Case 10 (Non-obese persons)

In this medical examination, your test results for indicators of diabetes were normal.

You should continue to undergo regular medical checkups to monitor your health condition.

*Source: "Evidence-based Practice Guideline for the Treatment of Diabetes in Japan 2010 (in Japanese only)," and "Treatment Guide for Diabetes 2012-2013 (in Japanese)".

It was ensured that the recommendations conformed to the recommended level of health guidance and medical treatment of the specific health guidance service.

Example expressions to advise people to stop smoking

* Please use a combination of the messages listed in the following two sections.

1. Messages to emphasize the importance of quitting smoking

Case 1 Persons with increased blood pressure

Smoking and hypertension are the two leading causes of death among the Japanese. People who smoke and who have hypertension have a four-fold greater risk of dying from a stroke or heart disease as compared with those who do not have hypertension and a smoking habit. Considering your medical checkup results, it is recommended that you should stop smoking.

Case 2 Persons with hyperlipidemia

Smoking decreases the level of good cholesterol (high-density lipoprotein, HDL) and increases the levels of neutral fat (triglycerides) and bad cholesterol (low-density lipoprotein, LDL) in the blood. A combination of smoking and hyperlipidemia aggravates arteriosclerosis and increases the likelihood of a cerebral or myocardial infarction. Considering your medical checkup results, it is recommended that you should stop smoking.

Case 3 Persons with hyperglycemia

Smoking increases blood glucose levels, and increases the likelihood of diabetes by about 1.4 times. This is the result of the increase in sympathetic tone caused by smoking, which results in an increase in blood glucose. Moreover, smoking impairs the effectiveness of insulin, a hormone secreted by the pancreas. Furthermore, a combination of smoking and diabetes aggravates arteriosclerosis and increases the risk of dying from a cerebral or myocardial infarction by about 1.5–3 times (as compared to the risk of those who do not smoke). In addition, renal function is more likely to be impaired. Considering your medical checkup results, it is recommended that you should stop smoking.

Case 4 Persons with the metabolic syndrome

Smoking decreases the level of good cholesterol (high-density lipoprotein, HDL) in the blood and increases the level of neutral fat (triglycerides) and glucose. These conditions accelerate the development of metabolic syndrome. A combination of smoking and metabolic syndrome aggravates arteriosclerosis and increases the likelihood of a cerebral or myocardial infarction by about 4–5 times (as compared to the risk of those without metabolic syndrome and a smoking habit). Considering your medical checkup results, it is recommended that you should stop smoking.

Case 5 Persons without the above abnormalities

In this medical checkup, your blood pressure, lipid levels, and blood glucose were all within the normal limits. However, if you continue to smoke, you may be at higher risk of developing certain cancers, including lung cancer, and other conditions such as cerebral or myocardial infarction, diabetes, and chronic obstructive pulmonary disease (COPD), and subsequently, you will not be able to maintain the present satisfactory conditions. Considering your medical checkup results, it is recommended that you should stop smoking.

2. Recommending effective ways to quit smoking

Case 1 Persons who intend to stop smoking immediately (within one month), or those who are motivated to stop smoking after hearing the above messages

You can stop smoking by yourself but visiting a smoking cessation clinic or using smoking cessation aids will help you stop smoking relatively easily, and you will not have to worry about nicotine withdrawal symptoms. These antismoking strategies are 3–4 times more successful than the unaided strategy. If your antismoking therapy is covered by health insurance, you can receive the therapy at a hospital, at a monthly cost as low as one-third or half of the money you may spend on cigarettes (if you smoke 20 cigarettes a day).

Case 2 Persons who do not intend to stop smoking

While you currently do not plan to stop smoking, you may be motivated to do so in the future. When you do, you should remember the following advice.

You can stop smoking by yourself, but visiting a smoking cessation clinic or using smoking cessation aids will help you stop smoking relatively easily. These antismoking strategies are 3–4 times more successful than the unaided strategy. If your antismoking therapy is covered by health insurance, you can receive the therapy at a hospital, at a monthly cost as low as one-third or half of the money you may spend on cigarettes (if you smoke 20 cigarettes a day).

[References]

- 1. Ikeda N., et al. Adult mortality attributable to preventable risk factors for non-communicable diseases and injuries in Japan: a comparative risk assessment. PLoS Med 2012; 9: e1001160.
- 2. Hozawa A., et al. Joint impact of smoking and hypertension on cardiovascular disease and all-cause mortality in Japan: NIPPON DATA80, a 19-year follow-up. Hypertens Res 2007; 30: 1169-1175.
- 3. Craig WY., et al. Cigarette smoking and serum lipid and lipoprotein concentrations: an analysis of published data. Br Med J. 1989; 298: 784-788.
- 4. U.S. Department of Health and Human Services. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General, 2010.
- 5. Willi C., et al. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis.

- JAMA 2007; 298: 2654-2664.
- 6. Cryer PE., et al. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. N Engl J Med 1976; 295: 573-577.
- 7. Chiolero A., et al. Consequences of smoking for body weight, body fat distribution, and insulin resistance. Am J Clin Nutr 2008; 87: 801-809.
- 8. Sasaki A., et al. A Follow-up Study of Non-Insulin-Dependent Diabetic Patients (NIDDM) over a Mean Period of 15 Years. Journal of the Japan Diabetes Society 1996; 39: 503-509.
- 9. Al-Delaimy WK., et al. Smoking and mortality among women with type 2 diabetes: The Nurses' Health Study cohort. Diabetes Care. 2001; 24: 2043-2048.
- 10. De Cosmo S., et al. Cigarette smoking is associated with low glomerular filtration rate in male patients with type 2 diabetes. Diabetes Care. 2006; 29: 2467- 2470.
- 11. Nakanishi N., et al. Cigarette smoking and the risk of the metabolic syndrome in middle-aged Japanese male office workers. Ind Health 2005; 43: 295-301.
- 12. Higashiyama A., et al. Risk of smoking and metabolic syndrome for incidence of cardiovascular disease-comparison of relative contribution in urban Japanese population: the Suita study. Circ J 2009; 73: 2258-2263.
- 13. Kasza KA., et al. Effectiveness of stop-smoking medications: findings from the International Tobacco Control (ITC) Four Country Survey. Addiction 2013; 108: 193-202.
- 14. The Japanese Circulation Society, The Japan Lung Cancer Society, Japanese Cancer Association, The Japanese Respiratory Society. Standard operation procedures for smoking cessation therapy Ver. 5. 2012. (in Japanese)

Example expressions to notify findings related to urine protein

*Use these expressions for people without serum creatinine measurements

[Classification of medical checkup results and advice]

| Medical checkup results | | Advice | |
|-------------------------|--------------------------------------|---|--|
| Abnormal | Urine protein: positive (1+/2+/3+) | 1) Seek medical attention promptly. | |
| ↑ | Urine protein: slightly positive (±) | 2) Visit a hospital for reexamination of the urine. | |
| ↓ Normal | Urine protein: negative (-) | 3) Receive regular medical checkups. | |

What does "chronic kidney disease (CKD)" mean?

CKD is a pathological condition in which a positive result from the urine protein test or deterioration in renal function [glomerular filtration rate (GFR) $< 60 \text{ ml/min/1.73 m}^2$] continues for more than 3 months.

[Example expressions to explain the results to the concerned persons]

Case 1 Urine protein (≥ 1+): positive test

According to the medical checkup results, you are strongly suspected of having advanced chronic kidney disease (CKD). Please visit a hospital promptly.

As compared to persons without CKD, those with CKD have a 10-fold greater risk of progressing to terminal renal failure, which requires dialysis therapy. In addition, their risk of stroke/cardiovascular diseases, including angina pectoris and myocardial infarction, and of dying from these diseases is more than twice that of persons without CKD. These risks, however, can be reduced by appropriate treatment; therefore, early initiation of treatment is recommended.

Case 2 Urine protein (\pm) : slightly positive test

According to the medical checkup results, the possibility that you may have chronic kidney disease (CKD) cannot be ruled out. You should have your urine reexamined. If the reexamination reveals a "positive (+) test for protein," you need to receive treatment immediately. As a precaution, <u>please go to a hospital for reexamination of the urine.</u>

As compared to persons without CKD, those with CKD have a 10-fold greater risk of progressing to terminal renal failure, which requires dialysis therapy. In addition, their risk of stroke/cardiovascular diseases, including angina pectoris and myocardial infarction, and of dying from these diseases is more than twice that of persons without CKD. These risks can be reduced by appropriate treatment; therefore, getting early

treatment is of great importance.

Case 3 Urine protein (-): negative test

According to the medical checkup results, your renal function seems to be normal.

You should continue to undergo regular medical checkups to monitor your health condition.

If you meet any of the conditions mentioned below (*), you may be predisposed to developing CKD. As compared to persons without CKD, those with CKD have a 10-fold greater risk of progressing to terminal renal failure, which requires dialysis therapy. In addition, their risk of stroke/cardiovascular diseases, including angina pectoris and myocardial infarction, and of dying from these diseases is more than twice that of persons without CKD

To reduce your risk of developing CKD, you should improve your dietary habits and manage your obesity, if applicable. Persons with hypertension should reduce salt intake. Smoking cessation is also important.

(*) Risk factors for CKD:

Obesity, metabolic syndrome, hypertension, diabetes, hyperlipidemia, hyperuricemia (under treatment or requiring treatment), family history of CKD, abnormal findings in past urinalysis, and old age (≥ 65 years).

Example expressions to notify the findings related to urine protein and serum creatinine

*Use these expressions for people with serum creatinine measurements

[Classification of medical checkup results and advice]

| Medical checkup results (Unit for eGFR: ml/min/1.73 m²) | | Urine protein (-) | Urine protein (±) | Urine protein ≥ 1+ |
|---|------------|-----------------------------------|---------------------------------|-----------------------|
| Abnormal | eGFR < 50 | 1) Seek prompt medical attention. | | |
| ↑ | eGFR 50–59 | 3) Improve your lifestyle. | 2) Visit a hospital | |
| Normal | eGFR≥60 | Undergo regular medical checkups. | for reexamination of the urine. | |

What does "chronic kidney disease (CKD)" mean?

CKD is a pathological condition in which a positive result on the urine protein test or deterioration in renal function [glomerular filtration rate (GFR) $< 60 \text{ ml/min/1.73 m}^2$] continues for more than 3 months.

How is renal function [glomerular filtration rate (GFR)] assessed?

The GFR estimation (eGFR) is based on serum creatinine, age, and sex.

Normal eGFR is about 100 ml/min/1.73 m².

[Example expressions to explain the results to the concerned persons]

Case 1 [Urine protein (+) or eGFR < 50]

According to the medical checkup results, you are strongly suspected of having advanced chronic kidney disease (CKD). <u>Please visit a hospital promptly.</u>

As compared to persons without CKD, those with CKD have a 10-fold greater risk of progressing to terminal renal failure, which requires dialysis therapy. In addition, their risk of stroke/cardiovascular diseases, including angina pectoris and myocardial infarction, and of dying from these diseases is more than twice that of persons without CKD. These risks, however, can be reduced by appropriate treatment; therefore, early initiation of treatment is recommended.

Case 2 [eGFR \leq 50 and urine protein (\pm)]

According to the medical checkup results, the possibility that you may have chronic kidney disease (CKD)

cannot be ruled out. You should have your urine reexamined. If the reexamination reveals a "positive (+) test for protein," you need to receive immediate treatment. As a precaution, please visit a hospital for a urine reexamination.

As compared to persons without CKD, those with CKD have 10-fold greater risk of progressing to terminal renal failure, which requires dialysis therapy. In addition, their risk of stroke/cardiovascular diseases, including angina pectoris and myocardial infarction, and of dying from these diseases is more than twice that of persons without CKD. These risks, however, can be reduced by appropriate treatment; therefore, receiving early treatment is of great importance.

Case 3 [eGFR 50–59 and urine protein (-)]

According to the medical checkup results, you are strongly suspected of having chronic kidney disease (CKD). As compared to persons without CKD, those with CKD are more likely to suffer from terminal renal failure and require dialysis therapy. In addition, they are at a higher risk of developing stroke/cardiovascular diseases, including angina pectoris and myocardial infarction, and of dying from these diseases.

The results of your urinalysis indicate no urgent hazardous condition, but further aggravation of CKD must be prevented. Therefore, you should make an effort to improve your dietary habits and manage your obesity, if applicable. If you suffer from hypertension, make an effort to limit your salt intake. Smoking cessation is also important.

To confirm if your lifestyle improvements are leading to desirable results, you should undergo regular medical checkups.

Note: If you are younger than 40 years, these data suggest that your renal function is inferior to the renal function of most people of the same age. Therefore, you should seek appropriate medical attention. In this case, you are likely to develop chronic kidney disease.

Case 4 [eGFR \geq 60 and urine protein (-)]

The medical checkup results indicate that you are not very likely to have chronic kidney disease (CKD).

However, you should continue to undergo regular medical checkups to monitor your health condition.

However, if you meet any of the conditions shown below (*), you may be predisposed to developing CKD. To prevent this, you should improve your dietary habits and manage your obesity, if applicable. Persons with hypertension need to reduce their salt intake. Smoking cessation is also important.

(*) Risk factors for CKD:

Obesity, metabolic syndrome, hypertension, diabetes, hyperlipidemia, hyperuricemia (under treatment or requiring treatment), family history of CKD, abnormal findings in a past urinalysis, and old age (≥ 65 years).

[Reference] Risk levels corresponding to the numerical data as compared to the persons without CKD (Unit for eGFR: ml/min/1.73 m²)

| Risk of requiring dialysis therapy due to | Urine protein | | |
|---|----------------|-----------|-------------|
| terminal renal failure | (-)-(±) | (+) | (2+)-(3+) |
| eGFR < 50 | 50–1,000 times | 300 times | 2,000 times |
| eGFR 50–59 | | 50 times | 150 times |
| eGFR ≥ 60 | | 10 times | 20 times |

| Risks for developing cardiovascular diseases and of dying from them | Urine protein | | |
|---|---------------|---------|-----------|
| | (-)-(±) | (+) | (2+)-(3+) |
| eGFR < 50 | 3–8 times | 3 times | 8 times |
| eGFR 50–59 | | 3 times | 4 times |
| eGFR ≥ 60 | | 2 times | 3 times |

[References]

- 1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39(2 Suppl 1): S1-266.
- 2. Imai, E., M. Horio, et al. Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. Clin Exp Nephrol 2007; 11: 156-163.
- 3. Matsuo, S., E. Imai, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009; 53: 982-992.
- 4. Levey, A. S., P. E. de Jong, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2011; 80: 17-28.
- 5. Japanese Society of Nephrology. Evidence-based Clinical Practice Guideline for CKD 2012, Tokyo Igakusha, Tokyo, 2012. (in Japanese)
- 6. "Health guidance material for prevention of progression of CKD," Research project for prevention of kidney disease supported by MHLW Scientific Research Grant (Study on how specific medical checkup and specific health guidance should be promoted to prevent progression of CKD) 2012. (in Japanese)

Example expressions to notify the findings related to uric acid

*Use these expressions for people with uric acid measurements

Note: These example expressions have been prepared on the assumption that the persons do not complain of any common symptoms such as lower limb joint pain in gouty arthritis.

If the persons complain of any pain, advise them to visit a hospital for appropriate treatment.

[Classification of medical checkup results and advice]

| Medical checkup results (Unit: mg/dL) | | Advice | |
|---------------------------------------|-------------------------|--|--|
| Abnormal | Serum uric acid ≥ 8.0 | 1) First, try to improve your lifestyle. If your serum uric acid does not improve with these lifestyle changes, you should seek medical attention. | |
| Î | Serum uric acid 7.1–7.9 | 2) You should improve your lifestyle. | |
| Normal | Serum uric acid 1.5–7.0 | 3) You should continue to undergo regular medical checkups. | |
| ↓ Abnormal | Serum uric acid < 1.5 | 4) You should seek medical attention. | |

[Example expressions to explain the results to the concerned persons]

Case 1 (Serum uric acid $\geq 8.0 \text{ mg/dL}$)

The results of this medical checkup indicate that you suffer from hyperuricemia. If you leave it untreated, you may develop gouty arthritis (also called "gout") and experience strong lower limb joint pain. In addition, a high level of serum uric acid increases the risk of developing renal disorder, urinary lithiasis, and metabolic syndrome.

First, you should improve your lifestyle and resolve your obesity. For example, you can improve your dietary habits by decreasing your intake of sugar. In addition, you need to exercise regularly to increase your activity level. Sufficient intake of water is also important. Because alcoholic beverages increase serum uric acid level, irrespective of whether they contain purines, you should limit your consumption of any kinds of alcoholic beverages.

You should make an effort to improve your lifestyle. Then, you should continue to undergo regular medical checkups to monitor your health condition. However, it may be that even after implementing lifestyle improvements, your serum uric acid level may exceed 9.0 mg/dl. In such a situation, you are advised to receive drug therapy. You should visit a hospital and show the results of this medical checkup to your physician.

Case 2 (Uric acid 7.1–7.9 mg/dL)

This medical checkup result indicates that you suffer hyperuricemia. Your test results indicate that you are not at an immediate risk of developing gouty arthritis (also called "gout"). However, in the future, you may develop this condition, which is often accompanied by strong lower limb joint pain. In addition, high levels of serum uric acid increase the risk of developing renal disorder, urinary lithiasis, and metabolic syndrome.

First, you should improve your lifestyle and resolve your obesity. For example, you can improve your dietary habits by decreasing your intake of sugar. You should also exercise regularly to increase your activity level. Sufficient intake of water is also important. Because alcoholic beverages increase serum uric acid level, irrespective of whether they contain purines, you should limit your consumption of any kinds of alcoholic beverages.

You should continue to undergo regular medical checkups to monitor your health condition.

Case 3 (Uric acid 1.5–7.0 mg/dL)

The results of this medical checkup indicate that your serum uric acid is within the normal limits.

You should continue to undergo regular medical checkups to monitor your health condition.

Case 4 (Uric acid < 1.5 mg/dL)

This medical checkup result indicates that your serum uric acid is extremely low.

If you are receiving drug treatment for some disease, the dose may need to be adjusted. You should see your primary care doctor and show the results of this medical checkup.

If you are not currently receiving any drug treatment, the uric acid excretion from your kidney may be excessive. If left untreated, this may result in acute renal failure or urinary lithiasis. You should visit a hospital and show the results of this medical checkup to your doctor to undergo a complete medical checkup.

[References: Serum uric acid levels and treatment plans]

- 1. Campion EW, Glynn RJ, DeLabry LO: Asymptomatic hyperuricemia; Risks and consequences in the Normative Aging Study. Am J Med 82:421-6, 1987
- 2. Johnson RJ, Kang DH, Feig D, et al.: Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 41: 1183-90, 2003
- 3. Alderman MH, Cohen H, Madhavan S, et al.: Serum uric acid and cardiovascular events in successfully treated hypertensive patients. Hypertension 34: 144-50, 1999
- 4. Hoshoya T, Kono H, Ikeda H, et al.: A Study of prognosis of asymptomatic hyperuricemia. Journal of the Japan College of Rheumatology; 25: 369-371, 1985 (in Japanese)
- 5. Shoji A, Yamanaka H, Kamatani N: A retrospective study of the relationship between serum urate level and recurrent attacks of gouty arthritis; Evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum 51: 321-325, 2004

- 6. Li-Yu J, Clayburne G, Sieck M, et al.: Treatment of chronic gout. Can we determine when urate stores are depleted enough to prevent attacks of gout? J Rheumatol 28: 577-580, 20001
- 7. Sarawate CA, Patel PA, Schumacher HR, et al: Serum urate levels and gout flares; Analysis from managed care data. J Clin Rheumatol 12: 61-65, 2006

[References: guidelines]

- 1. Committee for creation of Japanese guideline for the management of hyperuricemia and gout: Guideline for the management of hyperuricemia and gout (first edition). Tokyo, Japanese Society for Gout and Nucleic Acid Metabolism, 2002. (in Japanese)
- 2. Committee for creation of Japanese guideline for the management of hyperuricemia and gout: Guideline for the management of hyperuricemia and gout (second edition). Medical Review Co., Ltd., Tokyo, 2010. (in Japanese)
- 3. Committee for creation of Japanese guideline for the management of hyperuricemia and gout: Guideline for the management of hyperuricemia and gout (supplement to Ver. 2). Medical Review Co., Ltd., Tokyo, 2012. (in Japanese)
- 4. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken). 2012 Oct; 64(10): 1431-46.

