

# JMAJ

## Japan Medical Association Journal

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#### *Correction: Error in Author Name*

In the article titled, "Protein Restriction Diet as an Essential Tool in Treating Uremia: Myth or Truth?" published in the JMAJ Vol.45 No.2, 2002, pages 80–83, the second author's name was misspelled. It should have appeared as Tatsuo SIIGAI. We regret the error.

# Measures Taken from the Aspect of Nursing Jobs to Prevent Medical Accidents

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**Abstract:** Those engaged in nursing are likely to become the parties concerned with a medical accident because of the characteristics associated with this profession. A nurse is always at work closely to the patient and it is through a nurse that the patient actually receives a treatment in many cases. Therefore, a nurse is often held responsible for an error originally caused by other medical staffs. The roles a nurse is expected to play are physical care of the patient, treatment of the patient according to the instruction of physician, and psychological support to the patient. In compliance with the demand and request of the patient and other medical staffs, a nurse has to perform these roles each of which is different in nature. Under such a circumstance, it is difficult for a nurse to systematically perform the work assigned to her and this constitutes a cause for an error. To prevent medical accidents caused by error, 1) use of appropriate devices and procedures, 2) establishment of competent system and management, and 3) nurturing of organizational climate to place priority on the safety and the training of staffs in this regard are necessary.

**Key words:** Accident prevention; Nursing jobs; Team medical care; Fail-safe; Organizational climate

Many medical accidents have been reported since last year. Frequently, it is the nurse who is reported as the person related to medical accidents. As an urgent plan to prevent medical accidents, the Japan Nurse Association made 4 proposals in April last year. They were; appropriate positioning of manpower, systematic training of nursing staffs after they have completed required courses, establishment of a team medical care system that runs 24 hours a

day, and clarification of the range of work allocated to those engaged in medical care and their responsibility.

At the same time, the Association established a risk management study committee and prepared a “risk management guideline”. This “guideline” was distributed to the institutions where more than 2 members of the Association are working and a request was made to fully utilize it for prevention of accidents. When we

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This article is a revised English version of a paper originally published in the *Journal of the Japan Medical Association* (Vol. 124, No. 6, 2000, pages 878–882). The paper is a transcription of a presentation in the Seminar on Patient Safety held at the JMA office in Tokyo on July 16, 2000.

Table 1 Nursing Staff Often Becomes the Party Concerned with the Accident for the Following Reasons

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· Nurse is around the patient 24 hours a day.
· Nurse is expected to provide direct medical care to the patient in the forefront of medicine.
· Though the nurse checks the work done by other staffs, there is no system to check the work done by the nurse.

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recently investigated the use of this guideline, many institutions answered that they were using it in taking measures to prevent accidents in hospitals.

We have already learned about concrete measures to prevent medical accident in the morning session. What I am going to mention may overlap in some part, but I would like to suggest the preventive measures from the standpoint of nursing.

### **Nursing Staff Often Becomes the Party Concerned with the Accident**

In many of medical accidents, it is the nurse who is reported as the person concerned. However, in view of the work performed by the nurse, this is quite natural (Table 1).

Because the nurse is always around the patient, chances of encountering any accident in the patient are high.

Furthermore, working in the forefront of medical care, the nurse directly provides medical care to the patient. In this case, however, the physician who also directly provides medical care such as treatment, operation, etc. becomes the party concerned as well.

As the medical care is consequently given by the nurse, another role played by the nurse is to check the work performed by other staffs. It often occurs that a simple mistake in the physician's instruction or in pharmacist's prescription is discovered by a nurse. Also, when a nurse makes such a mistake, the colleague may discover it and correct it.

As a nurse is comparable to the last runner in

Table 2 Three Roles a Nurse is Expected to Play

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· To assist the daily life activities of the patient so as to avoid any disorder during his/her hospitalization.
· To support the patient, physician, and other medical staffs so as to provide necessary treatment in a proper manner.
· To treat patients and to cope with the anxiety and questions they may have during his/her hospitalization.

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a race, the patient is exposed to a danger if the nurse fails to find the errors accumulated in the process of giving medical care to the patient.

### **Roles the Nurse Is Expected to Play**

What are the roles played by the nurse in giving medical care? There are so many, but we roughly classify them into 3 categories (Table 2).

The work related to assisting the patients in their daily activities during their stay in hospital is one category. In the case of elderly patients, their physical function becomes deteriorated by hospitalization and staying in bed. To prevent aggravation of health status, the nurse helps them perform their daily activities such as changing their postures preventing the onset of bed sore in the invalid.

The second category includes the work to support the patients, physicians, and other medical staffs so as to provide the necessary treatment for the patients in an appropriate manner. Many accidents have occurred during this support to the treatment. As the quality of medical care is improved if a nurse can effectively support the medical staffs, this is a very important role.

The third category includes the work to deal with the anxiety and doubts the patients have about the disease, its treatment, and the stay in hospital. Though the patients also consult the attending physician about their worries, there are matters they hesitate to mention to the physician. Some patients wait until others have gone to bed at night and come to a nurse to talk about their worries, for examples, deformation

of their body after operation, failure to perform the role of a family member, and deteriorated family relation due to hospitalization. Psychological support is necessary for this type of patient.

### Characteristics of Nursing Duty

How are the roles mentioned above performed? Nurses work on a 24 hour shift. At the end of a shift, the nurses hand over the duties to those on the next shift. Therefore, taking records, case study meeting, and the duration provided for duty transfer are very important.

Nursing is a work in which a night shift is indispensable. The recent revision of Labor Law now allows women to work during the night but there was a special provision in the past to allow nurses to work throughout the night.

According to "Handbook for Shift Work of Nurse" published by the American Nursing Association, some nurses are not suited for the night shift and have to be excluded from it. As any nurse is expected to perform a night shift in Japan, those who cannot handle it have to resign or find a place where they need not work at night.

The influence of night shift on nurses has never been fully investigated. For example, there is a survey result indicating that a clockwise change in the shift lessens the fatigue. Another research result reported recently is that a nap during night will improve the awakening in the morning and that a nurse finds it difficult to stay awake and is likely to commit more mistakes unless a nap is taken before the shift change in the morning. In Japan, the only restriction on the total night shift hours per month of one nurse is stipulated in the rules of the medical treatment fees but nothing more.

Another characteristic of nursing is that most of the work are performed in compliance with the demand made by others. The instructions given by the physician and the patient's care are mostly performed as routine works. Upon

arrival at the place of work, a nurse generally prepares the schedule for the day but it is rare that the nurse can carry out the work smoothly according to the schedule. First of all, nurses have to cope with the frequent nurse calls from patients. When a physician comes to examine and treat the patient, a nurse has to be there to assist the physician.

In this regard, I heard that a physician is expected to examine and treat the patient by himself/herself without summoning a nurse for assistance in the United States. When one of my friends went to the States for training, she/he went to assist a physician on his/her round. However, the physician said, "Why did you come? You have your own work to do". Such a case is very rare in Japan where a nurse is usually summoned.

A nurse has often to stop her work to cope with the nurse call made by the patient. This constant discontinuation of work is said to be responsible for making errors.

In addition, other medical staffs, for example, the X-ray technician or laboratory staff, may come to the ward to perform their work according to their own schedule. In such a case, a nurse is always summoned when the patient in question cannot move freely. In other words, a nurse has to do this and that by the request made by others. This frequently results in a mistake in a nursing job. For example, when a nurse who is in the process of giving an injection is summoned by a nurse call and a considerable time is spent in dealing with the call, she/he may not be able to pick up what is left midway upon returning in a hurry and may make a mistake then and there.

The same applies to the physician. If each staff wishes to perform the work assigned to them satisfactorily, a certain rule has to be established for all the staffs in the ward, for example, setting the time limit for making demand on other staff at 3:00 or 4:00 p.m. in the afternoon (though this rule is established in many hospitals but hardly anyone pays attention to it at present).

Table 3 Number of Beds per Ward and the Number of Patients per Nurse (from the desk schedule)

Country	Number of beds	Nurse	Assistant	Number of patients per nurse	
Japan	43~52	16~30	1	Daytime: 8~9	Night: 14.3~22.6
AU	20~30	12~31	2~4	Daytime: 2.7~6.7	Night: 3~10
UK	Private rooms: 9, Surgeries: 16	9 16 + 3 student nurses	2 1	Daytime: 2.3~9	Night: 4.5~9
USA*	30	35	13	Daytime: 3.8~4.5	Night: 4.4~5
Korea	34	11~12	1~2	Daytime: 5.6~8.5	Night: 11~17

\*The circulatory organ ward in USA.

On the other hand, physicians are also working by a hard schedule. It is not rare in Japan that a physician has to examine and treat outpatients in the morning after a night duty, and perform operations in the afternoon. Any unexpected change for the worse in a patient prevents a physician from performing his duties within the stipulated time range. Due to the small number of medical staffs, such cases occur at all times.

An error is caused either by a mistake or through a slip. In view of the factors inducing an accident and measures to prevent an accident, a mistake occurs by an intentional choice of a wrong target. For example, it is a type of accident in which an oral drug is intravenously administered because a nurse, etc. thinks the drug can be both orally and intravenously given. Such an accident is caused by a newly recruited staff who has not been trained sufficiently or who does not have the knowledge to cope with sophisticated medical care. This type of accident is likely to occur when a staff whose expertise is below the standard of the institution where the latest and most advanced medical treatment is given.

We have started a course for infection management this year. Nurses equipped with such specialty should be positioned for prevention of nosocomial infections.

One measure to prevent this is the systematic improvement of clinical training for the

nurse. The Nursing Association provides the courses for specialist nurse and certified nurse. The incidence of accidents is expected to go down if those who have taken these specific courses are appointed to the institutions where sophisticated medical care is given.

If a nurse unconsciously connects a tube for drip infusion even though she/he knows that it is an oral drug, this is an example of accident caused by a slip. Such an accident often occurs when the nurse has too much work to concentrate on any specific job or when feeling accumulative exhaustion because of the night shift and the like.

To prevent this type of accident, it is advisable to consolidate a team medical care system. A team work does not simply mean the provision of care to the patient by the physician and nurses as members of a team. A team care includes other medical staffs such as technicians, X-ray engineer, pharmacist, nutritionist, laboratory staff who are independently responsible for their specialties and who can directly give care to the patient. However, these people still serve as the back-up staff to the physician and nurse in Japan. As the medical care reaches the patient only through the physician and nurse, most of the work have to be consequently handled by the nurse. To improve the team medical care system is an effective measure to reduce the number of accidents caused by a slip.

Another important and absolutely necessary

Table 4 Three Aspects of Measures to Prevent Accidents

· By use of appropriate devices and procedures	: Introduction of fail-safe system
· By establishment of competent system and management	: Positioning of competent staffs to cope with the advanced level of medical care
	: Establishment of safety management committee and appointment of special staffs
	: Establishment of accident information reporting system
· Nurturing of organizational climate to place priority on the safety and the training of staffs in this regard	: Clarification of safety ideas and safety training of all the staffs
	: Favorable communication across the board

measure is to increase the number of nursing staffs.

The number of beds per ward and the number of patients per nurse are shown in Table 3. The Welfare & Science Study conducted in 1997 investigated the number of nursing staffs in the hospitals in Japan and abroad. In Japan, a nurse on day shift looks after 6 to 8 patients, which is considerably a large number, but the number increases to 14–23 at night. In no country other than Japan, a nurse has to look after so many patients alone.

One of the reasons why such a situation has been allowed to go on is a longer hospitalization period (33.5 days) in the Japanese hospitals. The length of hospitalization cited here is based on the data obtained in 1977 but it is still true at present that longer duration in hospital has contributed to reducing the number of accidents. However, the length has been shortened to less than 2 weeks in many high function hospitals and nucleus hospitals in the district. As is expected, more mistakes committed by the nurse have been reported there.

### Three Aspects of Measures to Prevent Accidents

I would like to summarize the measures to prevent medical care accidents in the following.

They are roughly classified into 3 categories

(Table 4).

The first of them is to prevent accidents by appropriately setting the devices and procedures. For example, the introduction of a fail-safe system such as changing the diameter of a 3-way cock to prevent a tube intended for the digestive tract from being inserted into the vein. One of the measures classified into the second category is to assign competent staffs who can cope with sophisticated medical care to crucial positions. This calls for immediate attention because the number of medical staffs including nurses is fewer in Japan compared with the status abroad. It is also important to establish a safety management committee and accident information reporting system as well as assignment of special staffs to strategic positions.

Concerning the third category, it is necessary to create an environment within the institution to place top priority on safety and to train the staffs in this regard. It is difficult to build a relationship in which mistakes made are frankly checked and discussed among the staffs. Unless this concept is held as the across-the-board ideal by the hospital, it will end up as an official stance to which nobody pays much heed. One cannot ignore the hierarchy within the institution where some are in the position to give orders while others have to comply with them. In such a situation, a staff cannot frankly point out a mistake made by his/her superior. However, if he/she doesn't, this may result in an accident to the patient. Therefore, it is important to create an organizational climate for anyone to freely tell others to pay more attention if any mistake occurs.

Safety training for all the staffs is also important. As physicians and nurses are likely to become parties concerned in an accident, they are more meticulous about the measures to prevent accidents. When a spill of water is in the hallway of a hospital building, any staff including clerical staffs should mop, thinking that this may cause someone a fall or slip. Such organizational climate that all the staffs working in a hospital contribute to maintaining safety

must be created from now on.

Lastly, I would like to raise a question about the current method of dealing with medical care accidents in Japan.

When an accident occurs, the police immediately intervenes to investigate who is responsible and who is the culprit. As a result, it is difficult to contrive effective measures to prevent a similar accident the next time.

When the Japan Nurse Association directly asks the head of the nursing department at the hospital where an accident has occurred through a telephone call to obtain relevant information, details are not given because the person in charge refuses to give any information, saying "we are requested by the police not to talk about the accident". Furthermore, apart from the ethical aspect, the party concerned may think justified for not giving any information that is disadvantageous to her/him if he/she is prosecuted.

However, to prevent a medical accident, it is essential to collect all the information including

the disadvantageous one by those concerned for preventing another similar accident. Under the circumstance, this important information is not made available in most of the cases.

The problem lies in the present system in Japan. The patient appeals to the police because this is the only way to obtain the relevant information which he/she desperately needs. In this regard, it is necessary to establish a third party organ or to allow outside experts to collect and analyze the information, and to make use of the result in other medical institutions as well.

The number of those engaged in medical care has to be increased but this requires money. For the general public to understand that safety in medical care cannot be assured without money, hospitals should disclose the information on medical care accident and make appropriate amends if the accident is caused by a mistake. In other words, hospitals should contrive to eliminate accidents with the cooperation from the general public.

# Drug Treatment of Toxemia of Pregnancy —Indications and Limitations—

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**Abstract:** The cause of toxemia of pregnancy is still unclear, and therefore this condition is only treated symptomatically. Edema, hypertension, and proteinuria are the three key elements of this condition, but drug treatment generally targets only hypertension. Although hydralazine hydrochloride and methyldopa have long been used as antihypertensive therapies, newer drugs such as calcium antagonists have also become used frequently in recent years. The clinical use of these drugs, however, raises major issues, since some of them are contraindicated for pregnant women because of excessive fear of adverse drug reactions in the fetus. Conventional diuretics may cause excessive hemoconcentration during pregnancy, and therefore, it has become common practice to use them only in the puerperium. Since toxemia of pregnancy is viewed, in a sense, as chronic disseminated intravascular coagulation (DIC), anticoagulant therapy with aspirin is a treatment option. This paper describes practical drug treatment of toxemia of pregnancy and the issues involved in light of the aforementioned considerations.

**Key words:** Toxemia of pregnancy; Treatment; Antihypertensive drugs

## Introduction

The etiology and pathology of toxemia of pregnancy still remain to be clarified, and toxemia of pregnancy even now is jokingly called a disease in theory only. Treatment of this condition is, therefore, no more than symptomatic treatment.

The present paper outlines the use of drugs in the treatment of toxemia of pregnancy, focusing on antihypertensive drugs with some dis-

ussion of sedatives and anticonvulsants.

## Considerations in Drug Treatment of Toxemia of Pregnancy

### 1. Concept of toxemia of pregnancy and pathologic states subject to drug treatment

The cause of toxemia of pregnancy is still unclear, and therefore its treatment is restricted to symptomatic treatment. The triad of this condition comprises hypertension, proteinuria, and

edema. Edema localized in lower limbs is not considered to adversely affect the pregnancy, and hence is not the target of treatment. However, edema associated with hypoproteinemia, which is often accompanied by pleural effusion or ascites, should not be left untreated. If maintenance of pregnancy is required for a prolonged period, additional protein supplements are necessary. However, since no radical treatment is available for the cause of hypoproteinemia, i.e., leakage of protein into the urine, except for termination of pregnancy, the pregnancy should be terminated as needed after judging whether the fetus is viable outside the uterus.

Hypertension can be treated with various antihypertensive drugs. Thus, hypertension in toxemia of pregnancy is the best target of drug therapy in this condition. However, in such cases, placental function is often decreased, and fetal development delayed. These cases may often require termination of pregnancy as fetal distress becomes apparent along with the progression of pregnancy.

## 2. Considerations in drug treatment in pregnancy and puerperium

Drug treatment of this condition does have effects on the fetus during pregnancy and the neonate via milk, which should be considered. Drug treatment in pregnancy is also greatly restricted at present due to the increased risk of malpractice suits and enforcement of the Product Liability Law in Japan. As an extreme example, some drugs whose administration in pregnant women is permitted in western countries are contraindicated for pregnant women in Japan. The end result in some cases may be that the only way obstetricians can protect themselves from legal liability is to tell the patient that the condition is untreatable and advise termination of the pregnancy in light of the poor prognosis for the fetus. A further issue that must be addressed is that clinical trials in pregnant women are difficult to perform, and even if a pharmaceutical company overcomes

Table 1 Antihypertensive Drug Therapies for Severe Toxemia of Pregnancy

	No. of cases	Efficacy rate (%)
No. of patients on medication	140	52.1
Calcium antagonists	70	52.8
$\beta$ - or $\alpha/\beta$ -blockers	29	48.3
Hydralazine hydrochloride	78	56.4
Methyldopa	17	58.8
Furosemide	12	66.7
ACE inhibitors	3	66.7

(Including overlapping medication)

(Adapted from reference<sup>1)</sup>)

technical difficulties, the reality is that they will not make a profit.

Japan Society for the Study of Toxemia of Pregnancy has discussed this matter at great length to establish guidelines for the use of these drugs to provide appropriate medical care. However, at present, when we consider the prognosis of a markedly immature fetus, obstetricians have no way to maintain a pregnancy other than using drugs for which pregnancy is specified as a contraindication or to be handled similarly to a specific contraindication, as long as the safety of the drug has been widely accepted (Table 1).<sup>1)</sup>

In general, when medication for toxemia of pregnancy is necessary after delivery, it is also often the case that breastfeeding is not permitted to allow the mother to rest. Many drugs are, unfortunately, secreted into breast milk and adversely affect the infant thus requiring the prohibition of breastfeeding. However, lactation should not immediately be allowed to stop, because if the period of medication is to be short, breastfeeding can be commenced after the end of medication.

## Use of Antihypertensive Drugs and Considerations

### 1. Goal of pressure lowering and precautions

It is necessary to maintain sufficient placental

blood flow during pregnancy. In cases of toxemia of pregnancy, increased blood pressure actually contributes to maintenance of placental circulation. In particular, placental function is often markedly lowered in patients with this condition, accompanied by delayed fetal development in the uterus. In such cases, caution should be taken to avoid an excessive drop in pressure because a drop in maternal blood pressure may lead to fetal distress. The target blood pressure reading is 140/90 mmHg, taking into consideration the minimum blood pressure necessary for maintaining placental blood flow, and blood pressure should not be allowed to fall below this level. In addition, candidates for antihypertensive therapy should be restricted to those patients with severe toxemia of pregnancy and a blood pressure of over 160/100 mmHg to 180/110 mmHg, and the therapy should be given only while the patient is hospitalized.

It should also be kept in mind that the objective of antihypertensive therapy for toxemia of pregnancy during pregnancy is to avoid eclampsia and hypertensive encephalopathy while maintaining fetal well-being.

## **2. Antihypertensive drugs used to treat toxemia of pregnancy**

### **(1) Drugs commonly used to treat toxemia of pregnancy**

Antihypertensive drugs commonly used to treat toxemia of pregnancy include hydralazine hydrochloride (Apresoline®) and methyldopa (Aldomet®).

Hydralazine hydrochloride is reported to be associated with teratogenicity in mice, and it has been suggested that there is a risk of thrombocytopenia in human fetuses. This drug should be used during pregnancy only when the benefit would surpass the risk. Oral formulations of this drug are easy to use, with toxemia of pregnancy specified as an indication in the package insert. Injectable formulations of the drug are indicated for hypertensive emergencies including eclampsia. In general, pressure control during pregnancy should be attempted with oral

medication if possible, and injections should be used only during labor or when pressure must be rapidly reduced. Oral therapy should begin with an initial dose of 30–40 mg/day, and should not exceed 200 mg/day. Although the package insert specifies intramuscular or gradual intravenous injection of 1 A (20 mg) when the injection formulation is used, an intravenous drip infusion is recommended for patients in the obstetric field, particularly during pregnancy. Although this drug is reportedly unstable in glucose solution, usually 1 or 2 A dissolved in 500 ml of 5% glucose solution are used for patients with toxemia of pregnancy, in order to avoid an overdose of sodium. The infusion rate should be controlled while monitoring blood pressure. This drug is difficult to use after delivery because of its transfer into milk.

The safety of methyldopa during pregnancy and breastfeeding has not yet been established. However, its use is indicated when the benefit surpasses the risk, and is useful in lowering blood pressure in the puerperium. However, only oral formulations are available for this drug, and therefore difficult to use when pressure must be rapidly lowered or during labor. Therapy should begin with an initial daily dose of 1–3 tablets (250–750 mg), which should be increased by 250 mg at intervals of several days. The maintenance dose is 250–2,000 mg/day, taken as divided doses. Quick increases in the dose are necessary in toxemia of pregnancy since it takes a considerable time to achieve a sufficient drop in blood pressure. However, it is difficult to control pressure during pregnancy employing this therapy.

### **(2) Antihypertensive therapy with other drugs to treat toxemia of pregnancy**

#### **a. Calcium antagonists**

Calcium antagonists not only have a depressor effect through inhibition of smooth muscle contraction, but also seem to improve uterine and placental blood flow through inhibition of uterine muscle contraction. Therefore, these drugs can be used to treat patients with toxemia of pregnancy before delivery. However,

these agents have been found to be teratogenic in animal experiments. Deformities generally occur in the early stage of pregnancy, but it is reasonable to think that these agents may be administered in the second or third trimester of pregnancy. However, the instructions for use of nifedipine (Adalat<sup>®</sup>) list pregnant women in the contraindications. In addition, the package insert for nicardipine (Perdipine<sup>®</sup>) states that the drug should not be used in pregnant women, although it is not listed as a contraindication.

In light of these problems, we do not necessarily recommend calcium antagonist therapy. However, they have potent depressor and uterine contraction-inhibiting effects, and sublingual administration of nifedipine 5–10 mg is extremely effective in immediately lowering blood pressure. A survey of the Japan Society for the Study of Toxemia of Pregnancy (Table 1) revealed that calcium antagonists are frequently used for treatment of severe cases of toxemia of pregnancy, ranking next to hydralazine hydrochloride.

#### **b. $\beta$ -Blockers and $\alpha/\beta$ -blockers**

These classes of drugs have the advantage in that they do not cause reflex tachycardia.  $\beta_1$  blockade can be anticipated, but drugs having  $\alpha$ -blocking actions as well are also used for preventing peripheral circulatory failure. The  $\beta$ -blockers include atenolol (Tenormin<sup>®</sup>), and the  $\alpha/\beta$ -blockers include labetalol (Trandate<sup>®</sup>). The possibility of causing delayed fetal development in the uterus has been raised for atenolol, but since it is easy to use, it is indicated when the benefit surpasses the risk. On the other hand, as noted in the package insert, labetalol is not to be used in pregnant women, with this population included in the list of contraindications because its safety in pregnant women has not been confirmed yet. It may be safer to use drugs with high  $\beta_1$  selectivity because  $\beta_2$ -stimulants are generally used to inhibit uterine contractions.

#### **c. Diuretics**

Furosemide (Lasix<sup>®</sup>) was once used regularly to reduce edema in toxemia of pregnancy, but no

depressor effect can be expected from this drug. In addition, recent investigations have indicated that increased vascular permeability and hemoconcentration are among the pathological features of toxemia of pregnancy. The view that use of this drug during pregnancy worsens placental circulation by promoting hemoconcentration is becoming widely accepted. However, potent diuresis is necessary for water retention such as puerperal pulmonary edema, and therefore active use of this drug is recommended, in addition to d-mannitol and supplementation therapy for postpartum hypoalbuminemia.

Since the safety of Lasix<sup>®</sup> has not been established, the use of this drug in the early stage of pregnancy is limited to cases where the benefit surpasses the risk. In addition, the risk of hemoconcentration is specified for trichlormethiazide (Fluitran<sup>®</sup>), but it may be used during pregnancy when the benefit surpasses the risk.

#### **d. Angiotensin converting enzyme (ACE) inhibitors**

ACE inhibitors are used frequently in the field of internal medicine. However, the renin-angiotensin system is enhanced during pregnancy and since one of the pathological features of toxemia of pregnancy is that the degree of such enhancement is lower than in normal pregnancy, medication with this series of drugs may be problematic. Furthermore, influences on the fetal kidney and severe oligohydramnios due to decreased fetal urine volume have been reported. Thus, ACE inhibitors are considered to be unsuitable as drugs to be used during pregnancy as an antihypertensive agent. The Captopril<sup>®</sup> package insert states that the drug should not be used in pregnant women. However, it also states that if it is used due to the lack of an alternative, administration should be minimal, and the condition of the fetus and the volume of amniotic fluid should be monitored.

#### **Use of Sedatives and Anticonvulsants**

Sedatives are used for the purpose of lowering blood pressure by rest or to prevent the

onset of eclampsia. Phenobarbital (Phenobal<sup>®</sup>) and chlorpromazine (Contomin<sup>®</sup>) are commonly used sedatives. Since the fetus is also affected, caution is necessary for the diagnosis of fetal distress on the fetal cardiogram.

If eclampsia is imminent or has developed, intravenous administration of diazepam (Cercine<sup>®</sup>) is effective. Combined use of an intravenous drip infusion of magnesium sulfate (Magnesol<sup>®</sup>) is also recommended.

## Other Drugs

### 1. Anticoagulant therapy

Since toxemia of pregnancy is, in a sense, chronic disseminated intravascular coagulation (DIC), anticoagulant therapy is a treatment option for toxemia of pregnancy. Decreased antithrombin III (ATIII) and increased fibrin degradation products (FDP) are common findings, and ATIII supplementation is often required. Gabexate mesilate (FOY<sup>®</sup>) is used when DIC has developed. Attempts to use ATIII and heparin as therapies for toxemia of pregnancy have been reported in recent years.

These therapies are used to inhibit the formation of microthrombi. Aspirin, which has a platelet aggregation-inhibition action, is used to prevent the occurrence of this condition. Usually, Bufferin<sup>®</sup> for children, at a dose of 1 tablet/1 to 2 days, is given. Although the usefulness of this prophylactic method is documented in the high-risk group, the efficacy is not clear in the low-risk group for prevention of toxemia of pregnancy.

### 2. Other drugs used for toxemia of pregnancy

Dipyridamole (Persantin<sup>®</sup>) may be used for the treatment of proteinuria as another drug therapy for toxemia of pregnancy. Chinese herbal medicines such as *Sairei-to* have also been prescribed, but they have not been found to be effective in the treatment of severe toxemia of pregnancy for which drug treatment is generally indicated.

There are a number of reports on the use of

Table 2 Maternal Indications of Pregnancy Termination<sup>2)</sup>

1. Premature delivery or premature rupture of membrane
2. Eclamptic attack or encephalopathy
3. Pulmonary edema
4. Acute renal failure
5. Persistent thrombocytopenia
6. Poor control of maternal blood pressure
7. HELLP syndrome

Chinese herbal medicines in patients with toxemia of pregnancy, such as those documenting that the prophylactic use of *Sairei-to* in patients with a history of severe toxemia of pregnancy was equivalent to aspirin in preventing the onset of another episode of toxemia of pregnancy. However, these are not standard clinical studies using a sufficiently large number of patients or a strict method of double blinding.

## Limitations of Drug Treatment

It is true that drug treatment of toxemia of pregnancy during pregnancy has its limitations, particularly in light of the effect on the fetus. In general, this condition often improves after pregnancy has ended. Therefore, artificial termination of pregnancy may be chosen if the fetus can live outside the uterus, but no absolute guidelines have been set down to help make this choice. The maternal indications for pregnancy termination proposed by Miyake *et al.* are shown in Table 2 as a reference.<sup>2)</sup>

## Conclusion

Drug treatment of toxemia of pregnancy is still restricted to symptomatic therapies. Although it is true that there are many limitations due to considerations of the effect on the fetus and other factors, a favorable prognosis for the mother and the fetus even in severe cases is now becoming achievable with the careful use of drugs.

Better treatment targeted at the cause of tox-

emia of pregnancy including anticoagulant therapy, hopefully will be developed in the future.

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# Establishing the Concept of Visceral Fat Syndrome and Clarifying Its Molecular Mechanisms

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**Abstract:** In atherosclerotic disease, multiple risk factor syndrome characterized by abnormal glucose tolerance, hypercholesterolemia, hypertension, etc., has drawn increasing attention. We show that the accumulation of intraperitoneal visceral fat is the most important factor in the onset of multiple risk factor syndrome and demonstrate the concept of “visceral fat syndrome.” To clarify the molecular mechanism, we studied the biological characteristics of adipocytes and found that it acts to store excess energy as conventionally believed and excretes diverse physiologically active substances such as cytokines, growth factors, compliments etc. PAI-1, related to thrombus formation, was actively synthesized in visceral fat. When visceral fat accumulated, PAI-1 was excreted into the blood and operated to induce factors of atherosclerotic disease. We discovered adiponectin, a collagen-like protein, and showed that it prevents diabetes and atherosclerosis onset. Adiponectin is also shown to markedly decrease in the blood in the obese subjects especially with visceral fat accumulation. We showed that excess and decreased excretion of adipocytokines associated with adipocyte accumulation plays an important role in the onset of multiple risk factor syndrome. We therefore propose an adipocentric hypothesis that places adipocytes at the center of the mechanism underlying common diseases.

**Key words:** Adipocytokine; Adiponectin; Aquaporin adipose; Adipocentric hypothesis

## Introduction

The pathogenesis of atherosclerotic diseases, which are leading causes of death in the Japa-

nese population, involves many factors and is extremely complex. Epidemiological studies have been conducted for many years to identify the risk factors for this group of diseases and to

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clarify the mechanisms involved in the onset and progression of vascular lesions associated with atherosclerotic diseases. To date, elevated serum cholesterol was believed to be the most important risk factor. The significance of increased levels of low-density lipoprotein (LDL), which transports cholesterol, has also been demonstrated. It would not be an exaggeration to state that phenomena that underlie the onset and progression of atherosclerosis, such as expression of adhesion factors on the surface of endothelial cells, migration and proliferation of smooth muscle cells, and cholesterol accumulation in macrophages, have all been clarified primarily through studies focusing on oxidative LDL.

However, studies conducted in Japan to analyze the background of patients with atherosclerotic diseases revealed that there are not many cases in which hypercholesterolemia was found as the only factor related to the disease. More often, a combination of relatively weak risk factors, e.g., hypertriglyceridemia, abnormal glucose tolerance, and hypertension, plays a crucial role in the onset of atherosclerotic diseases, such as myocardial infarction, cerebral infarction, etc. For example, in the study conducted by the Ministry of Labor study group (composed of the author and other investigators), which addressed the host factors involved in the pathogenesis of work-related atherosclerosis, it was found that the risk of development of ischemic heart disease was 30- or more times higher in individuals having three or four of the risk factors, namely, obesity, abnormal glucose tolerance, hypertriglyceridemia, and hypertension, as compared to individuals without any of the four risk factors.<sup>1)</sup>

### **Visceral Fat Accumulation Underlies the Development of the Multiple Risk Factors**

The significance of the multiple risk factor syndrome in the onset of atherosclerotic diseases has been attracting close attention in

Western countries. This syndrome is also called syndrome X, or the death quartet (upper body obesity, diabetes mellitus, hypertriglyceridemia, and hypertension). However, the exact nature of this syndrome, and the mechanism underlying the onset and progression of atherosclerosis associated with this syndrome have not yet been fully clarified.<sup>2)</sup>

Based on the unsupported knowledge that insulin resistance probably underlies its development, syndrome X is sometimes referred to as insulin resistance syndrome. To date, however, it has not yet been established whether insulin resistance, i.e., resistance of cells to the insulin effects, or compensatory hyperinsulinemia in insulin resistant state is responsible for the onset of the multiple risk factors and the development of atherosclerotic vascular lesions. Even assuming that insulin resistance plays an important role in the development of this syndrome, it remains unknown as to how such resistance develops in the first place.

We have been studying the mechanism of development of diseases associated with obesity. Our study was motivated by the finding that while some individuals weighing even up to 200 kg do not show any signs of diabetes mellitus or hyperlipidemia, in others, diabetes mellitus or hyperlipidemia either develop or deteriorate following a body weight increase of only one kg. We considered that it is of crucial importance to explain this difference. In 1983, we reported for the first time, a method of analyzing the volume of adipose tissue *in vivo* using CT scans. This technique does not only allow accurate measurement of the body fat volume (the initial goal of this study), but also the quantification of fat tissue in body lumens.<sup>3)</sup> Our study revealed that the body fat volume determined using this technique is not a superior index for morbidity to the conventional BMI (body mass index) based on body weight. On the other hand, analysis of the fat distribution, in particular, of intraabdominal visceral fat accumulation, has demonstrated that visceral fat accumulation is closely related to the patho-

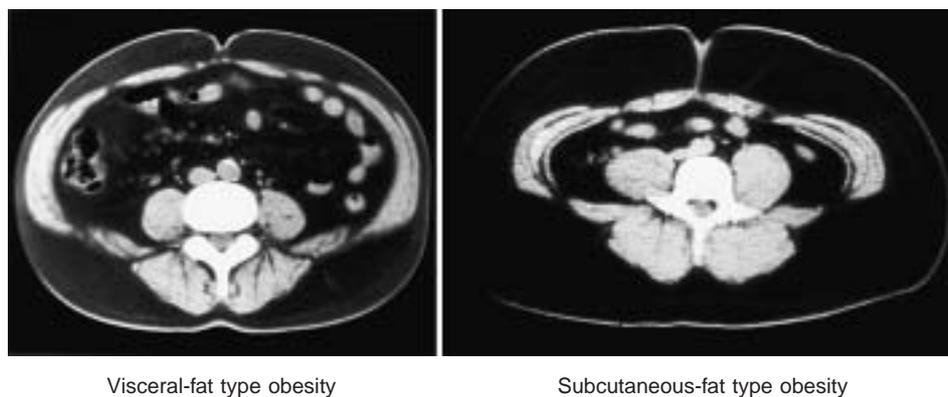


Fig. 1 Analysis of fat by axillary CT scans

Table 1 Conditions Related to Visceral Fat Accumulation

- |   |
|---|
| 1. Diabetes mellitus, insulin resistance<br>( <i>Metabolism</i> 1987; 36: 54, <i>Diabetes Care</i> 1996; 19: 287) |
| 2. Hyperlipidemia<br>( <i>Metabolism</i> 1987; 36: 54, <i>Hepatology</i> 1998; 27: 557)                           |
| 3. Hypertension<br>( <i>Hypertension</i> 1990; 16: 484)   |
| 4. Coronary artery disease<br>( <i>Atherosclerosis</i> 1994; 107: 239, <i>Int J Obes</i> 1997; 21: 580)           |
| 5. Left ventricular dysfunction<br>( <i>Am J Cardiol</i> 1989; 64: 369)   |
| 6. Sleep apnea syndrome<br>( <i>J Int Med</i> 1997; 241: 11)  |

( ) = Reported by the author and his co-workers

genesis of atherosclerotic diseases, as well as the common diseases mentioned above (Fig. 1).

Table 1 lists the diseases associated with visceral fat accumulation, as reported by the author and co-workers to date. Considering that accumulation of visceral fat forms the basis for the development of various risk factors for atherosclerotic diseases (including insulin resistance), the presence of multiple risk factors in the same individual cannot be deemed to be an accidental occurrence. It can probably be explained if we consider that visceral fat accumulation underlies the development of all these risk factors. It has been shown that visceral fat accumulation may be seen not only in obese individuals, but also in individuals of normal weight. It has also been confirmed that even in normal-weight individuals, the accumulation of

visceral fat is associated with abnormal glucose metabolism, hyperlipidemia, etc., and with the development of coronary vascular diseases.<sup>4)</sup> We thus conclude that in both obese and non-obese individuals, visceral fat accumulation serves as the basis for the development of the multiple risk factor syndrome (including resistance to insulin), and propose that the condition therefore be called “visceral fat syndrome”.<sup>5)</sup>

### Pathogenesis of the Visceral Fat Syndrome, with Emphasis on the Molecular Mechanisms Underlying the Development of Atherosclerosis

The visceral fat syndrome can be deemed as being essentially identical to syndrome X, or the deadly quartet. Its pathogenesis has been ex-

plained primarily on the basis of insulin resistance and hyperinsulinemia. However, it is difficult to explain the mechanism of onset of all the risk factors on the basis of insulin resistance or hyperinsulinemia. From the two viewpoints mentioned below, the authors have attempted to clarify the mechanisms by which visceral fat accumulation, which probably underlies the development of insulin resistance, may be involved in the onset of diverse diseases.

### 1. Significance of free fatty acids and glycerol released from adipocytes

It is known that the adipocytes which constitute adipose tissue store excess energy in the form of triglycerides; these triglycerides are hydrolyzed to supply free fatty acids (FFA) and glycerol systemically when energy is needed, or in the case of starvation. This reaction is known to be more active in visceral fat than in subcutaneous fat. As compared to subcutaneous fat, visceral fat allows earlier expression of lipoprotein lipase (LPL) and glucose transporter (Glut4), which are involved in energy uptake, and of acyl coenzyme A (CoA) and acyl synthetase (ACS) which are involved in fat synthesis, in cases of obesity. It is also known that during exercise, the expression of the aforementioned molecules decreases sharply.<sup>6,7)</sup>

We may say that visceral fat cells possess a high potential for synthesizing and decomposing fat, and that in individuals with excess visceral fat, the release of FFA and glycerol, which are products of (triglyceride) hydrolysis, occurs in amounts corresponding to the volume of visceral fat accumulated. Intraperitoneal visceral fat (mesenteric fat) can be anatomically characterized as being in direct linkage with the liver through the portal vein. Therefore, FFA and glycerol, which are released from the visceral fat, flow directly into the liver. It is known that FFA entering the liver stimulate fat synthesis and suppress insulin catabolism, which results in the onset of peripheral hyperinsulinemia.

We have shown that besides acting as a precursor of fat synthesis, FFA also serve as ligands

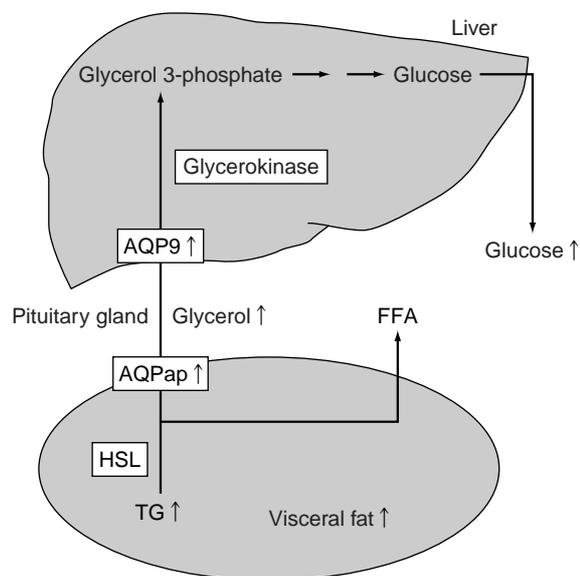


Fig. 2 Enhanced glycerol transfer and glucose release from the liver in the presence of visceral fat accumulation  
HSL: hormone-sensitive lipase  
TG : triglyceride (Source: Reference 10)

for the peroxisome proliferator activated receptor (PPAR)-alpha and hepatic nuclear factor (HNF), which are expressed in the liver, and are involved in the gene transcription of several enzymes such as ACS, in a way similar to other physiologically active substances; these result in enhanced transcriptive activity of microsomal triglyceride transfer protein (MTP, a rate-limiting protein involved in the secretion of very low density lipoprotein, VLDL), and the onset of hyperlipoproteinemia.<sup>8)</sup>

Although glycerol had not attracted attention in this connection before, we discovered an adipocyte-specific glycerol channel (aquaporin adipose, AQPap)<sup>9)</sup> among the genes encoding the expression of proteins in adipocytes. AQPap has been reported to be abundantly expressed in the presence of visceral fat pools and has been shown to play a principal role in the molecular mechanism involved in glycerol release from adipocytes. Aquaporin-9 (AQP9), which had recently been discovered in the liver, serves as a portal of entry for glycerol into the liver. It seems that glycerol, which is released in large

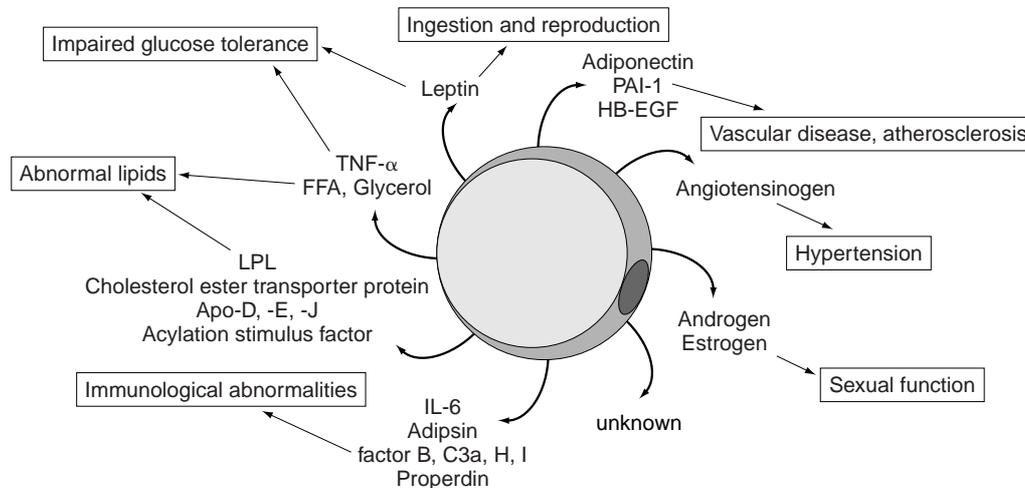


Fig. 3 Physiologically active substance derived from adipose tissue (adiopocytokine) and the adipocentric hypothesis (Source: References 11 and 20)

amounts via AQPap in the presence of visceral fat pools, enters the liver via AQP9, and is converted into glucose by glycerokinase and other enzymes, which are eventually released from the liver. Thus, a new mechanism for the onset of hyperglycemia in the presence of visceral fat pooling was proposed<sup>10)</sup> (Fig. 2).

## 2. Significance of adipocytokine, a physiologically active substance secreted from adipocytes

To elucidate the molecular characteristics of adipocytes, we conducted analyses of genes encoding proteins expressed in adipocytes by means of large-scale random sequencing, in collaboration of the Osaka University Institute for Molecular and Cellular Biology.<sup>11)</sup> Of all the genes encoding protein expression in adipocytes, about 60% remain unknown and novel genes. When the remaining known genes were classified by their function and subcellular localization, it was revealed that an unexpectedly large number of genes encoding secretory proteins are expressed abundantly in adipocytes. Many of these proteins were physiologically active. Genes encoding such proteins accounted for 20% of all genes found in subcutaneous fat tissue and 30% of all the genes found in visceral

fat tissue. It was thus shown that adipocytes, which were conventionally thought of as cells that store energy, are actually endocrine cells.

The physiologically active substances which we named adipocytokines found in visceral fat include: (1) Cytokines such as tumor necrosis factor (TNF)-alpha and interleukin (IL)-6, (2) growth factors such as heparin-binding epithelial growth factor (EGF)-like growth factor (HB-EGF), (3) various complements, (4) factors acting on the fibrinolytic system such as plasminogen activator inhibitor (PAI)-1, and (5) vasopressors such as angiotensinogen. It is considered that an increase or decrease in the volume of adipose tissue, depending on the nutritional status, may alter the secretion of these bioactive substances and affects the host defense system and metabolic regulation, and may thus be related to pathogenesis of diseases (Fig. 3). It has been shown, for example, that excessive expression of TNF-alpha in adipocytes in obese individuals impairs insulin signal transduction and is thus related to insulin resistance and the pathogenesis of diabetes mellitus.

We then paid attention to the expression of PAI-1 in adipose tissue in view of the report that blood PAI-1 levels are elevated in patients with the multiple risk factor syndrome or syn-

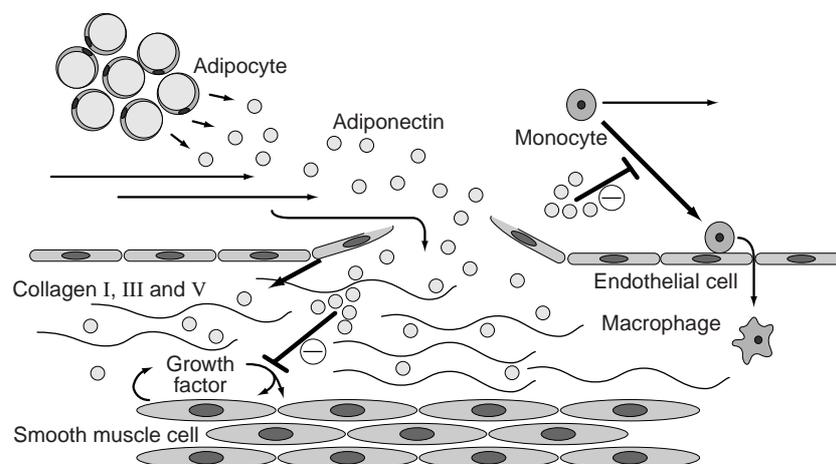


Fig. 4 Antiatherosclerotic actions of adiponectin

Adiponectin, secreted from adipocytes, suppresses the adhesion of monocytes to vascular endothelial cells, interacts with collagen I, III, and C in the subendothelial layer, and suppresses the proliferation of smooth muscle cells stimulated by the growth factor secreted from vascular smooth muscle cells. (Source: References 15 and 16)

drome X, and the fact that PAI-1 has been reported to be closely involved in thrombus formation and the development of atherosclerosis. In our study of clinical cases, a significant positive correlation was found between blood PAI-1 levels and the amount of visceral fat as measured in CT scans. When we studied the expression of the PAI-1 gene in adipose tissue during the course of development of obesity in obese rats, we found that PAI-1 mRNA expression in visceral fat increased markedly as fat accumulated. This suggests the possibility that enhanced synthesis and secretion of PAI-1, which occur in association with visceral fat accumulation, are related to the onset of vascular lesions. This provides a direct mechanism for the onset of vascular lesions in association with the visceral fat syndrome.<sup>12)</sup>

Among the unknown genes detected in adipocytes, a gene specific to adipocytes which was expressed in abundance, was found to encode a secretory protein.<sup>13)</sup> This protein, which was composed of 244 amino acids, possessed a collagen-like motif (G-X-Y), and was homologous to complement C1q, collagen X and collagen VII. We named this protein "adiponectin"

and developed a technique for measuring its levels in the blood. Adiponectin is synthesized and secreted only by adipocytes. Unlike leptin, which is another secretory protein specific to adipocytes, adiponectin is found in lower levels in the blood of obese individuals, and its blood level had a strong negative correlation with the amount of visceral fat accumulation.<sup>14)</sup> It has also been reported that the expression of adiponectin mRNA was markedly decreased in accumulated visceral fat. In addition, plasma levels of adiponectin were lower in patients with diabetes mellitus coronary artery disease when body mass index was matched.

To examine the relationship between low blood adiponectin levels and the development of disease, we conducted a biological study of vascular cells in relation to the pathogenesis of atherosclerosis. The study showed that adiponectin suppresses the expression of adhesion molecules, such as TNF-alpha-dependent vascular cell adhesion molecule (VCAM-1), intercellular adhesion molecule (ICAM)-1 and E-selectin, on vascular endothelial cells. This, in turn, suppresses the adhesion of monocytes to the endothelial cells.<sup>15,16)</sup> Regarding the mo-

lecular mechanisms involved in this action of adiponectin, it has been demonstrated that adiponectin suppresses the phosphorylation of inhibitor- $\kappa$ B (I- $\kappa$ B) and thus regulates the actions of nuclear factor- $\kappa$ B (NF- $\kappa$ B), resulting in suppressed transcription of the aforementioned adhesion molecules. Adiponectin has a strong affinity for binding to collagen I, III, and V, which are matrix proteins found in the vascular wall. In fact, it has been confirmed that adiponectin, which is not normally expressed in the subendothelial layer, was accumulated in the subendothelial layer of the carotid artery of rats following balloon-induced injury of the artery.<sup>17)</sup> In addition to its effects on endothelial cells, adiponectin also acts on vascular smooth muscle cells to suppress their proliferation, and on macrophages to suppress fat accumulation in them.

As described above, adiponectin is secreted from adipocytes into the blood and seems to play a role resembling that of a fireman, i.e., binding to the injured vascular wall to repair them or suppress the onset of atherosclerosis<sup>18)</sup> (Fig. 4). Decreased secretion of adiponectin in the presence of obesity (especially visceral fat accumulation) can facilitate the onset of atherosclerosis.

### Conclusion—Proposal of Adipocentric Hypothesis

We have shown that adipocyte accumulation, especially accumulation of visceral fat, promises to be as an important theme of medical research to clarify the pathogenesis of vascular diseases which is as important target as the pathogenesis of cancer in the 21st century, and have established the disease entity “visceral fat syndrome”. As described in this paper, visceral fat accumulation can promote the development of diverse diseases associated with daily habits or lifestyle through inducing excessive or reduced secretion of adipocyte-derived factors, such as FFA, glycerol and adipocytokines. It is possible that the presence of a combination of these diseases

can lead to the development of atherosclerosis. Another important finding is that abnormal secretion of adipocytokines such as PAI-1 and adiponectin can directly induce vascular lesions.<sup>20)</sup> This probably explains why the visceral fat syndrome may serve as the major basis for the development of atherosclerotic diseases. In conclusion, we emphasize the importance of the adipocentric hypothesis, which places adipocyte accumulation at the center of the mechanisms underlying the onset of various common diseases, including atherosclerosis (Fig. 2).

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# Alcoholic Liver Disease in Women

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**Abstract:** Recently in Japan, the percentage of drinkers among women has increased markedly. Clinical epidemiological studies have demonstrated that women are more susceptible to liver cirrhosis upon exposure to shorter-term and lower alcohol consumption than men. Genetic polymorphism of the genes encoding alcohol dehydrogenase and aldehyde dehydrogenase plays a role in how the Japanese respond to habitual drinking. Alcoholic liver disease in women is characteristically prone to progress to cirrhosis or severe alcoholic hepatitis, even though their genetic backgrounds are the same as those of men. This article reviews recent reports on the greater susceptibility of women to alcoholic cirrhosis and hepatitis.

**Key words:** Alcoholic liver disease; Sex differences; Alcohol dehydrogenase; Sex hormones; Alcoholic cirrhosis

## Introduction

The Ministry of Health, Labour and Welfare launched a campaign named “National Health Promotion Movements of the 21st century (Healthy Japan 21)” and established a sectional committee on alcohol consumption as one of the committees. Aiming to diminish alcohol related health problems, the Ministry set the following three targets: 1) to diminish the number of heavy drinkers drinking greater than 3 go of sake (= 60 g of ethanol) daily on an average; 2) to discourage underage from drinking; and 3) to increase the awareness that “adequate alcohol consumption is approximately

1 go (= 20 g of ethanol) daily.”

The percentage of drinkers consuming greater than 60 g of alcohol (three flagons of beer, 3 go of sake, or three double whiskeys) daily is estimated to be 4.1% of men and 0.3% of women at present. However, a comparison of the percentage of drinkers in 1968 with that in 1987, disregarding the amount of alcohol consumed, shows a marked increase in women drinkers (Fig. 1). Based on this tendency in the drinking population, clinical epidemiological studies have demonstrated that women are more susceptible to alcoholic liver disease developing to alcoholic cirrhosis upon exposure to shorter-term and lower alcohol consumption than men

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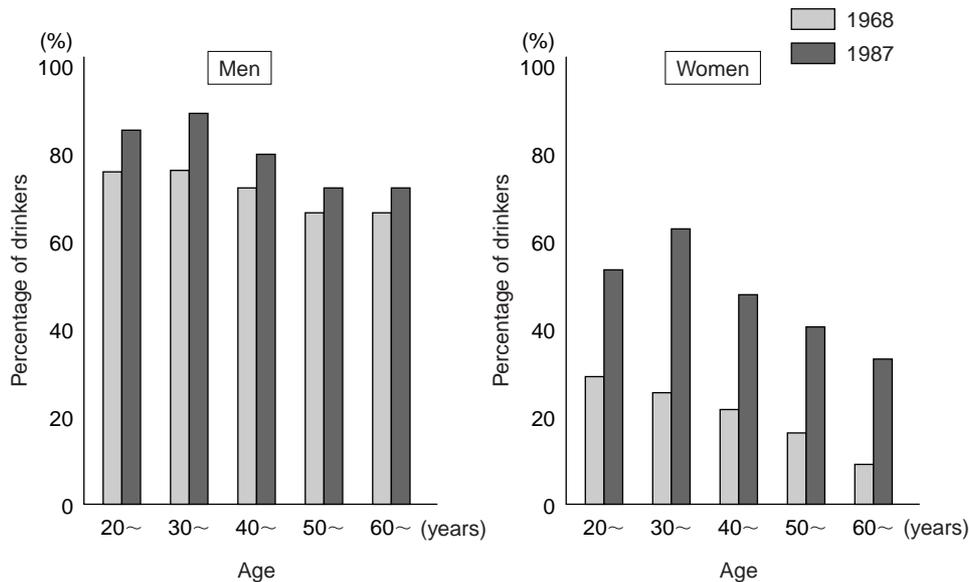


Fig. 1 Comparison of the percentage of drinkers between 1968 and 1987 by gender and age

are, though the number of patients with alcoholic liver disease is higher among men, who are more prone to practice habitual drinking than women due to different social circumstances.

This article reviews recent studies on the characteristics of alcoholic liver disease in women and the causes of the greater susceptibility of women to alcoholic cirrhosis.

### Genetic Backgrounds Relating to the Response to Habitual Alcohol Consumption

How one responds to alcohol consumption depends on the genotypes of two enzymes, alcohol dehydrogenase (ADH2) and aldehyde dehydrogenase (ALDH2). When alcohol is consumed, it is at first metabolized by ADH2 into acetaldehyde, which causes hangovers, and then further metabolized by ALDH2 to acetate. There are three genotypes, types 1/1, 1/2, and 2/2, for each enzyme. There are differences in metabolizing activity of ethanol and acetaldehyde among the types of ADH and ALDH proteins encoded by each genotype. Response to alcohol consumption depends on ALDH2

genotype.

Acetaldehyde metabolism is ranked on the basis of ALDH2 genotypes as follows:  $ALDH2^1/2^1 > ALDH2^1/2^2 > ALDH2^2/2^2$ . Those with the  $ALDH2^1/2^1$  genotype do not present with facial flushing even after consumption of large quantities of alcohol, because acetaldehyde is rapidly metabolized in the body. Acetaldehyde metabolism is moderate in those with the  $ALDH2^1/2^2$  genotype who present with facial flushing when drinking but are capable of habitual drinking. Those with the  $ALDH2^2/2^2$  genotype cannot metabolize acetaldehyde. In these subjects, a rapid accumulation of acetaldehyde in the body causes facial flushing and an unwell feeling, and so they are so-called "lightweights" that cannot drink to any great extent. They are unable to become habitual drinkers and therefore do not develop alcoholic liver disease (Fig. 2).<sup>1)</sup> Those with the  $ALDH2^2/2^2$  genotype cannot drink alcohol because of the onset of uncomfortable symptoms, regardless of the genotypes of ADH2 mentioned below. Thus, the ALDH2 genotypes are the most important genetic factors contributing to an individual response to alcohol consumption.

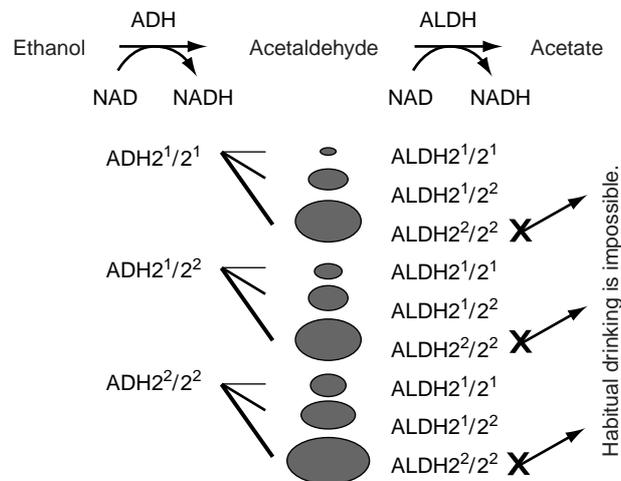


Fig. 2 Relationship between genetic polymorphism of the genes encoding alcohol metabolism-related enzymes and degree of acetaldehyde accumulation (size of circle)

ADH2 genotypes are associated with extensive alcohol consumption and the development of liver disease. Ethanol oxidation (acetaldehyde production) is ranked on the basis of ADH2 genotypes as follows:  $ADH2^2/2^2 > ADH2^1/2^2 > ADH2^1/2^1$ . Those with the last genotype produce the lowest amount of acetaldehyde and are capable of drinking large quantities of alcohol. In fact, individuals with the  $ADH2^1/2^1$  genotype account for approximately 3% of healthy subjects but for as high as 30% of habitual drinkers in Japan. It has been shown that those with the  $ADH2^2/2^2$  genotype are susceptible to liver disease caused by acetaldehyde, due to rapid production of the compound in the body.<sup>2)</sup>

Regarding combinations of the genotypes of the two enzymes, excluding individuals with the  $ALDH2^2/2^2$  genotype who are incapable of habitual drinking, those with any of the six combinations (three genotypes of ADH2  $\times$  two genotypes of ALDH2) are capable of habitual drinking. Concerning alcoholic liver disease in drinkers, the developmental mechanisms can be easily understood in terms of the differences in acetaldehyde accumulation in individuals with the genotype combinations shown in Fig. 2.

### Clinical Epidemiological Results Showing the Higher Susceptibility of Women to Alcoholic Liver Disease

It has been reported that women are more susceptible to alcoholic cirrhosis upon exposure to shorter-term and lower alcohol consumption than men.<sup>3-5)</sup> The initial report was published by Spain in 1945.<sup>3)</sup> In this report, the age on death was compared in 190 male and 60 female patients who were diagnosed with cirrhosis at autopsy. The average age on death was 55.1 years in men and 45.7 years in women, indicating that women are susceptible to cirrhosis at a significantly younger age than men.

In a subsequent cohort study by Wilkinson *et al.*<sup>4)</sup> on patients with alcoholism for 1-year and 5-years, the data for 825 male and 175 female alcoholics were compared. Of these, 69 (8.4%) of men and 29 (16.6%) of women had cirrhosis with the incidence of cirrhosis higher in women. Furthermore, the age that the women started drinking was older than for men, and the average daily alcohol consumption was 265 g in men and 170 g in women. Thus the duration of drinking was 18.8 years in men and 12.6 years in women, therefore showing that female patients

Table 1 Clinical Backgrounds of Male and Female Alcoholics (from a cohort study)<sup>4)</sup>

	Men	Women
Number of alcoholics	825	175
Number of cirrhosis patients	69 (8.4%)	29 (16.6%)
Age at which drinking started	Less than 30 years of age	More than 30 years of age
Average daily alcohol consumption (g)	265 ± 110	170 ± 65
Duration of drinking (years)	18.8 ± 8.1	12.6 ± 11.2
Age at onset of alcoholism (years)	44.7 ± 9.9	48.3 ± 9.9
Number of heavy drinkers	75 (9%)	12 (7%)

\*Mean ± SD unless otherwise specified.

Table 2 Comparison of Daily Alcohol Consumption between Male and Female Cirrhosis Patients<sup>5)</sup>

	Alcohol consumption (g/day)	Cirrhosis patients	Healthy controls	Morbidity index
Men	0~20	10	110	9
	21~40	7	116	6
	41~60	10	141	7
	61~80	10	67	15
	81~100	18	61	30
	101~120	22	21	105
	121~140	18	14	129
	141~180	17	7	243
	181~240	11	3	366
	241~560	21	2	1,050
	Total	144	542	
Women	0~20	23	455	5
	21~40	15	105	14
	41~60	14	24	58
	61~80	11	2	550
	81~220	20	1	2,000
		Total	83	587

progressed to cirrhosis after significantly lower exposure to alcohol for a shorter period of time when compared with male patients (Table 1).

Pequignot *et al.*<sup>5)</sup> reported that daily alcohol consumption was more critical than duration of drinking for progression to alcoholic cirrhosis, and that daily alcohol intake of 60 g or less in men and 20 g or less in women rarely caused alcoholic cirrhosis. These results demonstrated that the level of alcohol consumption considered to be safe was significantly lower in women than men (Table 2).

Also, Norton *et al.* reported that the threshold of daily alcohol consumption that results in cirrhosis was 40 g in women. In the U.S. and Europe, almost all individuals have the active ALDH2<sup>1</sup>/2<sup>1</sup> genotype, whereas 30% of Japanese have the ALDH2<sup>1</sup>/2<sup>2</sup> genotype. In women with the ALDH2<sup>1</sup>/2<sup>2</sup> genotype, the daily alcohol consumption considered theoretically to be safe is estimated at 10 g or less in Japan. Therefore when setting the level of alcohol consumption that is considered to be adequate in Japan, genotypes as well as sex differences should be

well considered.

### **Types of Alcoholic Liver Disease in Women**

Alcoholic liver disease encompasses fatty liver, non-specific change, liver fibrosis, cirrhosis, alcoholic hepatitis, and hepatocellular carcinoma.

A nationwide survey to determine the status of alcoholic liver disease in Japan demonstrated remarkable results on proportions of women with each type of alcoholic liver disease. Women accounted for a larger proportion in alcoholic hepatitis than in the other types of alcoholic liver disease. This characteristic was not observed in men. The incidence of alcoholic hepatitis in women was 16.5% (39 of 236) compared with 9.1% (232 of 2,556) for all types of alcoholic liver disease. The difference was considered to be statistically significant.<sup>6)</sup> Of the various types of alcoholic hepatitis, women frequently develop severe alcoholic hepatitis, which is often complicated by hepatic encephalopathy, pneumonia, acute renal failure, gastrointestinal hemorrhages, or endotoxemia, resulting in death within one month of onset in most cases.

Alcoholic liver disease in women is often accompanied by menstrual irregularity or amenorrhea, symptoms which are different from those associated with viral liver disease. Furthermore, the number of young female patients with alcoholism accompanied by eating disorders such as anorexia nervosa has been increasing recently.

### **The Mechanism of Progression to Cirrhosis Following Shorter-term Exposure to Lower Alcohol Consumption in Habitual Female Drinkers**

I will introduce an interesting case of alcohol cirrhosis that I experienced recently. A male patient with gender disorder had been taking an oral medium-dose contraceptive pill and receiving self-injections of a female hormone preparation with a desire for feminization from

18 years of age. He had been drinking 10 glasses of whiskey with water for four days weekly since the same age. When he began working at a catering establishment at the age of 20, his consumption of alcohol increased further. He was admitted to a hospital for cirrhosis with ascites and esophageal varices at the age of 26, by which time his cumulative alcohol consumption had reached 480 kg. Liver biopsy showed micronodular alcoholic cirrhosis with a fatty change of the liver and pericellular fibrosis. The patient's condition progressed to alcoholic cirrhosis much more rapidly than in other male patients with the disease, based on the age and cumulative alcohol consumption of the patient. This case suggests that when even a man habitually drinks while being administered with female hormones, he becomes susceptible to alcoholic cirrhosis after a shorter time period than would normally be expected.

With respect to the influences of sex differences on the progression of alcoholic liver disease, several studies have been conducted from a viewpoint of the effects of sex differences on alcohol metabolism and also from another viewpoint, that is the reactivity of Kupffer cells to endotoxin. In terms of alcohol metabolism, it has been shown that female rats exhibit a higher activity of liver ADH than male rats, indicative of a higher capacity for alcohol metabolism, i.e. higher acetaldehyde production in females than in males.<sup>7)</sup> However, the activity of gastric mucosal ADH in humans is lower in women than in men,<sup>8)</sup> indicating that the area under the curve showing the blood ethanol concentration is larger in women than in men when they drink the same amount. These differences in alcohol metabolism resulting from sex differences are considered to be factors responsible for the increased sensitivity of women to alcoholic liver disease.

A recent study reporting the influence of estrogen on the reactivity of Kupffer cells to endotoxin has been attracting attention. In 1997, an animal study<sup>9)</sup> demonstrated that female rats developed fatty change, necrosis, or inflamma-

tion in the liver more frequently than did males. This study group used an intragastric tubing model by Tsukamoto and French, a rat model with necrotic/inflammatory cell infiltration and liver fibrosis useful for studying alcoholic liver disease. Furthermore, it was subsequently reported using this model that histological findings of alcoholic liver disease improved after ovariectomy and worsened after administration of estrogen.<sup>10)</sup>

In this model as in humans, blood endotoxin levels increased in alcohol-treated groups. It has been hypothesized that this higher level of endotoxin activates Kupffer cells, which accelerates production of cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), which in turn enhances the expression of intercellular adhesion molecule 1 (ICM-1) in hepatocytes and sinusoidal endothelial cells, resulting in liver disease. This study group has reported that inactivation of Kupffer cells with gadolinium chloride or suppression of endotoxin production with antibiotics (polymyxin B and neomycin) completely prevented alcoholic liver disease in the Tsukamoto-French model.

Compared with male rats, female rats exhibit higher blood endotoxin and TNF- $\alpha$  levels. Female rats also exhibit enhanced expression of myeloid cell-specific leucine-rich glycoprotein (CD14), an endotoxin receptor in Kupffer cells, and of ICAM-1 in the liver, leading to more severe neutrophilic infiltration and necrosis. In consequence, the difference in activation of Kupffer cells between males and females has been pointed out to play an important role in the mechanisms responsible for the more severe alcoholic liver disease in female rats. It has also demonstrated that Kupffer cells cultured with estrogen, enhance expression of CD14 and accelerate production of TNF- $\alpha$ , and that these are correlated with intracellular calcium concentrations.<sup>11)</sup>

According to these reports, estrogen administration in alcoholic liver disease could accelerate activation of Kupffer cells resulting in an increase in the extent of liver injury.

## Comparison of Alcoholic and Non-alcoholic Liver Disease in Women

In chronic viral liver disease due to hepatitis B and C viruses, women develop liver fibrosis more slowly and cirrhosis less frequently than men, showing the opposite clinical result to that in alcoholic liver disease.

A study was conducted to compare the effects of estradiol on liver fibrosis in male and female rats treated with dimethylnitrosamine, a model of liver fibrosis due to chronic viral liver disease. This study demonstrated that administration of high doses of estradiol suppressed fibrosis, and that inactivation of endogenous estradiol with anti-estradiol antibodies aggravated fibrosis in male rats.<sup>12)</sup> In female rats, it was revealed that 1) ovariectomy resulted in fibrosis, 2) administration of high doses of estradiol suppressed fibrosis completely, and 3) estradiol suppressed production of type I collagen in Ito cells that contribute to liver fibrosis.

The similarities between vascular smooth muscle cells involved in arteriosclerosis and Ito cells have been reported for a long time, and it has also been demonstrated that estrogen suppresses fiber formation in vascular smooth muscle cells. Epidemiological surveys have demonstrated that men and postmenopausal women are susceptible to arteriosclerosis, and a similar tendency is also observed in viral liver disease. These results have suggested that estrogen inhibits fibrosis not just in liver cells but also in other cell types.

To date, sex differences in each type of liver disease are partly ascribable to estrogen, which suppresses fibrosis caused by Ito cells in viral liver disease, and enhances the reactivity of Kupffer cells to endotoxin, leading to acceleration of cytokine production in alcoholic liver disease.

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# Present State of Gene Diagnosis and Future Prospects

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**Abstract:** The entire base sequence of the human genome has almost been clarified. In the post genome era of the 21st century, both genetic alterations and epigenetic abnormalities, especially abnormalities in the gene expression caused by methylation of DNA or acetylation of histones can be analyzed easily and quickly with new technology including DNA chip, RNA chip and protein chip. Therefore it is necessary to establish the TNM-G classification with criteria both for genetic abnormalities associated with cancer and precancerous lesions and epigenetic abnormalities. According to the new “TNM-G classification” it is possible to achieve the following: more precise diagnosis; precognition of malignancy, metastasis and recurrence; diagnosis of susceptibility to drugs or cancer and development of new therapies. When a patient with cancer receives the most suitable treatment and prevention based on the characteristics of the patient, the mortality and morbidity rates in this country will decrease by around 2030. In the case of gene diagnosis, the protection of private information at the ethics level and cancer notification must be kept in mind. It is expected that common guidelines on genetic analysis will be drawn up as soon as possible.

**Key words:** Gene diagnosis; Characteristic diagnosis of cancer; Hereditary tumor; TNM-G

## Introduction

The multistage carcinogenesis and the precancerous lesion in each organ was analyzed extensively at the molecular level over the last decades. The results show that abnormality of structure and function in the oncogene, tumor suppressor gene, DNA repair enzyme gene, and other cancer-related genes causes the mul-

tistage process of carcinogenesis.<sup>1)</sup> The combination and order of various kinds of genetic abnormalities depend on the place of carcinogenesis and tissue-type of cancer.<sup>2)</sup> Furthermore, susceptibility to carcinogenesis, sensitivity to the anticancer drug, and drug tolerance can be understood beforehand by analyzing the genetic polymorphism.

Currently, genetic alterations relating to the

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Table 1 Abnormality of the Tumor Suppressor Gene and Cancer

Tumor suppressor gene	Non-hereditary tumor	Hereditary tumor	Gene locus	Function
<i>Rb</i>	Retinoblastoma, lung cancer, breast cancer, osteosarcoma	Familial retinoblastoma	13q14.2	Transcriptional control
<i>p53</i>	Colorectal cancer, breast cancer, lung cancer, and others	Li-Fraumeni syndrome	17p13.1	Transcriptional control
<i>WT1</i>	Wilms tumor	Wilms tumor	11p13	Transcriptional control
<i>APC</i>	Colorectal cancer, stomach cancer	Familial adenomatous polyposis	5q21	beta-catenin, DLG binding
<i>p16</i>	Malignant melanoma, esophagus cancer	Familial malignant melanoma	9p21	CDK inhibitor
<i>NF1</i>	Malignant melanoma, neuroblastoma	Neurofibromatosis type 1	17q11	Activation of GTPase
<i>NF2</i>	Meningioma, neurilemoma	Neurofibromatosis type 2	22q12	Binding to cytoskeleton
<i>VHL</i>	Kidney cancer	von Hippel-Lindau disease	3p26	Transcriptional elongation control
<i>BRCA1</i>		Familial breast cancer	17q21	Transcriptional control
<i>BRCA2</i>		Familial breast cancer	13q12-13	Transcriptional control
<i>DPC-4</i>	Pancreatic cancer	Juvenile polyposis	18q21.1	Transcriptional control
<i>SMAD2</i>	Colorectal cancer		18q21	Transcriptional control
<i>PTEN/MMAC1</i>	Glioblastoma	Cowden disease	10q23	Phosphatase, cell motility
<i>PTC</i>	Basal cell carcinoma of the skin	Gorlin syndrome	9q22	Shh receptor
<i>TSC1</i>		Tuberous sclerosis	9q34	
<i>TSC2</i>		Tuberous sclerosis	16q13.3	
<i>EXT1</i>		Multiple cartilaginous exostosis	8q24	
<i>EXT2</i>		Multiple cartilaginous exostosis	11q13	

(Quoted from reference)<sup>3)</sup>

carcinogenesis and progress of cancer in each organ acts as the most suitable marker for establishing guidelines on the prevention and treatment of cancer. This report describes the genetic abnormalities of the representative cancer and precancerous lesion, as well as the significance and present conditions surrounding gene diagnosis. Finally, we explore future prospects in the area of gene diagnosis and propose a new type of classification in which TNM classification is combined with the gene diagnosis of cancer.

### Genetic Abnormalities in Cancer

Cancer is a disease of the gene that develops through a multistage process of abnormality in genes such as the oncogene, tumor suppressor

gene, and DNA repair enzyme gene according to genetic and environmental factors. The oncogene can be activated by a single mutation in the allele (point mutation, gene amplification, and DNA rearrangement (chromosomal translocation)), or the tumor suppressor gene can be inactivated by two mutations in the allele (referred to as “two hits” and defined in most cases as a point mutation and deletion)

#### 1. Hereditary and familial tumors

Causative genes of hereditary and familial tumors include oncogenes, tumor suppressor genes, and DNA repair enzyme genes, etc. Since these genes are inherited by the reproductive cell, cancer develops frequently within members of the same family (Table 1).<sup>3)</sup> Abnormality of the tumor suppressor gene, especially,

occurs often in the hereditary tumor. In other words, cancer develops from a mutation that occurs in one allele of the reproductive cell of a parent (that is, the first hit) or in the other allele (the second hit).

Hereditary nonpolyposis colorectal cancer (HNPCC), commonly referred to as the Lynch Syndrome, comprises about 10% of all colorectal cancers and is divided into two types. Lynch type I develops only in the large intestine (mainly right colon) while Lynch type II can also develop in the uterus and ovaries. HNPCC arises from gene instability caused by a reproductive cell mutation of the DNA repair enzyme gene (*hMSH2*, *hMLH1*, etc.). Thus far, identified target genes include the TGF-beta II type receptor gene, BAX gene, E2F4 gene, etc. Therefore, it is possible to predict cancer risk and conduct early detection and early treatment by testing for reproductive cell mutation of the tumor suppressor gene and DNA repair enzyme gene.

## 2. Nonheritable tumors

In most human cancers, the mutations of multiple genes including the oncogene and tumor suppressor gene, induced by carcinogens in the environment such as heterocyclic amines and benzo (alpha) pyrene, and radiation, accumulate in one cell, as described above, leading to cancer development. However, there is an unexpectedly lengthy natural history of about 20 years, that functions as a very important preventive measure to cancer. To stop smoking in the younger generation of 10 to 20-year-olds will likely prevent developing into cancer later.

Cancer development through a multistage carcinogenesis process encompasses the following six biological characteristics<sup>4)</sup>: 1. The signal for cell proliferation is continuous. 2. The signal for cell control disappears. 3. Deviate from apoptosis. 4. Maintenance of telomeres or infinite proliferation of cell. 5. Angiogenesis. 6. Invasion or metastatic capability. Cancer metastasis or invasion depends on acquirement of the above six characteristics by the cancer cell. The com-

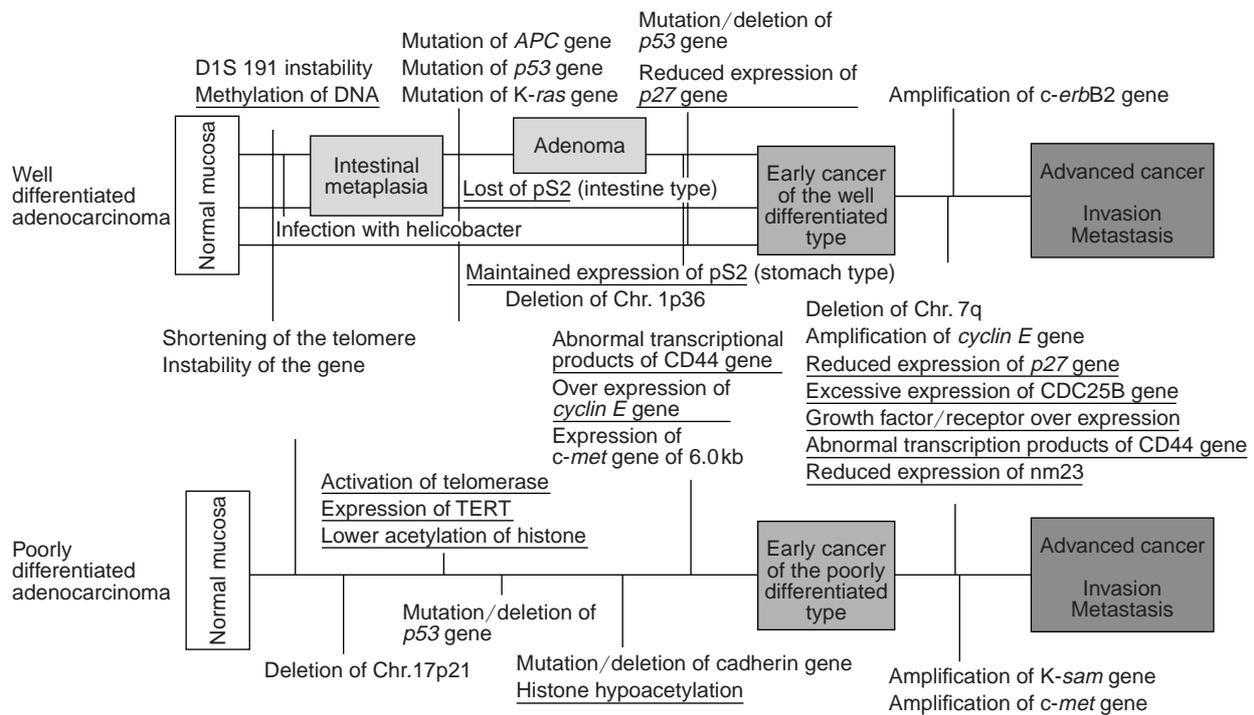
bination of these six characteristics or the order of the carcinogenesis process differs with the place of carcinogenesis and tissue type of cancer. In addition, there are various differentiation levels. Carcinomas and sarcomas differ in gene abnormality. DNA rearrangement (chromosomal translocation) is rarely observed in the carcinoma. On the contrary, there is a known characteristic chromosomal translocation in sarcoma, leukemia, and lymphoma.

The interaction pattern between cancer cell and stroma through growth factor or cytokine also differs significantly depending on the organ.

For example, deletion and mutation of the *PTEN/MMAC 1* gene are observed in 60 percent of malignant gliomas. Furthermore, deletion of the *p16* gene and amplification of the *CDK4* and *EGFR* genes correlate with the progress and malignancy of glioma. In neuroblastoma, one of the representative pediatric tumors, there are clones with different biological properties. In one case, cancer recesses naturally, while in the other case there is a poor prognosis of disease concerning the gene amplification of *MYC*.

Amplification of the *EGFR* and *cyclin D1* genes is reported as a prognostic factor in patients with esophageal cancer, independent from TNM classification. In colorectal cancer, the 18q LOH gene is a separate and important prognostic factor at TNM stage II or TNM stage III. In gastric cancer, gene amplification and excessive expression of the *K-sam* gene is an important prognostic factor. In lung cancer, usually subject to TNM classification in Japan, the mutation of exon 8 in the *p53* gene (especially in codon 273 and the H2 alpha helix) is a prognostic factor for patients with non-small cell lung cancer. In prostate cancer, deletion of the 8p21–22 genes and acquisition of the 8q24 gene occurs frequently. Reportedly, increase in *MYC* copy number and deletion of the 8p22 gene are separate risk factors related to the progress of prostatic cancer at stage III and the cause of death.

The most common genetic abnormality in



(Tahara, 2000)

Fig. 1 Molecular mechanisms of multistage carcinogenesis of gastric cancer

Underlined abnormalities: Observation of the epigenetic abnormalities (The gene is unchanged but the amount or function of the protein is changed by modification at the transcriptional level or after transcription).

human cancer is mutation in the *p53* gene. It is supposed that the tumor cell with a mutated *p53* gene is resistant to apoptosis induced by hypoxia; therefore, cloning of the tumor cell with the mutated *p53* gene is selected for development.

There are various human oncogenic DNA viruses including EBV, HPV, and HBV and various human oncogenic RNA viruses including HCV and HTLV-1. The mechanism of carcinogenesis underlying these viruses differs from that of the chemical carcinogenesis, radiation carcinogenesis, and enzymatic radical carcinogenesis previously mentioned. Generally the viral protein directly binds to another protein produced by a tumor suppressor gene such as the *p53* gene or *Rb* gene, etc. Otherwise the viral protein acts as a transcription factor and plays a role in the expression of various genes including the oncogene and growth factor, etc.,

leading to malignant transformation of the cell.

### Genetic Abnormality in Precancerous Lesions

The genetic abnormalities observed in cancer are frequently detected in the precancerous lesion. Molecular analysis of the multistage carcinogenesis of lung cancer shows that in the smoker, LOH of the 3p and 9p21 genes frequently appears in the bronchial epithelium, which is observed as morphologically normal, after which LOH of the 13q (*Rb*) gene and 17p (*p53*) gene appears. In addition, many chromosomal deletions are detected in 30–40% of ductal hyperplasias in the mammary gland. LOH of the 3p and 9p genes and inactivation of the *p16* gene relates to the carcinogenesis of atypical epithelia of the head, cervix, or esophagus.

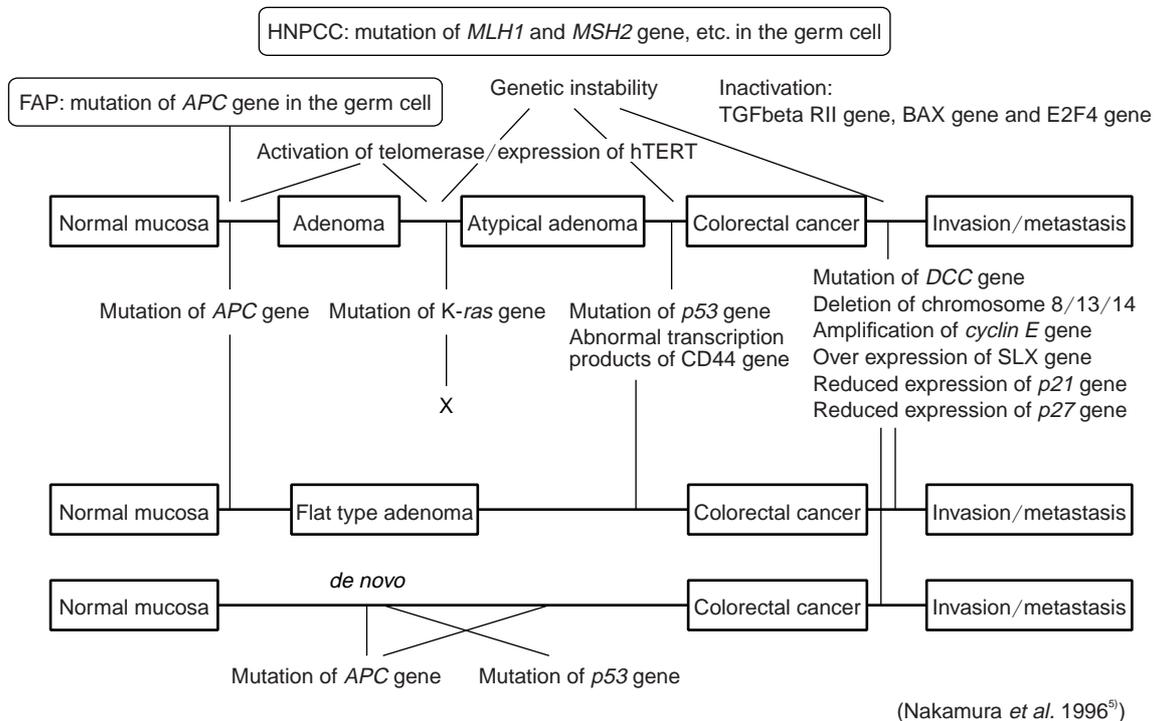


Fig. 2 Molecular mechanisms underlying colorectal cancer

The same genetic abnormality observed in intestinal-type gastric cancer is observed in at least 30% of intestinal metaplasias of the stomach. In other words, there is an observed shortening of the telomere, instability of the DIS 191 gene, and mutation of the *APC* gene and *p53* gene (Fig. 1).<sup>6)</sup> In various adenomas of the large intestine, mutation of the *K-ras* gene, *APC* gene, and *p53* gene develop frequently. It is the mutation of *p53* that plays an important role in the malignant transformation from these precancerous lesions (Fig. 2).<sup>7)</sup>

By introducing the genetic abnormalities found in precancerous lesions into practical medicine, it is possible to distinguish between benign and malignant lesions, and to identify malignant transformation of the precancerous lesion and high risk. While it is possible to decrease the incidence of cancer by improving lifestyle, another method of preventing cancer is based on gene diagnosis.

## Significance and Present Condition of Gene Diagnosis

Gene diagnosis is of clinical significance in the following five ways. 1) Differential diagnosis between benign and malignant lesions can be carried out. 2) A property diagnosis or quality diagnosis of cancer (malignancy, prognosis, evaluation of susceptibility to chemotherapy and radiation therapy) can be carried out. 3) Diagnosis of the existence and type of cancer can be carried out. 4) Identification of the hereditary tumor and risk diagnosis in the precrisis stage can be carried out. 5) A new treatment for cancer can be developed.

Gene diagnosis in Japan is mainly carried out by identifying 4 items in the hereditary tumor and assessing risk at the precrisis stage. We have routinely practiced molecular pathological diagnosis (gene diagnosis) of digestive tract cancer in cooperation with the Hiroshima Medical Association since 1993.<sup>7,8)</sup> According to genetic abnormalities of the *p53* gene and

*APC* gene, 10% of the gastric adenomas from 1,132 cases were diagnosed as gastric adenoma with a high potential of malignancy. Genetic abnormality of the *p53* gene and gene instability were detected in 22% of gastric borderline lesions that could not be distinguished histologically as regeneration, metaplasia, or cancer and were diagnosed as cancer. Over expression of the *C-erbB2* gene, *c-met* gene, and *cyclin E* gene and deletion of the *p27* gene were observed in 12% of the 2,822 cases of gastric cancer (80% of these cases were early cancer (T1N0M0)), and were detected as highly malignant gastric cancer. Analysis of genetic instability in 700 cases of gastric cancer showed that 4% of the cases revealed a high frequency of genetic instability (MSI-H) and half of these were identified as simultaneously or separately generated multiple cancers. However, since this is a novel system of gene diagnosis that provides information to enable future diagnosis at the genetic level of gastric tract cancer, there must be further evaluation and follow-up of the prognosis.

### Proposal of TNM-G Classification

Based on our current knowledge of genetic alteration and gene diagnosis of cancer, the establishment of a TNM-G method of classification, which includes TNM classification<sup>9)</sup> and genetic alteration in cancer, is supported by the UICC (Union Internationale Contre le Cancer) committee for practical cancer medicine in the 21st century. Our goal is to construct an international method of evaluation and standard of prognostic factors based on concrete reasoning by integrating information from the TNM system with the analysis of genetic information of cancer. TNM-G classification will support “order-made-therapy” or “tailored therapy” based on a diagnosis of characteristics at the insistence of a clinician and a surgeon. Thus, it is necessary to organize a UICC committee for the discussion of “G” as soon as possible.

### Future Prospects

The entire base sequence of the human genome has almost completely been elucidated. Therefore, in the post genome era of the 21st century, both genetic alteration and epigenetic abnormality, especially abnormalities in gene expression caused from the methylation of DNA or acetylation of histone, can be analyzed easily and in a short period of time with new technology including a DNA chip, RNA chip, and protein chip.<sup>10)</sup> For this purpose, TNM-G classification must be established using the criteria of both genetic abnormalities by cancer and precancerous lesions and epigenetic abnormalities. According to the new “TNM-G classification”, it is possible to formulate a more precise diagnosis, have a precognition of malignancy, metastasis, and recurrence, determine susceptibility to drugs or cancer, and develop new therapies. Once the cancerous patient is introduced to the most suitable method of treatment and prevention based on the characteristics of the cancer, the mortality rate and the morbidity rate around the year 2030 will decrease in this country.

In the case of gene diagnosis, the protection of private information on an ethical level and cancer notification must be reinforced. It is expected that common guidelines on genetic analysis will be formed as soon as possible.

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# Gastric Cancer

## —Prevention and Early Diagnosis—

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**Abstract:** The morbidity rate of gastric cancer in Japan has gradually decreased and with the increase in number of early gastric cancer, post-therapeutic results have greatly improved. The factors responsible for these phenomena include the decreased incidence of gastric cancer as a result of primary prevention and early detection by secondary prevention. In terms of dietary factors, salt promotes carcinogenesis, whereas green and yellow vegetables, fruit, and green tea suppress it. It is important for the prophylaxis of carcinogenesis to consume abundant fresh vegetables and fruits and to avoid hyperchloric diet. *Helicobacter pylori* has been implicated in cancer cell proliferation after cancerization. The significance of mass examination for early detection is attracting much attention, but it is not economically feasible in many countries. Occult blood reaction, tumor markers, and a forward endoscope with a small diameter are superior to mass examination in making the diagnosis in terms of specificity, and they are more economical. The kind and characteristics of typical early gastric cancer cases and important points in diagnosis are outlined for the protruding type (0-I, 0-IIa), depressed type (0-IIc, 0-III), and flat type (0-IIb). In the treatment of early gastric cancer, surgical procedures for reduction, such as endoscopic mucosal resection (EMR) and partial resection of the stomach under laparoscopic observation, may be used, contributing to an improved quality of life for the patient.

**Key words:** Gastric cancer; Cancer prevention; Early diagnosis; Early treatment

### Introduction

The incidence of gastric cancer is the highest among cancers of various organs in Japan, with approximately 100,000 people per year suffering from this form of cancer. As a result of the

increased incidence of early gastric cancer and advances in therapeutic methods, the survival rate has improved, and the mortality rate associated with gastric cancer is now lower than that associated with lung cancer.<sup>1)</sup> The reasons for this decreased morbidity have been thought

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Table 1 Preventive Factors and Risk Factors for Gastric Cancer, Which Are Related to Diet  
— Summary from epidemiological studies by observation —

	Preventive factors	Risk factors
Certain factors	Vegetables and fruits The prevalence of refrigerators	
Almost certain factors	Vitamin C	Salt, Salty foods
Possible factors	Carotenoids Allium compounds included in vegetables of Welsh onions Unrefined grains Green tea	Starch Grilled meat Grilled fish
Inadequate evidence	Fiber Selenium Garlic Cow's milk	Smoked meat Nitroso compounds

Besides the factors related to diet, cigarette smoking, infection with *H. pylori*, and others have been considered to be risk factors for gastric cancer. World Cancer Research Fund, American Institute for Cancer Research: Food, Nutrition and the Prevention of Cancer: a Global Perspective. American Institute for Cancer Research, Washington, 1997. (Cited from a report by Tsugane.<sup>5)</sup> Partially modified)

to include changes in the Japanese diet and methods of food preservation. Attention is being paid to the correlation between gastric cancer and *Helicobacter pylori* as well as to the secondary prevention of cancer.

In treating early gastric cancer cases, EMR laparoscopic partial resection of the stomach, and other procedures have been employed, contributing to improvement in patients' post-operative quality of life (QOL). The prevention and early diagnosis of gastric cancer are important for QOL as well as patient outcome. If secondary cancer could be prevented post-operatively, the eradication of gastric cancer would be a distinct possibility. This article outlines the prevention and early diagnosis of gastric cancer.

## Prevention of Gastric Cancer

### 1. Primary prevention

The procedures for gastric cancer prevention can be divided into primary and secondary types. As a result of a case-control study (CCT) of gastric cancer and a cohort study of gastric cancer patients, diet and methods of food pres-

ervation have been attracting attention as means of primary prevention.<sup>2)</sup>

It is noteworthy that a high salt diet is correlated with gastric cancer, whereas salt itself is not carcinogenic. High concentrations of salt have been considered to disrupt the mucosal layer of the stomach to promote mucosal cell damage from gastric fluid and to cause inflammation that promotes carcinogenesis.<sup>3)</sup> Basic studies have revealed that vitamin C, carotenoids, and other components of green and yellow vegetables, fruit, and green tea exert an inhibitory effect on carcinogenesis via their antioxidative action.<sup>4)</sup>

In terms of methods of food preservation, the prevalence of refrigerators has increased the consumption of fresh vegetables and fruits. Furthermore, the indirect influences of decreased consumption of salty foods and protection of the gastric mucosa by increased consumption of cow's milk have been considered to be related to the primary prevention of gastric cancer.<sup>5)</sup>

The risk of gastric cancer among cigarette smokers has been reported to be 2–3 times higher than that in non-smokers, and the corre-

lation of the risk of cancer in the cardiac part of the stomach with cigarette smoking appears to be particularly high.<sup>6)</sup> It is therefore important for the prevention of gastric cancer to ingest plenty of fresh vegetables and fruits, particularly those with carotenoids and vitamin C, and to avoid the ingestion of salty foods and a hyperchloric diet (Table 1).

It is noteworthy that a correlation exists between *H. pylori* and the occurrence of gastric cancer, because *H. pylori* is involved in the development of chronic atrophic gastritis and the initial stage of gastric mucosal damage. *H. pylori* infection is present in 90% and 32% of differentiated and undifferentiated gastric cancer cases, respectively.<sup>7)</sup> Subsequent studies, however, have indicated that *H. pylori* may promote the proliferation of cancerized gastric cancer cells, based on the concept that *H. pylori* exerts a carcinogenic effect by inducing carcinogenic substances or DNA impairment of gastric mucosal epithelial cells.<sup>8)</sup> Therefore, the eradication of *H. pylori* has been thought to be effective in patients in whom the possibilities of secondary prevention of cancer and residual gastric cancer developing after gastrectomy are indicated.<sup>9)</sup>

## 2. Secondary prevention (early detection)

Secondary prevention means (mass) examination of cancer. X-ray photography is mainly used in mass examinations for gastric cancer, and many other medical resources have been employed. Odds ratios for mass examination of the stomach are approximately 0.3–0.6, suggesting that the mortality rate is slightly decreased by secondary prevention. Secondary prevention is generally not well suited for other countries because of its high cost. In the present situation in which the morbidity rate is decreasing annually, secondary prevention is being reconsidered.

As possible substitutes for X-ray photography of the stomach, screening and other procedures using occult blood reaction, tumor markers, and forward endoscopes with a small

diameter are considered to be excellent in terms of sensibility and specificity and to be more economical.

## Diagnosis of Early Gastric Cancer

The diagnosis of early gastric cancer is based on close examination of a high-risk group, which includes cancer medical examination. The definitive diagnosis of gastric cancer has conventionally been made by endoscopy and biopsy, as well as X-ray photography of the stomach, which is the main examination. Owing to the prevalence of forward endoscopes with a small diameter and electron scopes, the number of institutions in which endoscopic examination is the first choice even in the stage of screening is increasing. The incidence of early gastric cancer tends to increase annually and exceeds 70% in institutions where it is high. Morphologically, the incidence of type I early gastric cancer is decreasing, whereas those of type IIa, small gastric cancer (10mm in size), Borrmann 4 type, and multiple cancers are tending to increase. Therefore, much attention should be paid to these cancer types on medical examination. Ultrasonic endoscopic examination may be employed to examine mural invasion and mural lymph node metastasis, while macroendoscopic examination may be used to predict histological type.

Representative types of early gastric cancer, their characteristics, and important points in diagnosis are described below.

### 1. Protruded type of early gastric cancer (0-I, 0-IIa)

While it is not difficult to diagnose distinctly protruded lesions (type I), greater attention is needed for only slightly protruded type IIa lesions, as they are likely to be obscured because of hyperextension. The contrast method using pigment dispersion is useful for making the diagnosis, and the following points should be examined: (1) Presence or absence of frequent occurrence, (2) elevation of lesions, (3)

size and thickness, (4) superficial properties (presence/absence of central depression, properties and size of constituent granules, and color tone), and (5) properties of the peripheral mucosa. Lesions of 2 cm or more in size are commonly malignant and show an irregular surface. They are nodular and show uneven rubor. Hemorrhage may be occasionally associated with the lesions. Lesions must be differentiated from gastric adenoma, polyp, takoibo (varioliform) erosion, intestinal metaplasia, and hyperplastic changes, but most cases of gastric adenoma are 2 cm or less in size, and the superficial granules are irregular. Most of them do not show difference in size, and have a faded color.

Adenoma has conventionally been included in the category "atypical epithelial lesion". Many adenoma cases coexist with cancers, although adenoma is fundamentally benign. In other words, EMR and other procedures are needed for the following lesions, because it is highly likely that they will be malignant: lesions with a high proportion of protruded components, which correspond to type I early gastric cancer; lesions whose center shows a coarse structure, depressed and destructed foci, lesions of 2 cm or more in size, and lesions that show morphological changes during observation of the course. When a lesion is diagnosed as group III on biopsy, it should be carefully observed every 3–6 months.

## **2. Depressed type of early gastric cancer (0-IIc and 0-III)**

Ulcers are associated with some type IIc lesions (UI) and not others. The incidence of UI is high. If deformation of the stomach wall, convergence of mucosal folds, and white moss are observed at the depressed site, the lesion can be diagnosed. Mucosal folds invaded with cancer are slightly more depressed than the non-cancerous mucosa, and show a moth-eaten appearance. The following findings are also observed at the end of the afferent side of the convergence of mucosal folds: discontinuity or

rupture, stair-like depression, tapering off (thinning), clavate enlargement, and others.<sup>1)</sup> The stump of the mucosal folds is depressed inward.<sup>2)</sup> Of these malignant findings, the moth-eaten appearance is considered to be most reliable. The depressed site in the center frequently shows changes in which small granules with rubor, erosion with white moss, and slight bleeding coexist. When an open ulcer is associated with the depressed type, the diagnosis is difficult to make, since the histological inflammatory reaction of the ulcer obscures malignant findings and characteristic malignant findings are scarce. In such cases, the presence/absence of malignant findings needs to be confirmed at a site of peripheral mucosa distant from the ulcer.

## **3. Flat type of early gastric cancer (0-IIb)**

Type IIb lesions are classified as single (a lesion without another lesion) or combined (a lesion accompanying another lesion). The former is difficult to diagnose, and diagnosis is made only after slight rubor, a faded color, erosion, and the depressed surface of the mucosa have been observed and an accurate biopsy has been conducted. Lesions that are difficult to differentiate from gastritis are divided according to color tone into those mainly showing rubor and those mainly showing a faded color. The former type are frequently poorly demarcated, while the latter are commonly clear. In terms of histological type, the incidence of undifferentiated cancer tends to be high in the type mainly showing a faded color, while that of differentiated adenocarcinoma is high in the type mainly showing rubor. It is important in making the diagnosis to be careful to notice X-ray photographic and endoscopic findings of only slight deformation and minute abnormal findings on the mucosal surface, which include small granular protrusions and depressed sites.

## **Conclusions**

Among the mucosally invaded cancers (m

cancers), the following are the current indications for EMR; differentiated protruded or flat type of 2 cm or less in size; depressed type of 1 cm or less in size; and undifferentiated type of 5 mm or less in size, with which UI is not associated (–). In the case of surgery for submucosally invaded cancers (sm cancers), gastrectomy with laparoscopy conducted as a supplementary procedure and pylorus-preserving gastrectomy omitting lymph node dissection can be employed. The early diagnosis of gastric cancer is significant in that the patient's outcome and QOL may be markedly improved by minimal surgical invasion. Primary prevention as a prophylactic measure to counteract secondary cancer may be expected from the aspect of prophylaxis of relapse and the occurrence of double cancers.

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# Liver Cancer

## —Prevention and Early Diagnosis—

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**Abstract:** Primary liver cancer occurs mainly as a result of chronic liver disorders due to hepatitis virus infection. The important thing in preventing liver cancer is to prevent hepatitis virus infection and eliminate hepatitis virus in chronic hepatitis patients. In order to eliminate hepatitis virus in chronic viral hepatitis, therapies with interferon or recently introduced lamivudine are indicated for hepatitis B patients, and therapies with interferon and combination of interferon and ribavirin are indicated for hepatitis C. However, there exist patients for whom antiviral therapy is ineffective or not beneficial, and drugs to control inflammation act to delay onset of liver cancer in such patients. In patients of the high-risk group for liver cancer such as those with advanced chronic hepatitis or cirrhosis, early diagnosis of liver cancer is essential. For this purpose, it is recommended to perform cancer screening regularly by diagnostic imaging using ultrasonic examinations of the abdomen and measurements of liver cancer markers such as AFP or PIVKA-II.

**Key words:** Liver cancer; Hepatitis virus;  
Ultrasonic examination of the abdomen; Tumor markers

### Introduction

There are two types of liver cancers; primary carcinoma and metastatic tumor. The incidence is higher for the latter than for the former in clinical medicine. In prevention and early diagnosis of liver cancer, however, the focus is on primary carcinoma. According to the Japanese Ministry of Welfare & Health statistics, death by primary liver cancer is 34,000 in 1999, showing a gradual but steady increase. According to the report<sup>1)</sup> of the follow-up study for 1996–

1997 by the Japanese Study Group of Liver Cancer, 95% of primary liver cancer is hepatocellular carcinoma, followed by 3.4% of cholangiocarcinoma, and less than 1% of carcinomas of mixed origin, cystic liver carcinoma, hepatoblastoma, and sarcoma, respectively. Autopsy findings reveal that cirrhosis is concurrently found in 77% of hepatocellular carcinoma, and chronic liver disease in 93% including chronic hepatitis and hepatic fibrosis. Sixteen percent of hepatocellular carcinoma is HBs antigen positive, 75% is HCV antibody

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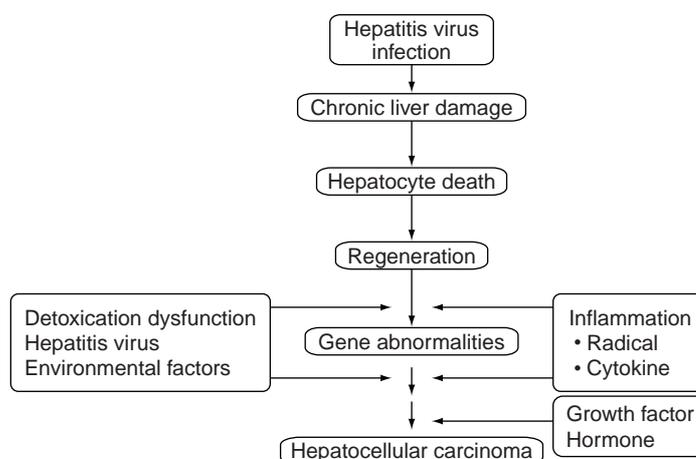


Fig. 1 Pathogenesis of hepatocellular carcinoma by hepatitis virus infection

positive, and at least 90% accompanies viral hepatitis. Hepatocellular carcinoma is found more in men than in women at the ratio of 3:1. No relation with viral hepatitis or sex difference is observed in liver cancers other than hepatocellular carcinoma.

Based on the above, the target for prevention and early diagnosis of liver carcinoma is mainly hepatocellular carcinoma that is accompanied by viral hepatitis.

### Prevention of Hepatocellular Carcinoma

Understanding the pathogenesis of hepatocellular carcinoma is essential for its prevention. Many studies indicate the pathogenesis of hepatocellular carcinoma as shown in Fig. 1. Since most hepatocellular carcinomas occur as a result of chronic viral hepatitis, preventing hepatitis virus infection leads to prevention of hepatocellular carcinoma.

Persistent infection with hepatitis B virus develops as a result of infection before the child is two years old, particularly by vertical transmission at the time of birth. Because of the prevailing practice in Japan of administering anti-HBs human immunoglobulin and hepatitis B vaccine to neonates of mothers who are

HBs-antigen positive, there are hardly any new cases with persistent hepatitis B in recent years. About 10% of persistent hepatitis B patients progress to chronic hepatitis, 20–30% of whom progress to cirrhosis, who then develop hepatocellular carcinoma. Therefore, elimination of virus or controlling hepatitis in chronic hepatitis B patients means prevention of hepatocellular carcinoma.

However, genes of hepatitis B virus are characteristically integrated into host genes, and if the site where genes are integrated is involved in carcinogenesis, hepatocellular carcinoma occurs without persistent hepatitis. It is reported that interferon therapy, steroid withdrawal therapy, or their combination, and administration of propagermanium targeting at elimination of hepatitis B viruses can be expected to succeed in 10–40% of the cases, particularly in cases with a smaller amount of virus and a high transaminase level.

In those with past history of jaundice or cirrhosis, these therapies cause severe liver damage by augmented immune responses, leading to hepatic insufficiency in some cases. Lamivudine, a recently introduced drug, is an anti-viral drug without function of immunomodulation and its administration for a year achieves virus exclusion in about 10%, normal-

ization of transaminase in about 60%, HBV DNA lowering, and transaminase improvement in about 80%,<sup>2)</sup> indicating that this will be the drug of first choice in treatment of chronic hepatitis B in the near future. This drug sometimes develops emerging of resistant viruses, and careless suspension may lead to rapid increase of viruses and severe hepatitis. To chronic hepatitis patients with a high transaminase level for whom anti-viral drug is ineffective or cirrhotic patients for whom anti-viral drug is not indicated, drugs acting on the liver such as 'Strong Neo Minophagen C' or urusodesoxycholic acid are administered.

Except for a few sporadic cases, there are hardly any new hepatitis C virus infection thanks to the use of disposable medical tools and hepatitis virus screening for blood transfusion. As for development of hepatocellular carcinoma in hepatitis C patients, only those with chronic liver disorders develop carcinoma since this virus is not integrated into the host gene.<sup>4)</sup> The cancer incidence is higher in those in whom liver fibrosis is more advanced, and 8% of cirrhotic patients develop hepatocellular carcinoma in a year.<sup>3)</sup> Accordingly, chronic hepatitis patients with liver damage and cirrhosis patients are needed to be treated.

Interferon is administered in anti-viral treatment for chronic hepatitis C, with only 20 to 30% successfully responding by sustained elimination of viruses. Less than 10% of those with Type 1 hepatitis C virus, which is highly prevalent in Japan, can successfully and persistently eliminate viruses with the current method of administration. While patients whose viruses have been eliminated successfully hardly develop liver carcinoma, there is an opinion that those patients, for whom virus elimination cannot be expected, should be given treatment since cancer development is restrained in those whose transaminase was normalized even temporarily<sup>4)</sup> as in the case of sustained transaminase normalization. A report overseas mentions improvement in those with Type 1 hepatitis C viruses by combining ribavirin with inter-

feron. Introduction of ribavirin in Japan is awaited.

Lowering of transaminase is attempted by administration of drugs acting on the liver of chronic hepatitis C patients for whom interferon is not at all effective or cirrhotic patients for whom interferon therapy is not indicated as in the case of chronic hepatitis B patients.

### Early Diagnosis of Hepatocellular Carcinoma

Patients with chronic liver diseases belong to a high-risk group for hepatocellular carcinoma and should be followed up regularly for early diagnosis. For regular follow-up, diagnostic imaging and measurement of tumor markers are used. For diagnostic imaging, the abdominal ultrasonography plays an important part. For those whose liver cannot be fully imaged by abdominal ultrasonography or whose echograms are too crude to image lesions clearly, contrast CT or MRI is performed.

Alfa-fetoprotein (AFP) and PIVKA-II are used as tumor markers for hepatocellular carcinoma. About 30 to 40 % of chronic liver diseases with hepatocellular carcinoma of less than 3 cm in diameter show more than 200 ng/ml of AFP that is hardly observed in chronic liver disorders without hepatocellular carcinoma. In advanced hepatocellular carcinoma showing a lesion greater than 6 cm in diameter, AFP is less than 200 ng/ml in about 25%. On the other hand, the positive ratio for hepatocellular carcinoma of less than 2 cm diameter measured by high sensitivity PIVKA-II is 40–50%, indicating the utility is about the same as that of AFP. However, the sensitivity of tumor markers for detecting hepatocellular carcinoma is lower than that of diagnostic imaging, and its utility in hepatocellular cancer screening is less than that of diagnostic imaging. It is thus more useful for monitoring treatment. There exists a fraction with different lectin-affinity in AFP, and L3 fraction is highly specific for hepatocellular carcinoma. In some patients with slightly elevated

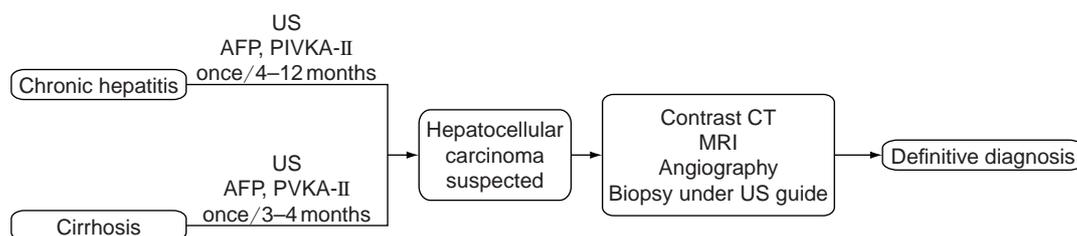


Fig. 2 Follow-up for chronic liver disease patients

AFP, L3 fraction is reported to increase before hepatocellular carcinoma is detected by diagnostic imaging.<sup>5)</sup>

In the follow-up of those with sustained hepatitis virus infection, abdominal ultrasonography and measurement of AFP or PIVKA-II once in six to twelve months are recommended for those with normal liver functions and chronic hepatitis with mild liver damage, once in four to six months for those with chronic hepatitis with advanced fibrosis, and once in three to four months in cirrhosis patients (Fig. 2).

Those in whom a tumor is detected in the liver by screening should be given contrast CT, MRI, angiography, CT with angiography, or biopsy of tumor if necessary in order to select the treatment policy.

## Conclusion

The basic step for preventing hepatocellular carcinoma are 1) to prevent hepatitis B and C virus infections, 2) to eliminate hepatitis viruses from chronic hepatitis patients, and 3) to control hepatitis.

Hepatocellular carcinoma usually occurs by reflecting the degree of liver fibrosis, and the

basis for early diagnosis is the regularly performed abdominal ultrasonography, complemented by AFP and PIVKA-II measurements.

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