glucose tolerance, and insulin secretion failure occurs, eventually progressing to NIDDM.

It has been clarified by a study on twins that hereditary factors play an important role in the onset of NIDDM. It is impossible at present to prevent NIDDM by correcting gene abnormality. From a viewpoint of prevention, it is important to change lifestyle including diet, exercise, smoking, and drinking.

Table 1 The Maximum BMI in the Past History and the Risk of DM

The maximum BMI in the past history			Risk of DM (OR)
(0%~10%)	vs.	(−10%~0%)	2.05
(+10%~+20%)	vs.	(−10%~0%)	4.10
(+20%~+30%)	vs.	(−10%~0%)	5.76
(+30%~+40%)	vs.	(−10%~0%)	10.21
(+40%~)	vs.	(−10%~0%)	16.79

[Investigation of the actual condition of DM sponsored by the Ministry of Health and Welfare (1998)]

3. High-risk Group—With reference to impaired glucose tolerance (borderline type)

Impaired glucose tolerance (IGT), whose blood sugar level is borderline type between the normal and DM types, is the precursor stage of DM, and with hyperinsulinemia indicating the slightly high blood sugar level and insulin resistance. The possibility of IGT progressing to NIDDM is high. Akazawa *et al.*[3] estimated the morbidity of IGT to be 22.8% in the people 40 years of age or older from the nationwide survey. It is very useful for prevention of NIDDM to take countermeasures against the onset in the stage of IGT.

4. Risk of NIDDM and Lifestyle

4-1. Age

The risk of NIDDM increases as age advances. A physiological factor, i.e., decrease in glucose tolerance with aging, underlies the phenomenon. Ito[4] has reported the epidemiological surveys of DM by 75 g glucose tolerance test on the residents of each district in Japan. The results of all surveys showed the increase in the morbidity of DM with aging. Since the risk of DM increases at age 40 years or over, the primary prevention under 40 years old is important.

4-2. Obesity

A variety of epidemiological surveys have pointed at obesity as a potent risk factor.

The investigation of the actual condition of DM sponsored by the Japanese Ministry of Health and Welfare shows that obesity distinctly increases the risk of DM. Table 1 shows the level of obesity [body mass index (BMI)] and the corresponding risk of DM; the risk of DM increases by ca. 4 times at BMI of +10%~+20%, ca. 6 times at +20%~+30%, and ca. 17 times at +40%.

Recently, body fat distribution, i.e., the site where fat accumulates, has become an issue, even if BMI is within the normal range. Some reports have shown that waist/hips ratio (WHR)[5] and visceral fat/subcutaneous fat area ratio (VSR),[6] which are indicators of body fat distribution, are useful as independent predictive markers indicating the risk level of the NIDDM onset.

Ohlson *et al.*,[7] who have carried out a 13.5-year follow-up study on the male

Swedes by dividing the subjects according to BMI (3 groups) and WHR (3 groups) and by combining each group with the risk of the DM onset, have reported that the risk of DM increases as WHR increases in each BMI group and that the incidence of NIDDM is 15.2% at high BMI and WHR, while the incidence is only 0.5% at low BMI and WHR. In the coexistence of abdominal obesity and systemic obesity, DM is more likely to develop. With regard to BMI and WHR, Warne *et al.*,[8] who have conducted a follow-up study in the residents of Pima, have reported that WHR is the indicator of obesity in men and BMI in women.

4-3. Diet

The increase in the incidence and morbidity of NIDDM in recent years is related to the westernization of the Japanese conventional lifestyle. The increase in fat intake and the decrease in routine physical activities are related to these changes of lifestyle. Kawade[9] has shown that the morbidity of DM in the immigrants of Japanese descent in Hawaii was significantly higher than that in the Japanese residents of Hiroshima as control group, and pointed out the following as the causes: Physical activity was low and intake of animal fat, sucrose, and fructose was high in the immigrants of Japanese descent, though there was no difference in total energy intake between the immigrant group and the control group.

With regard to lipids in dietary components, high fat diet is known to decrease the insulin sensitivity and to increase the risk of NIDDM. Recent follow-up studies[10,11] have also reported that high fat diet is a risk factor for NIDDM and ingestion of fishes, vegetables, and dietary fibers suppresses NIDDM.

Proteins and amino acids have been reported to promote insulin secretion, but there have been no reports mentioning the possibility of proteins and amino acids inducing insulin secretory disturbance.

With regard to diet, not only what to eat, but also when and how to eat becomes an issue. Of epidemiological surveys in Japan, Miyagawa[12] has reported that the risk of DM is high in the women who have no breakfast, and Watanabe *et al.*[13] have reported that working men in big cities frequently take food and drink at 9:00 pm or later, and that the risk of DM is high in the people who drink three cups of coffee or more a day with sugar, who like sweets, and who eat hurried meals. Kato *et al.*[14] have reported that, in male, there is a significantly high correlationship between the risk of DM and the meals with much seasoning at home.

4-4. Exercise

The concept that the reduced energy consumption due to underexercise causes obesity, which is followed by insulin resistance and DM, is widely accepted.

According to the investigation of the actual condition of DM sponsored by the Ministry of Health and Welfare (Table 2), the risk of obesity in the people who walk less than 4,000 steps a day is about 3 times as high as that in the people who walk 12,000 or more steps. These data indicate the possibility of underexercise causing DM via obesity. A study by Helmrich *et al.*[15] has also shown that the increase in physical activity prevents the onset and progression of NIDDM.

With regard to the contents of exercises, Sato *et al.*[16] have reported that not

Table 2 Relationship between Exercise and the Risk of Obesity

Quantity of motion (steps/day)	Risk of obesity (OR)
(8,000–12,000 steps) vs. (12,000 steps or more)	1.68
(4,000–8,000 steps) vs. (12,000 steps or more)	2.28
(Less than 4,000 steps) vs. (12,000 steps or more)	2.76

[Investigation of the actual condition of DM sponsored by the Ministry of Health and Welfare (1998)]

all the exercises are effective for prevention of DM or NIDDM; aerobic exercises like jogging and swimming are rather effective for improvement in the individual's insulin sensitivity than anaerobic exercises such as weight lifting. Sato *et al.*[16] have further concluded that the criteria for therapeutic exercise aiming at improvement in the insulin sensitivity in the people with IGT are that aerobic systemic exercises at 50% Vo_2 max (in general, 130 pulses/min, 120/min, and 110/min for the people in their 20s–30s, 40s–50s, and 60s–70s, respectively) are performed for at least 10–30 minutes at one setting at least 3 times per week.

Yamanouchi *et al.*[17] have reported that continuous exercise increases the individual's insulin sensitivity. The improvable effect of the training on the insulin sensitivity decreases within 3 days after discontinuation of the training, and it almost disappears in a week.[16] Therefore, continuation and establishment of the habit of doing exercise is important.

Intervention trials[18] regarding prevention of DM by walking and exercise using dumbbells were performed at Ogunicho in Yamagata Prefecture as an investigation of the feasibility of exercise. As long as the people with IGT were included as the subjects in the trials, those who frequently participated in the exercise and who did the exercise using dumbbells hard, showed improvements in the physical power and indicators.

Berger *et al.*[19] have reported that the combined therapy involving diet therapy of DM and therapeutic exercise prevents the onset of NIDDM in the groups with hereditary predispositions of hyperinsulinemia and central obesity. The investigators have also reported that training is particularly effective for prevention of arteriosclerosis as well, via the increased activity of the fibrinolytic system.

4-5. Smoking

It has conventionally been believed that there is no difference in the rate of smoking people among DM patients and that among healthy people.[20] It has not been proved whether smoking has influence on the onset of DM. A recent study by Rimm *et al.*[21] has concluded that smoking is an overt risk factor for DM, and shown that the relative risk value (RR) to non-smokers increased to 1.94 (the 95% confidence interval, 1.25–3.03) by smoking of at least 25 cigarettes a day in male Caucasians.

4-6. Drinking alcohol

In a study at Hisayamacho, Kiyohara *et al.*[22] have reported that alcohol con-

sumption of at least 20 g / day (ca. 180 m*l* for *sake*) is a significant risk factor for the onset of IGT, and that drinking of a small amount (less than 20 g / day) of alcohol suppresses the onset of IGT. According to this study, the RR to the risk level in the male drinkers of a small amount of alcohol, whose morbidity of DM was lowest, was 3.7 in the male drinkers of the moderate amount of alcohol or more and was 1.8 in the male non-drinkers. Thus, the risk of DM was significantly high in the drinkers of the moderate amount or more of alcohol. In the female non-drinkers, the RR to that in the female drinkers was 1.8, showing the same tendency as that of the male non-drinkers.

Kato *et al.*[14] have described that the risk of DM in women is significantly high by drinking 180 m*l* (*sake*) of alcohol or more a day.

Perry *et al.*[23] have reported that consumption of a moderate amount of alcohol improves insulin resistance and suppresses the onset of DM.

As described above, drinking a small amount of alcohol shows a tendency to prevent DM and heavy drinking shows a tendency to be a risk factor for the onset of DM.

4-7. Hypertension

In the survey at Aitoucho,[24] the RR to NIDDM was 1.32 in the male and female hypertensive subjects. Kuzuya *et al.*,[25] who analyzed the data from the people who had undergone medical examination, have reported that hypertension is an independent risk factor for NIDDM and the OR is 1.62. Nanjō[26] has reported that the morbidity of IGT was 34.6% high and the morbidity of DM was also significantly high in hypertension patients and the people with a family history of hypertension. These findings and observations support the presence of multiple risk factor syndrome via insulin resistance.

4-8. Stress and occupations

At present, the involvement of stress on the onset of DM is widely recognized from clinical experience. However, there have been only a few research on the direct involvement of stress on the onset of DM by epidemiological survey, probably because it is difficult to measure stress.

Watanabe *et al.*[13] have reported that the OR to that in the technological and clerical workers was 1.43 in the people engaged in management, sales, and independent business, which showed the elevated risk of DM.

As a result of a case-control study, Uehata *et al.*[27] have enumerated the following as risk factors for DM, which showed significantly high OR: Drinking of coffee in large quantities, stress of duties (compression by jobs, troubles with jobs, etc.), subjective stress (fatigue, anxiety, mental and physical exhaustion, etc.), experience of divorce, etc.

5. Conclusion

The number of DM patients is increasing steadily in Japan. Pressure on the family members due to progression of complications and the resultant medical expenses are increasingly enormous, as well as deterioration in the patient's quality

Table 3 General Summarization List of NIDDM

● Indicators of health

	Risk factor	Risk level	Risk value	95% confidence interval
Sex	Male	↑	1.68	1.02–1.65
Age	40 years of age or over	↑	1.58	1.16–2.14
Family history	Family history of DM	↑	1.65	1.16–2.36
BMI	≧24	↑	1.76	1.32–2.26
WHR	Males>0.9, Females>0.8	↑	1.47	1.14–1.91
Hypertension	≧140/90 mmHg	↑	1.92	1.39–2.65
Serum cholesterol	T-Cho≧220 mg/d*l*	↑	1.49	1.12–1.98
Triglycerides	TG≧150 mg/d*l*	↑	1.84	1.40–2.41
Insulin	F-IRI≧12μU/m*l*	↑ ↑ ↑	3.91	2.82–5.42
Blood sugar level	90–109 mg/d*l*	↑ ↑ ↑	4.15	2.86–6.07
Occupations	Management, Sales, Independent business	↑	1.43*	1.03–1.98

● High-risk behavior

	Risk factor	Risk level	Risk value	95% confidence interval
Smoking habit	Presence	↑	1.42	1.03–1.82
Alcohol drinking habit	Moderate amount or more	↑	1.80	1.34–2.42
Breakfast	No breakfast	↑ ↑	2.75**	1.05–7.24
Food intake at 9:00 pm or later	2–3 times/week・Every day	↑	1.64*	1.19–2.25
Quickness about meals	Quick・Ordinary	↑	1.55*	1.09–2.17
Coffee with sugar	At least 3 cups per day	↑ ↑	2.10*	1.48–3.00
Tastes for sweets	Liking for sweets	↑ ↑	2.07*	1.40–3.07

● Behavior aiming at health

	Risk factor	Risk level	Risk value	95% confidence interval
Physical activities	Moderate	↓ ↓	0.40	0.2–0.8

*: Only males **: Only females

of life. Since lifestyle relates to the progression of NIDDM, it can also be prevented by improvement in lifestyle. In order to demonstrate this, investigation of the feasibility by intervention trials including changes in behavior is needed. Malmö study[28] and DaQing study[29] are representatives for large-scaled intervention trials via diet therapy and therapeutic exercise, which aim at preventing the onset of NIDDM.

The Malmö study included a 5-year intervention trial via diet therapy and therapeutic exercise on IGT patients. The incidence of NIDDM was 10. 6% in the

group with the intervention, which was significantly lower than 28.6% in the group without the intervention.

The DaQing study in China included a 6-year intervention trial by dividing IGT subjects into 4 groups, i.e., the diet, exercise, diet + exercise, and control groups. As for the contents of the exercise used for the intervention, exercise in the spare time was increased by 80–160 kcal a day. The incidence of NIDDM in every group with the intervention was lower than that in the control group.

The data of these surveys suggest that correction of lifestyles mainly by diet therapy and therapeutic exercise is adequately effective for prevention of the onset of NIDDM. Such primary prevention may lead to reduction in medical expenses. It is therefore important to detect the people with IGT early, who are at the high risk group of NIDDM, and to guide them in the improvement of lifestyle mainly by diet therapy and therapeutic exercise. With regard to the diet and exercise therapy, social supportive measures should also be planned, because it is important to continue them and it is difficult to keep practicing them with personal efforts alone.

Since the risk of DM rapidly increases at age 40 years or over, guidance of health at age 39 years or under is also considered to be important.

In conclusion, general summarization list of influences of lifestyle on the onset of NIDDM is shown in Table 3.

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BEHAVIORAL SCIENCE FOR HEALTH EDUCATION

Yoshiharu AIZAWA* and Hitomi KARUBE**

**Professor, Department of Preventive Medicine and Public Health, Kitasato University School of Medicine*
***Professor, University of Human Arts and Science*

1. Introduction

Japan's aging of population, changes in living environment, and diversification of sense of values in recent years are accompanied by gradual increases of people developing lifestyle-related diseases and those complaining of fatigue and stresses.[1)] Regular health checkups at work places reveal that the ratio of those with abnormal findings is increasing yearly and the result of health examinations in 1999 found 41.7% of workers with some abnormal findings.[2)]

On the other hand, the society has achieved materialistic affluence, higher income, and increased leisure hours. Against such background, people's sense of values continues to diversify and individual needs are becoming more sophisticated.[1,2)] Patients are changing their attitude toward doctors; they no longer wish to seek or appreciate paternalistic guidance or orders from their doctors, but want relationship under which doctors respect and accept their individual lifestyle and personality and treat them as equals.[3,4)]

What is behavioral science? It may be defined as an academic discipline that attempts to elucidate systematically and demonstratively the human attitudes and habits as represented how people as individuals or as members of a group react physiologically and psychologically in addressing the environment.[3,5)]

According to a conventional way of thinking, health management and behavioral science are understood as two different entities without any point of contact or fusion. As discussed above, however, changes in people's daily life and the disease structure now require techniques to assist and support people to make free decisions in better mental conditions.

The authors have therefore reviewed and studied many Japanese and foreign references in order to establish effective techniques for health investment and devised a method of "applying behavioral intervention in health education". We present here the review of studies in this field.

2. From Adult Diseases to Lifestyle-related Diseases

Conventional measures for adult type diseases addressed cancers, cerebrovas-

Table 1 Stages of Behavioral Changes (J.O. Prochaska)[6]

Pre-contemplation stage:
(Those who have no desire to implement behavior in the predictable stage)
Contemplation stage:
(Those who intend to implement behavior during the six months to come, those who are troubled about sacrifices and merits of changes)
Preparation stage:
(Those who have realistic understanding about risks)
Action stage:
(Those who need the utmost efforts during the six months when outsiders can observe the changes)
Maintenance stage:
(Efforts should be continued for six to twelve months)

cular diseases, and heart diseases that increased with age, and attached an importance to secondary preventive measures of early detection and early treatment. Views were expressed, however, that the term "adult diseases" gives the impression that "they are diseases that develop after one gets old", and it was decided to use the term "lifestyle-related diseases" based on the report of Public Health Council of December 1996 on "Basic direction for disease prevention in view of lifestyles" and to promote disease measures focusing on primary prevention.[1,6]

Factors related to the onset and prognosis of diseases may roughly be classified into three; genetic factors, environmental factors and lifestyle factors. Lifestyles that are known to be closely related to occurrence of diseases are smoking and lung cancer and pulmonary emphysema, excessive animal fat intake and colon cancer, excessive salt intake and strokes, obesity and diabetes mellitus, and alcohol intake and cirrhosis. In other words, lifestyle-related diseases is one way of regarding diseases that shows the onset or progress of a disease may be prevented by improving lifestyle.

In order to ensure that our clients will implement the behavior of improving their lifestyle, we, health professionals, should not only diffuse accurate knowledge but also enable behavioral changes. The term "behavioral change" means changing of a behavior or habit and may be divided into "pre-contemplation stage", "contemplation stage", "preparation stage", "action stage" and "maintenance stage" as proposed by Prochaska (Table 1). Stopping to smoke may be carried out as in Fig. 1.

As discussed above, primary prevention means an attempt to prevent disease by acquiring good habits in life. The term "habit" is said to exceed the concept of disease prevention and to mean building the body and mind for becoming a better human being.[6]

3. Choosing Lifestyle and Behavior

Lifestyle means accumulation of daily choices. There are lifestyles considered good for health and those that are considered bad for health.[1] One example of the latter is cigarette smoking. To switch this lifestyle to "stopping smoking" requires

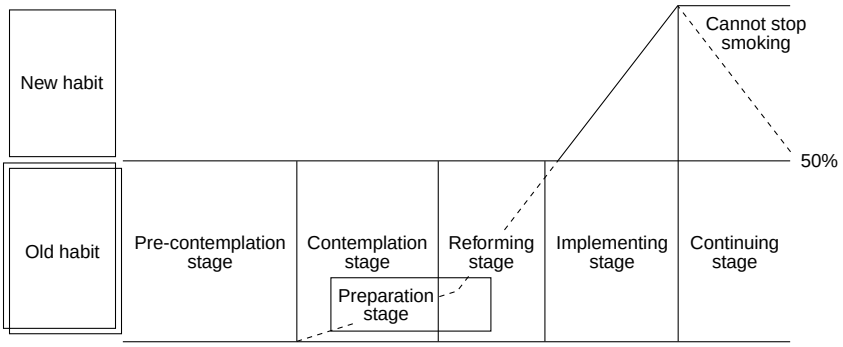

Fig. 1 Behavioral change toward smoking cessation (Hinohara, 1998)[6]

a certain motivation.[8–10] To start and continue a behavior for maintaining and promoting so-called healthy state or health activities such as stopping or decreasing smoking, decreasing salt intake, taking physical exercises, stopping of drinking, decreasing drinking, decreasing fat intake, and brushing teeth require considerable motives and background. From the viewpoint of behavioral science, health guidance means how to support people's subjective efforts for promoting and recovering their health.[8–11] The important thing for dealing with lifestyle-related diseases is to develop behavioral science techniques by finding out what kind of interventions are effective for health guidance and how they lead to changes in lifestyles.

In determining behaviors, rationale for implementing a behavior and its effectiveness should be recognized well by people who are implementing. Only after the clear-cut reason and effectiveness are recognized, they are motivated and become positive toward such behavior. Such reason and efficacy are not to be merely preached or educated by health professionals, but they should be realized, confirmed and implemented by the subjects themselves. We health professionals are always in a position to support them.[12]

Then, how do we actually proceed with the above-mentioned series of works of confirmation? For instance, the subject may be asked to write a list of reasons and effects of a certain behavior and helped to choose the behavior. This method enables the subject to continue a certain health activity and acquire the habit of such activity until the time when he/she is convinced with the reason and effects, and even to enhance positive willingness.[11]

4. How to Incite Desire for Healthy Behavior

As discussed above, health guidance based on behavioral science means to support and assist the subject in many areas. It means to help him/her not to become frustrated or lose confidence as he/she is motivated to start the behavior, experiences the psychological burden in continuing the behavior, to firmly establish the rationale for the behavior and to confirm its effectiveness.[5,13]

One should take note of individual differences both physically and psychologi-

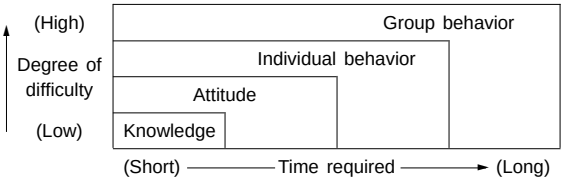

Fig. 2 Time required for change and degree of difficulty[16)]

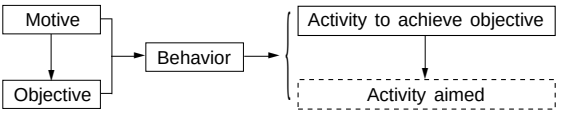

Fig. 3 How motivation works[16)]

cally in those starting or about to start a health activity. Their environment in life, work, and home differs and their lifestyle and sense of values regarding life also differ. Therefore, advice or assistance deemed pertinent by the supporter may be interpreted as criticism, slander or even contempt depending on sensitivity or physical and psychological conditions of those receiving such advice, etc., and may invite the result contrary to original purposes. The quality of mutual relationship between the party behaving and those assisting can be an extremely important key.[14,15)]

4-1. Level of changes

Behavioral science captures changes occurring to humans at four levels. They are changes in knowledge, changes in attitude, changes in behavior, and changes in group behavior or organizational behavior.[16)]

Figure 2 shows the time required for these changes to occur without pressure or submission and the relative difficulties. As shown, changes in knowledge occur most easily, followed by changes in attitude. Factors constituting attitude are different from those of knowledge in that emotional factors such as positiveness or negativeness are included. On the other hand, changes in behavior entail more difficulty and time compared to these two changes. Changes in group or organizational behavior are most difficult and time-consuming among these four changes.

4-2. Behavior

Behavior is basically preceded by an objective. In other words, our behavior is motivated by a desire to achieve an objective. However, rationale for behavior is not necessarily clear in conscience. Freud is one of those who first recognized the importance of subconscious motive. According to him, motive is defined as a desire inherent in an individual, a sense of psychological dissatisfaction, drive or impulse.

On one hand, an objective exists outside an individual. Objectives are described as “desirable” compensations that direct the motive, and psychologists

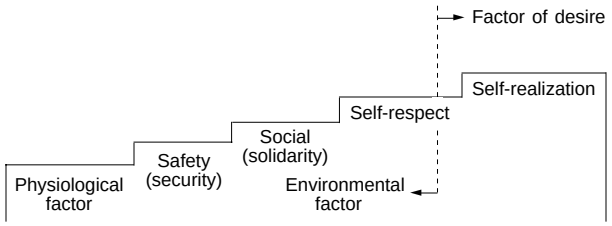

Fig. 4 Motivation: Relation between theory of environment and Maslow's stages of desire[16)]

define them as incentives.

Figure 3 shows the relation among motive, objective, and behavior. The most intense motive induces behavior to realize or achieve an objective, but since not all the objectives can be realized, the dotted line indicates them.[16)]

On the other hand, factors that determine human behavior are the preceding factor, the resulting factor and the cognitive factor according to Bandura.[17)] He attached the greatest importance to the expectant function as a preceding factor and divided it into the expected result and the expected efficacy, and clearly showed that they are the factors that affect behavioral changes. An individual's cognition of expected efficacy before implementing behavior is described as self-efficacy and studies made clear that this is the determinative factor for starting and continuing a behavior.[18,19)] Cognition of how much self-efficacy is possessed by an individual is known to be useful for predicting behavioral changes, to restrain emotional reaction, and to ameliorate stress reactions.[18)]

4-3. Staging and motivation of desire

Behavior in a specific scene is generally determined by the desire that is strongest at that time. Therefore, it is necessary to understand important desires that are common to all humans. As for the intensity of specific desires, Maslow proposed that physiological desires, desires for safety or security, desires for society or solidarity, self respect and self realization (to maximize capabilities of the self) generate in a stepwise fashion. In other words, it is necessary to see in which stage the desire of the subject or the group is. Figure 4 shows this theory.

4-4. Support for health activities

Well known methods of support for health activities are described below.

(1) Method of association of motives

This method associates the motive for an activity, which the subjects find most important in life with the motive for health activities in order to enhance motivation for health activities.[3)]

(2) Self reward and punishment

This method rewards or punishes the self for continuing or failing an activity in order to intensify motivation for health activities.[3)]

(3) Support networking

A short or long-term network system is established among a group engaged

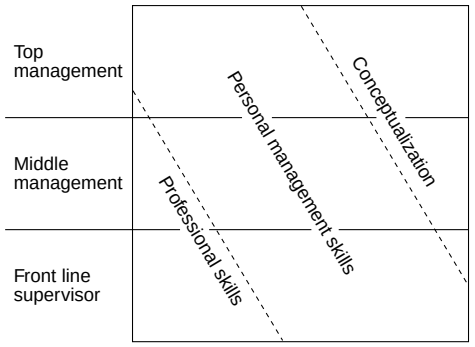

Fig. 5 Management skills required at different levels of organization[16)]

in a specific health activity for supporting each other by personal contacts. The supporters may support or assist this system.[3,20,21)]

(4) Autosuggestion

Motivation is intensified by imagining the ideal self, who is achieved by implementation of a health activity.[3)]

5. Behavioral Science Approach to Management

Physicians are the leaders of health professionals and are naturally expected to manage the health team with expertise.

Capabilities in at least three areas are considered necessary for good management; those of specialties, those of personal management, and those of conceptualization.[16)] Capabilities in specialties mean those for using the knowledge, methods, techniques, and tools required for certain business, and they can be acquired by experience, education, and training. Capabilities in personal management mean those for working with or through others and to make judgments and include understanding of psychology of motivation and effective application of the leadership. Capabilities in conceptualization mean understanding the complex structure of organization as a whole and where and how the self is incorporated in the organization. These capabilities differ according to the levels in the organization (Fig. 5).

6. What is Behavioral Medicine?

Behavioral medicine came into the limelight as medicine was re-examined during the past 30-odd years in the United States and is an academic discipline that entails practical activities. The review is still continuing,[22)] and has rapidly developed after the late 1970s. International Society of Behavioral Medicine was established in 1990 and Japanese Society of Behavioral Medicine in 1992. The Charter of the International Society of Behavioral Medicine (revised in 1993) defines that "behavioral medicine is a discipline which aims to advance and integrate studies of psychology, sociology, behavioral science, and biomedicine regarding health and

disease, and to apply them to disease prevention, elucidation of etiology, diagnosis, treatment, and rehabilitation". This is a new inter-disciplinary area across clinical sciences, socio-psychological behavioral science, basic medicine, public health, and preventive medicine.[23)]

The reason why behavioral medicine is attracting attention today is discussed below.

6-1. Reflection on conventional psychosomatic medicine

Psychosomatic medicine is interested mainly in elucidation of psychological factors related to the cause and onset of diseases. In other words, the treatment aims to enable patients to understand their psychological complications. Such attempts to clarify the psychodynamic structure have not necessarily been successful.

6-2. Importance of methods for behavioral intervention

One factor which promoted development of behavioral medicine is the change in disease structure. As acute diseases have been overcome to a certain degree and chronic diseases now play the principal role, approaches toward multiple factors became necessary. Epidemiological studies revealed that certain behaviors and lifestyles can become risk factors for cancer, coronary diseases and diabetes mellitus, and behavioral interventions have come to be recognized as effective means for preventing these diseases.[19,20)]

6-3. Bio-feedback and autonomous system training

These methods were developed for behavioral interventions discussed above and are said to be effective for headaches and chronic pains that have shown strong resistance toward conventional treatment.

7. Introduction of Consultation and Liaison Psychiatry

In the field of mental health and medicine, which is gaining importance in recent years, a theory of consultation and liaison psychiatry is considered very important.[5,13,25–27)] Generally, it is called liaison psychiatry, but the two entities differ in definition in a strict sense. Glickman and Hackett discuss differences as follows: "A consultation psychiatrist is a fire fighter who hurries to the site and distinguishes fire while a liaison psychiatrist is an equivalent of a fire department inspector who prevents or detects fires early by inspections and regular fire drills."

8. Conclusion

As discussed above, our daily life is full of changes and the time flies. Lifestyles of individuals are diverse and their sense of values toward life and labor has diversified. In Japan, people have become affluent and medicine and technology are leading the rest of the world.

When shifting our viewpoint to the actual scene of practical medicine, acute diseases have been controlled to some degree and chronic diseases are now the main streams. Conventional ways of doctors to unilaterally address therapy to

patients of terminal illnesses and intractable diseases have changed and now reflect patients' sense of values and views of life.

From the viewpoint of disease prevention, the most important challenge is how to address lifestyle-related diseases. Complex and diverse social life is still proceeding to reflect the disturbed rhythms of life, insufficient physical exercises, and accumulation of stresses. It is high time to re-examine the relation between lifestyle that are good for health and disease prevention.

In order to carry out specific health activities, there should be good human relationship between health professionals and patients in motivating patients and presenting the reason for implementation, by having them understand, appreciate, recognize, and continue the habits for an extended period of time. We believe that it is essential to introduce and apply behavioral science discussed above and behavioral medicine, which is application of behavioral science to medicine.

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INTERACTION BETWEEN GRAPEFRUIT JUICE AND DRUGS*

Junichi AZUMA**

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Abstract: There is a possibility that even a glass of grapefruit juice (GFJ) taken several hours before oral medication may enhance the bioavailability of many drugs, exaggerate the drug action, and increase the toxic effect by exaggerating the potency of the drug. This can be explained by inhibition of CYP3A4 in the small intestine by GFJ, thus suppressing drug metabolism. This interaction with GFJ is likely to occur mainly with those drugs that are metabolized by CYP3A4 and are associated with low bioavailability when given via an oral route. Thorough instruction on medication is necessary when these drugs are administered to patients. Examples of these drugs include: dihydropyridine calcium antagonists, terfenadine, cyclosporine, and carbamazepine.

Key words: Grapefruit juice; Cytochrome P450 (CYP); CYP3A4; Drug interactions; Enzyme inhibition

Introduction

Even a glass of grapefruit juice taken several hours before medication may increase the bioavailability of many drugs, raise the blood concentration of the drug, enhance drug potency, or exaggerate the toxic action of a certain drug. This occurs because of the inhibition of metabolic activity of CYP3A4, a molecular species of drug metabolizing enzyme, P450, that exists in the small intestine.

A drug that has been administered via an oral route is absorbed through the digestive tract, reaches the liver via the portal system, appears in the peripheral circulation, and is then distributed throughout the body. Part or most of a drug is subjected to a first-pass metabolism in the liver and small intestine. Many drugs are highly oil-soluble and they have to be metabolized by a metabolic enzyme called cytochrome P450 into water-soluble compounds that can be excreted in the urine or bile. The most important drug-metabolizing enzymes in the human are the following 5: CYP1A2, CYP2C9, CYP2C91, CYP2D6, and CYP3A4. Among the P450 enzymes that exist in the human liver, the amount of CYP3A4 is the greatest (about 30%). CYP3A4 also exists in the small intestine and is the most important enzyme, participating in more than one-half of the pharmaceutical agents.

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** Professor, Postgraduate School of Pharmaceutical Science, Osaka University

Drug Interactions: Grapefruit Juice

The development of adverse effects of drugs caused by "drug interactions", which has attracted attention recently, occurs when 2 or more drugs are taken simultaneously or almost at the same time. A typical example is an adverse effect of sorivudine, which is caused when the process in which 5 FU, an antineoplastic agent, is metabolized and inactivated is inhibited by the metabolites of sorivudine. If a drug-metabolizing enzyme is inhibited, the blood concentration of the active unchanged drug increases, thus amplifying the pharmacological action or causing adverse effects to develop.

An abnormal rise in the blood concentration of a drug is called an interaction by "inhibition" of a drug-metabolizing enzyme. The blood concentration of a drug that has been affected by inhibition rises but a clinical problem arises only with drugs (such as fluorouracil) that have a narrow safety range for their blood concentration and may readily develop serious adverse effects.

Recently, the drug interaction of grapefruit juice has been frequently reported. An interesting action of this juice in increasing the bioavailability of an orally taken drug was accidentally discovered about 10 years ago when it was given to cover the taste of ethanol during a study of the interaction between felodipine (a dihydropyridine type Ca blocker) and ethanol.[1)]

Later, it was shown that grapefruit juice raises the mean area under the felodipine plasma concentration-time curve (AUC) approximately 3-fold when the felodipine was administered orally to patients with borderline hypertension. It was reported that grapefruit juice exaggerated the antihypertensive effects of felodipine, raised the heart rate in clinical patients, and was frequently responsible for adverse effects due to vasodilation.[2)] Grapefruit juice significantly raised the maximum plasma concentration (Cmax) of felodipine but did not change its half-life (t1/2). Because this juice had no effect on the pharmacokinetics of felodipine when administered via an intravenous route, it was concluded that the action of grapefruit juice stems from its metabolic inhibition in the stage before the drug enters the circulating blood.

Mechanism Responsible for Interactions Caused by Grapefruit Juice

To discover the action of grapefruit juice on the drug-metabolizing enzymes of the small intestine and liver in man, a clinical study that is not possible in Japan was conducted.[3)] Consequently, it became evident that this juice selectively participated in post-translational regulation of CYP3A4 in the small intestine, reduced the CYP3A4 content by about 50%, and compromised the metabolic activity of the enzyme. Specifically, drinking grapefruit juice for 5 consecutive days caused a 3-fold increase in the AUC of felodipine and a 5-fold increase in Cmax. In this instance, there were no changes in the CYP3A4 mRNA level of the small intestine; but the protein contents of CYP3A4 and CYP3A5 were reduced by a mean of 62%. No changes were noted in the activity of the hepatic CYP3A4—detected by a method called an erythromycin breath-test—or the protein contents for CYP2D6 or CYP1A1 in the small intestine. Thus it was concluded that grapefruit

juice selectively inhibits a molecular species of CYP3A in the small intestine and raises the bioavailability of felodipine.

Orange juice is not associated with the inhibitory actions described above. Because the expression of a molecular species of CYP3A is reduced by grapefruit juice, it is evident that this inhibition is not a simple competitive action on the metabolism of the substrate. Grapefruit juice reduced the post-translational CYP3A4 protein content without affecting CYP3A4 mRNA in the small intestine, suggesting that this is an irreversible enzyme inhibition with probable enhancement of CYP3A4 decomposition. To restore the CYP3A4 activity, de novo synthesis of the enzyme becomes necessary.

The potency of the inhibitory action of grapefruit juice varies in individuals: Some are not much affected while in others the AUC and Cmax of the plasma felodipine rose to 6 times that when water was given instead of the juice. Because the expression of CYP3A4 protein in the small intestine is involved in the reaction and the inhibitory rate is exaggerated in individuals with greater CYP3A4 activity, it is suspected that this individual difference in the potency of the interaction caused by the grapefruit juice is at least partly due to some genetic difference. The details have yet to be elucidated.

It is presumed that in this phenomenon, a "certain component" in the grapefruit juice participates in the inhibition of CYP3A4 activity. It is understood that this "certain component", when taken orally, is trapped in the small intestine without reaching the liver and inhibits the CYP3A4 activity that is expressed by the villous cells of the small intestine. Initially, it was believed that flavonoids, such as naringen and naringenin, and 6′,7′-dihydroxybergamottin of the furanocoumarin type that are contained in grapefruit juice, were strongly suspected to be causative agents for inhibition. However, recent reports negated the possibility that these act as major causative agents in the interactions between grapefruit juice and a drug.

Recently, a component that potently inhibits CYP3A4 was discovered in an ethylacetate extract of grapefruit juice. Structural analysis revealed that this was a new furanocoumarin derivative.[4] However, clinical studies will be needed to prove its clinical significance in drug interactions.

Drugs That Are Affected by Grapefruit Juice

The drugs that may interact with grapefruit juice are those that are metabolized by CYP3A4. The most frequently investigated are dihydropyridine-type Ca blockers; their metabolic pathways are similar but the bioavailability of each drug varies widely. Nisoldipine has the lowest bioavailability and is most likely to be affected by grapefruit juice, followed by felodipine, nicardipine, and nitrendipine, while the effect on nifedipine and amlodipine are negligible.

It is known that the magnitude of the effect of grapefruit juice is proportional to the first-pass effect (the greater the first-pass effect, the lower the bioavailability). It is difficult to determine an individual's drug interaction for the dihydropyridine-type drugs with low bioavailabilities. Individual difference is at the greatest for nisoldipine. Among nifedipine-type drugs, the effect of grapefruit

Table Drugs That Are Affected by Grapefruit Juice

- Dihydropyridine-type Ca blockers:
  nisoldipine, felodipine, nicardipine, nitrendipine, nifedipine, etc.
- Drugs acting on the central nervous system:
  benzodiazepam-type hypnotic sedatives (triazolam and midazolam), carbamazepine, and diazepam
- HMG CoA reductase inhibitors:
  lovastatin, simvastatin, etc.
- Immunosuppressive agents:
  cyclosporine and tacrolimus.
- Anti-allergy agents:
  terfenadine and astemizole
- HIV protease inhibitors:
  saquinavir
- Others:
  cisapride and verapamil

juice is slightly more pronounced for enteric-coated preparations.

In addition to these dihydropyridine-type drugs, it has been confirmed that more than 20 drugs interact with grapefruit juice, resulting in clinical problems.[5] Even at this time, the results of a number of clinical studies attest to these effects. Among the drugs that are marketed in Japan and metabolized by CYP3A4, those that have known clinical problems due to their interactions with grapefruit juice are: Terfenadine, saquinavir, cyclosporine, midazolam, triazolam, and verapamil (Table). The plasma concentrations of those drugs that are raised significantly when combined with itraconazole or erythromycin, known inhibitors of hepatic CYP3A4 activity, are also affected by grapefruit juice. Cisapride and astemizole are also affected by grapefruit juice. It is believed that those drugs that are not very likely to be affected with the combination of CYP3A4 inhibiting drugs are also relatively untouched by the actions of grapefruit juice.

There are several recent reports on the different effect of grapefruit juice between water-soluble HMG-CoA reductases and oil-soluble preparations that constitute metabolic substrates for CYP3A4.[6] It is reported that grapefruit juice does not affect the pharmacokinetics of water-soluble preparations, while drinking of the juice together with oil-soluble preparations that are metabolized mainly by CYP3A4 results in significant increases in the plasma concentrations of these preparations (AUC, 1.4 to 15 times that when taken with water, though varying in degree for each drug).

Notes on Therapy

When a drug that may undergo an interaction with grapefruit juice is to be prescribed, it is necessary to give appropriate instructions to patients at medication. The following clinical notes are suggested.

The duration of the inhibitory action by grapefruit juice is an important clinical topic. The correlation between the consumption of grapefruit juice and

felodipine administration has been studied.[7] When a glass (220 m*l*) of grapefruit juice is consumed 4 hours before or at the time of drug administration, the rates of increases of AUC and Cmax became the greatest. The potency of the interaction attenuated as the interval between grapefruit juice ingestion and felodipine administration increased; but the Cmax of felodipine was still obviously high even when the drug was administered 24 hours after grapefruit juice ingestion.

We conducted a study on the effect of grapefruit juice on nisoldipine pharmacokinetics in 8 healthy Japanese subjects.[8] When nisoldipine was administered together with 250 m*l* of grapefruit juice, the Cmax and AUC of the plasma concentration of the drug increased 3 and 4.5 times, respectively, in comparison with the corresponding amounts when water was used instead of grapefruit juice. If the juice was given, followed by the drug together with water one hour later, Cmax and AUC increased about 4- and 5-fold, respectively. However, no notable changes in pharmacodynamics were noted when grapefruit juice was ingested one hour after medication.

The half-life of the inhibitory effect of grapefruit juice has been generally estimated to be 12 hours. Imbibing this juice on a single occasion may result in a sustained effect for more than 24 hours, which calls for special clinical attention.

What is important next is the extent of changes in the dynamics of the blood contents of the affected drugs. The following types of drugs are considered to pose a clinical risk when combined with grapefruit juice: (1) Those for which the pharmacological actions may be potentiated, causing excessive reactions or toxic responses when their plasma concentrations exceed twice the desired level: examples include some dihydroxypyridine-type Ca blockers, terfenadine, and saquinavir; (2) those drugs that are associated with sharply curved concentration (dosage)-response relationship; and (3) those with narrow therapeutic ranges and possible potentiation of the drug effects, resulting in excessive drug actions or toxic reactions; these should be watched carefully in clinically practice even when their plasma concentrations may not be excessively high; examples include cyclosporine, midazolam, triazolam, and verapamil.

Finally, the following patient factors are cited in relation to drug interactions with grapefruit juice: (1) Accentuated CYP3A4 activity of the small intestine; and (2) hepatic insufficiency.

The type and quantity of grapefruit juice consumed are also important. Interactions between commercially available grapefruit juice (frozen and concentrated, condensed or diluted, and fresh frozen) and felodipine have been proven; but their magnitude depends on the amount of the active components and may vary, even within each brand or lot. Many of the studies have used grapefruit juice that was condensed twice but it would be safe to assume that all grapefruit juice has the potential to act in the way that has been described here.

Even a single glass of grapefruit juice imbibed several hours earlier may augment the bioavailability, cause excessive drug effects, or exaggerate the toxic actions of the drugs that have been cited above. Particular attention should be paid to these matters in clinical practice.

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TOPICAL USE OF STEROIDS IN THE AGED*

Haruko HINO**

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Abstract: Steroid preparations for topical use include a variety of forms, among them hydrophobic ointments, emulsions, liquids, and gels. These drugs are chosen according to the status and site of the lesion and the patient's age. There are five grades of steroid preparations for topical use in terms of the potency of their clinical effect. The skin of elderly persons tends to be dry and therefore does not absorb steroids well. However, if steroids of high potency are used for a long period, elderly patients are apt to suffer side effects of steroid application, including enhanced atrophy, purpura, xeroderma, capillary telangiectasia, delayed wound healing, and susceptibility to infection, because their skin is atrophied. In the elderly, the skin becomes dry as it looses its ability to retain water. To treat pruritus and asteatotic eczema under these conditions, steroid preparations of mild to moderate potency and having a hydrophobic base should be used. If nummular eczema or autosensitization dermatitis has occurred as a result of scratching, steroids of higher potency should be selected. Emulsions are not suitable for moist lesions like erosions and ulcers, because of the issues of reabsorption and stimulation. Although seborrheic eczema and psoriasis are common in the elderly, the former requires short-term steroids of moderate or lower potency, whereas the latter requires the cautious use of stronger steroids.

Key words: Steroid preparations for topical use; Local side effects of steroids; Indications of topical steroid therapy in elderly patients

Introduction

Among various drugs available for the treatment of skin diseases, adrenocortical hormones are the most common and most frequently used because of their potent anti-inflammatory action. Although systemic steroid therapy by oral administration or injection is employed in some cases, topical steroids are generally used in the treatment of most dermatologic diseases. Some cautions, however, are important with regard to steroid use. The condition of the skin as well as the pharmacology of adrenocortical hormones (steroids) should be borne in mind when applying steroids to the skin.

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** Director, Department of Dermatology, Kanto Central Hospital

Steroid Preparations for Topical Use

1. Topical steroids

In 1952, Sulzberger and Witten first reported the topical application of a steroid in the treatment of dermatosis.[1)] The steroid used was 17-hydroxycorticosterone-21-acetate. Following their report, halogenation of the steroid skeleton at hydroxyl groups located at the C-6, -9, and -21 positions, esterification at C-17 and -21, and acetylation at C-16 and -17 were found to enhance the anti-inflammatory action of steroids, and various potent steroids for topical use have been developed. On the other hand, as more potent steroids have become available, accompanying side effects have arisen as a problem.[2)]

2. Types of topical steroid preparations and their effects on steroid efficacy

Various forms of topical steroids are available, and they are selected according to the lesion to be treated.[3)]

(1) **Hydrophobic ointments**

Hydrophobic ointments do not contain water, but have fat or oil bases like water-insoluble petrolatum. Although hydrophobic ointments are sticky, they are minimally irritating to the skin and are applicable to erosions and ulcers. Steroid ointments with a petrolatum base are widely used, and steroid ointments of this type are, in general, simply referred to as “steroid ointments”.

(2) **Emulsions**

Emulsions, which are a mixture of normally non-mixable fat and water emulsified with a surfactant, are divided into the oil-in-water (o/w) type and the water-in-oil (w/o) type. Steroid creams are mostly of the oil-in-water type and can be washed away with water. Because of this, they are reabsorbed from the erosive or ulcerative surface and therefore cannot be applied to a macerated surface. Creams of the w/o type are more difficult to wash away with water than those of the o/w type. Universal creams are used as bases of steroid creams.

(3) **Lotions**

Lotions are o/w- or w/o-type emulsified liquids. Most steroid lotions are of the o/w type. In recent years, shakable steroid-suspension lotions have become available.

(4) **Gels**

Steroid gels have solid or semisolid suspension bases that can be divided into hydrogel and lyogel bases. The former are transparent bases that form a capsule when applied to the skin, while the latter are also known as FAPG bases, and have a texture intermediate between ointments and creams.

(5) **Sprays**

Steroid sprays are steroid solutions atomized by gas pressure. Although they are advantageous in terms of extensive application, an important drawback is that it is difficult to estimate the exact amount being applied.

3. Indications of topical steroid therapy

Steroid preparations for topical use are generally classified into five grades: strongest, very strong, strong, medium or mild, and weak, in order of potency

Table 1 Major Steroids for Topical Use Ranked According to Clinical Efficacy
(Extension of citation from Shimao[2,5] and Aso[4])

Drug effect	Generic name	Proprietary name
Group I (strongest)	a. clobetasol propionate	Dermovate, Myalone
	a. diflorasone diacetate	Diflal, Diacort
Group II (very strong)	mometasone furancarboxylate	Fulmeta
	a. fluocinonide	Topsym, Simaron, Biscosal
	a. betamethasone dipropionate	Rinderon DP, Dermosol DP
	a. difluprednate	Myser
	a. budesonide	Budeson
	b. amcinonide	Visderm
	b. diflucortolone valerate	Texmeten
	b. hydrocortisone butyrate propionate	Pandel
	betamethasone butyrate propionate	Antebate
Group III (strong)	c. dexamethasone propionate	Methaderm
	c. dexamethasone valerate	Voalla, Zalucs
	a. halcinonide	Adcortin
	deprodone propionate	Eclar
	d. betamethasone valerate	Rinderon V, Betnevate, Hormezon, Muhibeta V
	d. beclomethasone propionate	Propaderm, Beclacin
	d. fluocinolone acetonide	Flucort, Fluzon, Coriphate
	d. prednisolone valerate acetate	Lidomex
Group IV (medium or mild)	d. triamcinolone acetonide	Ledercort, Kenacort A, Tricinolon, Nogiron
	d. flumethasone pivalate	Locorten, Testohgen
	clobetasone butyrate	Kindavate
	alclometasone propionate	Almeta
	d. hydrocortisone butyrate	Locoid, Plancol
	d. dexamethasone	Decaderm
Group V (weak)	methylprednisolone acetate	Veriderm Medrol Acetate
	d. prednisolone	Prednisolon
	d. hydrocortisone acetate	Cortes

a. Ointments and Creams are in the same group. b. Ointments rank one group above creams.
c. Ointments rank one group below creams. d. Difference between ointments and creams is unknown.

(Table 1).[2,4,5] Even when the same steroid is used, ointments and creams may rank differently because of the base that was used.[2,4]

Although steroid preparations may be selected on the basis of the diagnosis, most frequently the form and site of the lesion and the patient's age are decisive factors. While hydrophobic ointments are sticky and glossy, they can be used for almost all lesions, including erythema, papules, chronically lichenified surfaces, erosions, and ulcers. Since cream bases are water-soluble, being reabsorbed after having been dissolved in effusions, and are also irritants, they are not suitable for erosions and ulcers.[3]

4. Side effects of topical steroids

(1) Local side effects of topical application

1) Side effects of steroids themselves

Table 2 Local Adverse Effects of Topically Applied Steroids

1. Adverse effects due to inhibitory action on cell growth and fibrosis
Skin atrophy
Striae atrophicans
Steroid skin injury
Xeroderma / ichthyosiform cutaneous symptoms
Delayed wound repair
Asteroid uloid
Capillary telangiectasia
Rosacea-like dermatitis / peristome dermatitis
Steroid purpura / flush
Steroid elastosis
Steroid acne milium / colloid milium
Pigmentation disorder
2. Adverse effects due to hormone action
Acne
Excessive hair growth
3. Adverse effects due to induced decrease in immunocompetence
Susceptibility to bacterial, fungal and viral infections
4. Others
Contact dermatitis
Photodermatosis
Glaucoma / cataract (due to eye drops)

Table 2 shows possible adverse reactions to topical steroids.[2,4,5] The higher the grade of steroid and the longer its period of application, the more often adverse reactions occur. Adverse reactions are also more likely to occur when the steroid is applied by occlusive dressing therapy (ODT) than by simple topical application.

Contact dermatitis caused by steroids themselves is well known. If the disease state remains unchanged or is aggravated with the topical use of a steroid preparation, it is necessary to suspect contact dermatitis due to the steroid.

2) Side effects of the base or formulating ingredients

Surfactants used in the base, lanolin, propylene glycol, and supplemented aminoglycoside antibiotics such as neomycin may cause contact dermatitis.

(2) **Systemic side effects after topical application**

Percutaneously absorbed steroids can exert systemic effects. When a strong steroid at a dose of 15–30 g / day is applied by ODT, hypoadrenalism, eosinopenia of the peripheral blood, accumulation of Na and water retention, and cushingoid signs may occur. However, these changes resolve soon after the steroid is discontinued. It has been reported that hypoadrenalism seldom occurs after simple topical application at a daily dose of less than 10 g.[2]

To prevent systemic effects of steroids absorbed from the skin, various antedrugs have been developed. Steroids that are unlikely to be absorbed from the skin or that lose glucocorticoid activity and are metabolized within a short period of time, even if absorbed, are especially desirable. The recent development of topical steroids has been aimed at designing clinically effective preparations that are free

from undesirable systemic and local effects.[4)]

Steroid Preparations for Topical Use in Elderly Patients

1. Effects of topical steroids on the skin of elderly patients

In the elderly, the skin is dry and steroids are poorly absorbed. However, aged, atrophied skin is susceptible to steroid-induced skin atrophy, peliosis, and steroid skin injury, changes that are difficult to resolve once they occur. Senile dermatoses follow a chronic course, are intractable, and require prolonged topical application of steroids, which then can lead to adverse reactions to the drug. Steroids of an appropriate grade should be chosen according to the lesion and should be applied for as short a period as possible.

The skin of the face is thin, particularly in the perioral and periocular areas, as is skin in the genitocrural and perianal regions, and axilla. Since these areas are susceptible to steroid-induced atrophy, due caution is necessary in selecting the grade of steroid to be applied.

2. Common major dermatoses requiring topical steroids in the aged and the usage of such steroids

(1) **Pruritus**

This condition, in which the patient complains of severe itching although no particular eruptions are present, is especially common in the winter. Pruritus may accompany skin dryness in diabetes mellitus, chronic liver disease, and dialysis or visceral lesions including malignant tumors. Patients often suffer itching of the skin when they become warmer as a result of improved blood circulation, particularly after bathing, in bed, or while using an electric blanket. Patients may indeed scratch their skin until it becomes sore, a situation that is more apparent as people grow older, representing a common problem among the elderly.

Application of an oily ointment or body oil after bathing, when the skin is moist, is effective. When symptoms are severe, the use of a steroid ointment of the medium grade is recommended.

(2) **Asteatotic eczema**

An eczematous lesion that develops from pruritus through scratching is called asteatotic eczema. Application of a medium or strong steroid ointment is indicated. Simple embrocation once or twice a day is adequate. This lesion commonly occurs in winter, and is frequently located on the lateral sides of the lower legs and in the dorsolumbar region. In addition to people of middle or advanced age, this lesion has recently been seen in young people who work in dry, ventilated rooms.

(3) **Nummular eczema**

Pruritus complicated by scratching and infection with staphylococci or other bacteria forms a surface the size of a coin or egg yolk, accompanied with erosions, effusions, and sludgy crust formation.

Simple topical application of a steroid ointment is not adequate for this type of lesion, and superposing zinc ointment on the steroid ointment is required. After the crust has been eliminated, simple embrocation of the steroid ointment is employed. Strong or very strong steroid ointments are appropriate. Strongest

steroid ointment may also be used, but only for a short period of time.

(4) **Seborrheic eczema**

Although this type of eczema is particularly common in the neonatal period, puberty, and adolescence, it frequently occurs in people of middle or advanced age as well. The lesion involves the face or head, with the seborrheic area having an erythematous surface with pityroid desquamation. Antimycotic agents such as ketoconazole may be used for facial lesions. In intractable cases, a weak or medium steroid ointment may be used for a short period.

(5) **Psoriasis vulgaris**

This lesion occurs relatively frequently in people of middle or advanced age. Although treatment may vary according to the disease state, a strong steroid ointment is usually applied to rashes on the trunk.

An occlusive dressing may be employed on some occasions.

Conclusion

The skin of the elderly does not permit good percutaneous absorption. Further, it is thin and apt to be adversely affected by the application of topical steroids. Thus, local adverse reactions are likely to occur, leading to skin atrophy, purpura, and capillary telangiectasia.

Steroid preparations for topical use are available in various forms, which should be chosen according to the characteristics of the cutaneous lesion in question. Ointment bases such as petrolatum are applicable to a variety of lesions. In contrast, cream bases are not appropriate for moist lesions including erosions and ulcers because they are dissolved in effusions and reabsorbed. Steroid preparations for topical use are classified into five grades in terms of the potency of clinical effect. It is necessary to choose a steroid agent of the grade suitable for the cutaneous lesion and lesion site. Since cutaneous lesions in the aged are often intractable, due consideration of the potency and form of dosage is required when using topical steroid therapy.

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