Core Studies at the Sportology Center

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Two core studies were performed this decade at the Sportology Center. The first was the Sportology Center Core Study, in which we investigated the pathogenesis of metabolic disorders in non-obese individuals and found that insulin resistance in muscle may be a primary cause of metabolic diseases in non-obese Japanese men. The second is the ongoing Bunkyo Health Study, a prospective cohort study of elderly subjects in an urban community. This second study is designed to clarify the association of muscle mass, muscle strength, and muscle insulin sensitivity with the major diseases and risk factors leading to the need for long-term care. We believe that the results of these 2 core studies have provided valuable information for extending healthy lifespans.

Key words: insulin resistance, intramyocellular lipid, intrahepatic lipid, physical activity, long-term care, sarcopenia

Introduction

The Sportology Center was established at Juntendo University in 2007 as a center for achieving preventive medicine through exercise and sports. Various researchers in this center have contributed to 2 core studies for disease prevention. In the first of these, the Sportology Center Core Study, we investigated the pathogenesis of metabolic disorders in non-obese individuals. The aim of the second study, the Bunkyo Health Study, is to clarify the evidence for the prevention of long-term care in elderly people living in Bunkyo city. This review describes the contents of these 2 core studies.

Sportology Center Core Study

1. Background

Insulin resistance is induced by obesity and is considered to be an important cause of metabolic

abnormalities in obesity¹⁾. Previous studies suggested that circulating free fatty acids (FFAs) are one factor linking obesity and insulin resistance²⁾. On the other hand, recent studies using proton magnetic resonance spectroscopy (¹H-MRS) showed that circulating FFAs may cause ectopic fat accumulation in muscle³⁾ and liver⁴⁾, and ectopic fat is associated with insulin resistance in both tissue types⁵⁾. Thus, in the process of body fat accumulation, FFAs are gradually released from adipose tissue and then accumulate as ectopic fat, subsequently inducing insulin resistance by inhibiting insulin signaling.

In Asian countries, even non-obese Asians (<25 kg/m²) readily develop metabolic diseases such as metabolic syndrome and type 2 diabetes⁶⁾⁻⁸⁾. Thus, the World Health Organization has suggested that in Asians, overweight should be defined as a body mass index (BMI) ≥ 23 kg/m², and obesity as BMI ≥ 25 kg/m²⁹⁾, although in other ethnicities the definitions are BMI ≥ 25 kg/m² and BMI ≥ 30 kg/m².

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However, the role of insulin resistance in metabolic diseases in non-obese Asians has not been fully understood. Thus, over the past 2 decades, we initiated several studies to identify the mechanisms underlying metabolic diseases in non-obese Asians.

2. Development of techniques to assess ectopic fat and insulin resistance

Research on ectopic fat and insulin resistance in humans has been greatly facilitated by the development of ^1H -magnetic resonance spectroscopy (MRS). This method is a non-invasive means of separately measuring intramyocellular lipid (IMCL) and extramyocellular lipid (EMCL)¹⁰⁾. Lipids in skeletal muscle exist in two forms: IMCL and EMCL (adipose tissue), and previous studies demonstrated that IMCL, rather than EMCL, causes insulin resistance by impairing insulin signaling. ^1H -MRS is also applied for the measurement of intrahepatic lipid (IHL).

A technique to evaluate insulin resistance has also been developed. Insulin sensitivity was initially determined using a radioactive isotope to measure endogenous glucose production (EGP); however, a newer approach now uses a stable isotope (e.g., $[6,6-^2\text{H}_2]$ glucose), and this method has recently been commonly employed in Japan. Using a 2-step hyperinsulinemic euglycemic clamp with a stable isotope-labeled glucose tracer, we can separately evaluate insulin sensitivity in muscle and liver¹¹⁾. In addition, with a protocol involving infusion of low amounts of insulin, adipose tissue insulin sensitivity can be also measured¹²⁾.

In the Sportology Center Core Study, we used these two techniques, ^1H -MRS and 2-step hyperinsulinemic euglycemic clamp to evaluate metabolic conditions in humans.

3. How does intracellular lipid accumulate in muscle?

Using the ^1H -MRS method, several studies demonstrated that IMCL accumulation was closely associated with insulin resistance¹³⁾⁻¹⁵⁾. Although the mechanisms of IMCL accumulation are not yet fully understood, many studies have demonstrated that acute FFA elevation could acutely increase

IMCL level and decrease insulin sensitivity^{3) 16)}. Because circulating FFA elevation in obesity is associated with increased FFA release from adipose tissue¹⁷⁾, obesity may induce muscle insulin resistance through elevated FFAs and subsequent IMCL accumulation.

Other causal factors for IMCL accumulation may be reduced mitochondrial function^{18) 19)}, a high-fat (HF) diet, and lower physical activity level^{3) 20)-23)}. To identify factors that increase the likelihood of IMCL accumulation after a HF diet, we recruited 50 non-obese men and provided a HF diet for 3 days^{24) 25)}. Our data suggested that low daily physical activity with low fitness level and reduced mitochondrial content in muscle may be risk factors for post-diet IMCL accumulation^{24) 25)}. In addition, physical activity was shown to rapidly decrease IMCL levels in healthy subjects^{20) 26)}. Furthermore, 2-week calorie restriction with exercise (mainly brisk walking) decreased IMCL levels by 19% and increased peripheral insulin sensitivity by 57% in patients with type 2 diabetes, whereas these changes were not observed under calorie restriction without exercise²³⁾. In addition, the changes in physical activity levels were negatively correlated with changes in IMCL levels²³⁾.

Based on these findings, we theorized that IMCL accumulation and insulin resistance could be induced by HF diet, lower activity, lower fitness level, and lower mitochondrial level, and that their development would be independent of obesity. Thus, these factors may also contribute to insulin resistance and metabolic abnormalities in non-obese Asians, which was a primary hypothesis of the Sportology Center Core Study.

4. Insulin resistance as a central pathogenic mechanism underlying metabolic diseases in non-obese Japanese

Against this background, we developed the Sportology Center Core Study, a prospective observational study to support hypothesis-driven, hypothesis-generating research on the mechanisms underlying metabolic abnormalities in non-obese subjects²⁷⁾. We registered 114 subjects in the study and performed a 2-step (10 and 20 mU/m² body

surface area per minute) hyperinsulinemic euglycemic clamp study to precisely evaluate insulin sensitivity in muscle, liver, and adipose tissue. Based on research in this cohort, we reported several articles^{27)–32)} and associated studies^{33)–37)}. One of the main findings of the Sportology Center Core Study was that impaired insulin sensitivity occurred in muscle, but not in liver, in subjects with a BMI of 23–25 kg/m² (overweight subjects) who had as few as 1 cardiometabolic risk factor. Muscle insulin sensitivity in overweight subjects was correlated with visceral fat area, fitness level, daily physical activity, high molecular weight (HMW) adiponectin, protein intake, fat intake, and C-reactive protein level.

These data suggested that insulin resistance in muscle is important in the pathogenesis of metabolic disease in non-obese individuals, and physical activity and dietary composition, as well as moderate adiposity and low-grade inflammation, may cause insulin resistance in this population.

5. Other pathogenic mechanisms underlying metabolic diseases in non-obese Asians

1) Hyperinsulinemia

We found that insulin resistance in muscle could be an important pathogenic cause of metabolic diseases in non-obese Japanese; however, it remains to be determined when and why these metabolic diseases start. Initial steps preceding insulin resistance may be impaired insulin clearance and hyperinsulinemia^{32) 38)}. The metabolic clearance rate of insulin (MCRI) is calculated by the ratio of the insulin infusion rate to the insulin level elevated by exogenous insulin³²⁾. In animal³⁹⁾ and human⁴⁰⁾ studies, hyperinsulinemia during a HF diet occurred as a result of impaired insulin clearance rather than increased insulin secretion. In addition, a genetically modified animal model revealed that impaired insulin clearance secondarily induced obesity and insulin resistance as well as hyperinsulinemia^{41) 42)}. We addressed the role of insulin clearance in the Sportology Center Core Study in non-obese, apparently healthy Japanese men³²⁾. The results suggested that subjects with a low MCRI were characterized by moderate fat accumulation, low fitness level, hyperinsulinemia, and impaired insulin sensitivity in muscle but not in liver. In addition, the moderate insulin resistance in

muscle seemed to be fully compensated for by elevated insulin levels secondary to the decreased MCRI.

Endogenous insulin secretion, like insulin clearance, contributes to hyperinsulinemia. For example, exogenous insulin infusion impairs endogenous insulin secretion in a negative feedback system; however, this impairment is blunted in subjects with obesity and insulin resistance. Interestingly, we recently found that endogenous insulin secretion during hyperinsulinemic euglycemic clamp was not well suppressed by exogenous insulin in several non-obese, healthy subjects²⁹⁾ who were characterized by moderate insulin resistance in skeletal muscle.

Taken together, hyperinsulinemia can occur in apparently healthy subjects without significant insulin resistance due to impaired insulin clearance and impaired feedback inhibition of endogenous insulin secretion. These changes may constitute a method of compensating for moderate insulin resistance in muscle; however, it is also possible that these changes may subsequently induce an insulin-resistant state as well as weight gain^{41)–43)}.

2) Lipid spillover

A previous study revealed that greater adiposity was associated with lower accumulation of subcutaneous fat and higher accumulation of visceral fat in East Asians compared with other ethnic groups, including white, black, Hispanic, and Southeast Asian⁴⁴⁾. Thus, it has been suggested that in non-obese Asians, FFAs are readily released from adipose tissue by a slight increase in body fat accumulation, a phenomenon known as “lipid spillover”^{45) 46)}. Release of FFAs from adipose tissue is suppressed by insulin; however, in obese subjects, this effect of insulin is blunted by reduced adipose tissue insulin sensitivity (ATIS). We recently revealed that even some non-obese, apparently healthy Japanese men had reduced ATIS, and were characterized by moderate adiposity, moderate IHL accumulation, lower insulin clearance, and muscle insulin resistance⁴⁷⁾. We supposed that a percent body weight of ~20% may be the threshold for lipid spillover in Japanese men. We also found that non-obese Japanese men with fatty liver were characterized by insulin resistance in adipose tissue and muscle³⁰⁾. Similar observations

were found in non-diabetic, non-obese Japanese men²⁷⁾ and in non-obese Japanese with type 2 diabetes⁴⁸⁾. Thus, it is proposed that fatty liver results from muscle insulin resistance and alters the metabolic pathway of ingested carbohydrates away from skeletal muscle glycogen synthesis into de novo hepatic lipogenesis^{49) 50)}. Considering the fact that circulating FFAs directly cause muscle insulin resistance, liver fat accumulation⁴⁾, and reduced insulin clearance⁵¹⁾, lipid spillover may play an important role in insulin resistance and metabolic diseases in non-obese Asians.

3) Hepatic insulin resistance

It has been shown that alcohol intake reduces hepatic glucose production and decreases blood glucose level. However, high⁵²⁾ or moderately high⁵³⁾ alcohol consumption in Japanese is associated with an increased risk of type 2 diabetes among lean Japanese men (BMI ≤ 22.0 kg/m²)⁵⁴⁾. In the Sportology Center Core Study, hepatic insulin sensitivity was weakly but not significantly correlated with alcohol consumption ($r=-0.22$). In addition, we showed that 1-week alcohol abstinence improved hepatic insulin sensitivity and fasting plasma glucose in non-obese Japanese men with mildly elevated fasting plasma glucose levels who consumed alcohol³³⁾, and therefore alcohol may be one of the factors that induces hepatic insulin resistance in non-obese Asians.

6. Effect of exercise on metabolic status in skeletal muscle

Exercise is recommended to prevent metabolic diseases. In the Sportology Center Core Study, insulin sensitivity in muscle in non-obese Japanese

was closely associated with fitness and physical activity levels. In fact, we demonstrated that 2-week diet plus exercise therapy in type 2 diabetes decreased IMCL level and improved insulin resistance²³⁾; however, during this intervention, body weight was only decreased by 2%. Thus, it is expected that exercise therapy directly modulates lipid and glucose metabolism in skeletal muscle. Another study revealed that aerobic exercise (jogging) for 1 year enhanced not only muscle insulin sensitivity, but also insulin clearance in healthy young men⁵⁵⁾.

We previously investigated the IMCL level in subjects with a high fitness level. Interestingly, while their IMCL level was high, their insulin sensitivity level was supernormal (the so-called athlete's paradox)⁵⁶⁾. Accordingly, we found that expression levels of plasma membrane-associated fatty acid-binding protein (FABPpm) in skeletal muscle were associated with the athlete's paradox seen in non-obese, healthy Japanese men⁵⁷⁾.

7. Summary of the Sportology Center Core Study and impact on the Bunkyo Health Study

The Sportology Center Core Study identified several mechanisms of metabolic diseases in non-obese Japanese. The main ones may be ectopic fat accumulation and insulin resistance in muscle (Figure-1). Once moderate IMCL accumulation and insulin resistance occur as a result of physical inactivity and/or a HF diet, they can be compensated for by reduced insulin clearance, which subsequently elevates insulin levels. This hyperinsulinemia may further worsen insulin resistance and adiposity. Excess fat accumulation in adipose tissue also induces lipid spillover, which further

Figure-1 Mechanism of insulin resistance in muscle

facilitates insulin resistance. Thus, increasing physical activity and reducing fat intake may be an important strategy to prevent metabolic diseases in non-obese Asians. On the other hand, insulin signaling affects muscle not only by increasing glucose uptake, but also by promoting protein synthesis. Thus, it is possible that insulin resistance for glucose metabolism may also cause sarcopenia, then induce a “double burden” of both sarcopenia and insulin resistance in muscle later in life. Elderly individuals comprised 27.7% of the Japanese population in 2017⁵⁸⁾, which is the highest worldwide. Thus, many elderly people may experience the aforementioned double burden affecting muscle function, which will impact long-term care. This concept was carried over to the next core study at the Sportology Center, the Bunkyo Health Study.

The Bunkyo Health Study

1. Background

The Sportology Center Core Study showed that insulin resistance in muscle may be the main pathogenic cause of metabolic diseases in non-obese Asians. In a sub-study of the Sportology Center Core Study, insulin resistance and metabolic syndrome were closely associated with brain white matter alteration³⁶⁾, which is a risk factor and early marker for dementia and stroke. In addition, apoplexy and dementia are among the main reasons for long-term care in Japan, and insulin resistance is a known risk factor for both. Thus, prevention of

insulin resistance through exercise is an important strategy for avoiding the need for long-term care. On the other hand, sarcopenia, defined by age-related decreases in muscle strength and mass^{59) 60)}, has attracted attention. Reduced muscle strength and mass not only diminish physical performance, but may also cause diseases such as diabetes⁶¹⁾, dementia⁶²⁾, and stroke⁶³⁾, and may increase mortality⁶⁴⁾. Thus, to reduce the number of older people who require long-term care, it is important not only to improve muscle insulin resistance, but also to maintain or increase muscle strength and mass. However, when an individual has both insulin resistance and sarcopenia, it is still unclear which should be prioritized treatment-wise. Thus, we developed the Bunkyo Health Study to address this question.

2. Concept of the Bunkyo Health Study

The Bunkyo Health Study is a prospective cohort study of elderly subjects in an urban community, and was designed to clarify the relationship between muscle mass, muscle strength, and muscle insulin sensitivity, as well as to identify the risk factors and diseases that lead to the need for long-term care (Figure-2, 3). We recruited 1,629 elderly individuals aged 65–84 years living in 13 communities in an urban area (Bunkyo-ku, Tokyo, Japan). Then, we obtained baseline data on cognitive function, cerebral small vessel disease (assessed by brain MRI), body composition, bone mineral density, arteriosclerosis, physical function, muscle mass,

Figure-2 Bunkyo Health Study

Figure-3 Muscle functions and long-term care

muscle strength, and insulin sensitivity. We plan to re-evaluate cognitive function, brain MRI parameters and other parameters at 5 and 10 years after the baseline evaluation. The primary objective is to prospectively investigate the associations of muscle mass, muscle strength, and insulin sensitivity with the incidences of major diseases and risk factors leading to the need for long-term care.

One of the unique properties of the study is a plan to classify the participants into several groups according to muscle function (Figure-3). For example, one participant may have strong muscle strength and high muscle insulin sensitivity, while another participant may have strong muscle strength but low muscle insulin sensitivity. Categorizing all participants into tertiles of muscle strength and muscle insulin sensitivity will result in nine groups (Figure-3). However, it is still unclear which group is at greatest risk for diseases associated with long-term care. When this issue is clarified, we may be able to develop individualized exercise and dietary therapies to prevent long-term care. For example, it is still unclear what form of exercise therapy, namely aerobic or resistance, should primarily be prescribed in elderly people; aerobic exercise is recommended to improve muscle insulin resistance, while resistance exercise

and protein intake are recommended to increase muscle strength. If we can identify risk differences among the nine groups, we may be able to tailor exercise and diet therapies to each individual. While it is easy to recommend both, this approach may not be realistic. Further study is clearly needed to address this issue.

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References

- 1) Guilherme A, Virbasius JV, Puri V, Czech MP: Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. *Nat Rev Mol Cell Biol*, 2008; 9: 367-377.
- 2) Groop LC, Saloranta C, Shank M, Bonadonna RC, Ferrannini E, DeFronzo RA: The role of free fatty acid metabolism in the pathogenesis of insulin resistance in obesity and noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab*, 1991; 72: 96-107.
- 3) Bachmann OP, Dahl DB, Brechtel K, *et al*: of intravenous and dietary lipid challenge on intramyocellular lipid content and the relation with insulin sensitivity in humans. *Diabetes*, 2001; 50: 2579-2525.
- 4) Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J,

- Boldt MD, Parks EJ: Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. *J Clin Invest*, 2005; 115: 1343-1351.
- 5) Shulman GI: Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. *N Engl J Med*, 2014; 371: 1131-1141.
 - 6) Chan JC, Malik V, Jia W, *et al*: Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA*, 2009; 301: 2129-2140.
 - 7) DF Diabetes Atlas, 6th edition. In: Guariguata L, Nolan T, Beagley J, Linnenkamp U, Jacqmain O, eds. Belgium: International-Diabetes-Federation, 2013.
 - 8) Pan WH, Yeh WT, Weng LC: Epidemiology of metabolic syndrome in Asia. *Asia Pac J Clin Nutr*, 2008; 17 Suppl 1: 37-42.
 - 9) World-Health-Organization: The Asia-Pacific perspective: redefining obesity and its treatment. Sydney: Health Communications Australia, 2000.
 - 10) Szczepaniak LS, Babcock EE, Schick F, *et al*: Measurement of intracellular triglyceride stores by ¹H spectroscopy: validation in vivo. *Am J Physiol*, 1999; 276: E977-E989.
 - 11) Groop LC, Bonadonna RC, DelPrato S, *et al*: Glucose and free fatty acid metabolism in non-insulin-dependent diabetes mellitus. Evidence for multiple sites of insulin resistance. *J Clin Invest*, 1989; 84: 205-213.
 - 12) Ter Horst KW, van Galen KA, Gilijamse PW, *et al*: Methods for quantifying adipose tissue insulin resistance in overweight/obese humans. *Int J Obes (Lond)*, 2017; 41: 1288-1294.
 - 13) Krssak M, Falk Petersen K, Dresner A, *et al*: Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a ¹H NMR spectroscopy study. *Diabetologia*, 1999; 42: 113-116.
 - 14) Jacob S, Machann J, Rett K, *et al*: Association of increased intramyocellular lipid content with insulin resistance in lean nondiabetic offspring of type 2 diabetic subjects. *Diabetes*, 1999; 48: 1113-1119.
 - 15) Virkamäki A, Korshennikova E, Seppälä-Lindroos A, *et al*: Intramyocellular lipid is associated with resistance to in vivo insulin actions on glucose uptake, antilipolysis, and early insulin signaling pathways in human skeletal muscle. *Diabetes*, 2001; 50: 2337-2343.
 - 16) Boden G, Lebed B, Schatz M, Homko C, Lemieux S: Effects of acute changes of plasma free fatty acids on intramyocellular fat content and insulin resistance in healthy subjects. *Diabetes*, 2001; 50: 1612-1617.
 - 17) Mittendorfer B, Magkos F, Fabbrini E, Mohammed BS, Klein S: Relationship between body fat mass and free fatty acid kinetics in men and women. *Obesity (Silver Spring)*, 2009; 17: 1872-1877.
 - 18) Petersen KF, Befroy D, Dufour S, *et al*: Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science*, 2003; 300: 1140-1142.
 - 19) Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI: Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. *N Engl J Med*, 2004; 350: 664-671.
 - 20) Décombaz J, Schmitt B, Ith M, *et al*: Postexercise fat intake repletes intramyocellular lipids but no faster in trained than in sedentary subjects. *Am J Physiol Regul Integr Comp Physiol*, 2001; 281: R760-769.
 - 21) Schrauwen-Hinderling VB, Kooi ME, Hesselink MK, *et al*: Intramyocellular lipid content and molecular adaptations in response to a 1-week high-fat diet. *Obes Res*, 2005; 13: 2088-2094.
 - 22) Tamura Y, Watada H, Igarashi Y, *et al*: Short-term effects of dietary fat on intramyocellular lipid in sprinters and endurance runners. *Metabolism*, 2008; 57: 373-379.
 - 23) Tamura Y, Tanaka Y, Sato F, *et al*: Effects of diet and exercise on muscle and liver intracellular lipid contents and insulin sensitivity in type 2 diabetic patients. *J Clin Endocrinol Metab*, 2005; 90: 3191-3196.
 - 24) Sakurai Y, Tamura Y, Takeno K, *et al*: Determinants of intramyocellular lipid accumulation after dietary fat loading in non-obese men. *J Diabetes Investig*, 2011; 2: 310-317.
 - 25) Kakehi S, Tamura Y, Takeno K, *et al*: Increased intramyocellular lipid/impaired insulin sensitivity is associated with altered lipid metabolic genes in muscle of high responders to a high-fat diet. *Am J Physiol Endocrinol Metab*, 2016; 310: E32-40.
 - 26) Larson-Meyer DE, Newcomer BR, Hunter GR: Influence of endurance running and recovery diet on intramyocellular lipid content in women: a ¹H NMR study. *Am J Physiol Endocrinol Metab*, 2002; 282: E95-E106.
 - 27) Takeno K, Tamura Y, Kawaguchi M, *et al*: Relation Between Insulin Sensitivity and Metabolic Abnormalities in Japanese Men With BMI of 23-25 kg/m². *J Clin Endocrinol Metab*, 2016; 101: 3676-3684.
 - 28) Sugimoto D, Tamura Y, Takeno K, *et al*: Clinical Features of Nonobese, Apparently Healthy, Japanese Men With Reduced Adipose Tissue Insulin Sensitivity. *J Clin Endocrinol Metab*, 2019; 104: 2325-2333.
 - 29) Kaga H, Tamura Y, Takeno K, *et al*: Higher C-Peptide Level During Glucose Clamp Is Associated With Muscle Insulin Resistance in Nonobese Japanese Men. *J Endocr Soc*, 2019; 3: 1847-1857.
 - 30) Kadowaki S, Tamura Y, Someya Y, *et al*: Fatty Liver Has Stronger Association With Insulin Resistance Than Visceral Fat Accumulation in Nonobese Japanese Men. *J Endocr Soc*, 2019; 3: 1409-1416.
 - 31) Shioya-Yamada M, Shimada K, Nishitani-Yokoyama M, *et al*: Association Between Visceral Fat Accumulation and Exercise Tolerance in Non-Obese Subjects Without Diabetes. *J Clin Med Res*, 2018; 10: 630-635.
 - 32) Kaga H, Tamura Y, Takeno K, *et al*: Correlates of insulin clearance in apparently healthy non-obese Japanese men. *Sci Rep*, 2017; 7: 1462.
 - 33) Funayama T, Tamura Y, Takeno K, *et al*: Effects of alcohol abstinence on glucose metabolism in Japanese men with elevated fasting glucose: A pilot study. *Sci Rep*, 2017; 7: 40277.
 - 34) Furukawa Y, Tamura Y, Takeno K, *et al*: Impaired peripheral insulin sensitivity in non-obese Japanese patients with type 2 diabetes mellitus and fatty liver. *J Diabetes Investig*, 2018; 9: 529-535.
 - 35) Sai E, Shimada K, Yokoyama T, *et al*: Association between Myocardial Triglyceride Content and Cardiac Function in Healthy Subjects and Endurance Athletes. *PLoS One*, 2013; 8: e61604.
 - 36) Shimoji K, Abe O, Uka T, *et al*: White matter alteration in metabolic syndrome: diffusion tensor analysis. *Diabetes Care*, 2013; 36: 696-700.
 - 37) Shimoji K, Uka T, Tamura Y, *et al*: Diffusional kurtosis imaging analysis in patients with hypertension. *Jpn J Radiol*, 2014; 32: 98-104.

- 38) Watada H, Tamura Y: Impaired insulin clearance as a cause rather than a consequence of insulin resistance. *J Diabetes Investig*, 2017; 8: 723-725.
- 39) Mittelman SD, Van Citters GW, Kim SP, *et al*: Longitudinal compensation for fat-induced insulin resistance includes reduced insulin clearance and enhanced beta-cell response. *Diabetes*, 2000; 49: 2116-2125.
- 40) Erdmann J, Kallabis B, Oppel U, Sypchenko O, Wagenpfeil S, Schusdziarra V: Development of hyperinsulinemia and insulin resistance during the early stage of weight gain. *Am J Physiol Endocrinol Metab*, 2008; 294: E568-E575.
- 41) Poy MN, Yang Y, Rezaei K, *et al*: CEACAM1 regulates insulin clearance in liver. *Nat Genet*, 2002; 30: 270-276.
- 42) Al-Share QY, DeAngelis AM, Lester SG, *et al*: Forced Hepatic Overexpression of CEACAM1 Curtails Diet-Induced Insulin Resistance. *Diabetes*, 2015; 64: 2780-2790.
- 43) Mehran AE, Templeman NM, Brigidi GS, *et al*: Hyperinsulinemia drives diet-induced obesity independently of brain insulin production. *Cell Metab*, 2012; 16: 723-737.
- 44) Nazare JA, Smith JD, Borel AL, *et al*: Ethnic influences on the relations between abdominal subcutaneous and visceral adiposity, liver fat, and cardiometabolic risk profile: the International Study of Prediction of Intra-Abdominal Adiposity and Its Relationship With Cardiometabolic Risk/Intra-Abdominal Adiposity. *Am J Clin Nutr*, 2012; 96: 714-726.
- 45) Ebbert JO, Jensen MD: Fat depots, free fatty acids, and dyslipidemia. *Nutrients*, 2013; 5: 498-508.
- 46) Søndergaard E, Espinosa De Ycaza AE, Morgan-Bathke M, Jensen MD: How to Measure Adipose Tissue Insulin Sensitivity. *J Clin Endocrinol Metab*, 2017; 102: 1193-1199.
- 47) Sugimoto D, Tamura Y, Takeno K, *et al*: Clinical Significance of Insulin Sensitivity in Adipose Tissue in Apparently Healthy Nonobese Men. *Diabetes*, 2018; 67 (Supplement 1): 1914-P.
- 48) Furukawa Y, Tamura Y, Takeno K, *et al*: Impaired peripheral insulin sensitivity in non-obese Japanese patients with type 2 diabetes mellitus and fatty liver. *J Diabetes Investig*, 2018; 9: 529-535.
- 49) Rabøl R, Petersen KF, Dufour S, Flannery C, Shulman GI: Reversal of muscle insulin resistance with exercise reduces postprandial hepatic de novo lipogenesis in insulin resistant individuals. *Proc Natl Acad Sci U S A*, 2011; 108: 13705-13709.
- 50) Flannery C, Dufour S, Rabøl R, Shulman GI, Petersen KF: Skeletal muscle insulin resistance promotes increased hepatic de novo lipogenesis, hyperlipidemia, and hepatic steatosis in the elderly. *Diabetes*, 2012; 61: 2711-2717.
- 51) Najjar SM, Perdomo G: Hepatic Insulin Clearance: Mechanism and Physiology. *Physiology (Bethesda)*, 2019; 34: 198-215.
- 52) Tsumura K, Hayashi T, Suematsu C, Endo G, Fujii S, Okada K: Daily alcohol consumption and the risk of type 2 diabetes in Japanese men: the Osaka Health Survey. *Diabetes Care*, 1999; 22: 1432-1437.
- 53) Waki K, Noda M, Sasaki S, *et al*: Alcohol consumption and other risk factors for self-reported diabetes among middle-aged Japanese: a population-based prospective study in the JPHC study cohort I. *Diabet Med*, 2005; 22: 323-331.
- 54) Seike N, Noda M, Kadowaki T: Alcohol consumption and risk of type 2 diabetes mellitus in Japanese: a systematic review. *Asia Pac J Clin Nutr*, 2008; 17: 545-551.
- 55) Oshida Y, Yamanouchi K, Hayamizu S, Sato Y: Long-term mild jogging increases insulin action despite no influence on body mass index or VO2 max. *J Appl Physiol* (1985), 1989; 66: 2206-2210.
- 56) Coen PM, Goodpaster BH: Role of intramyocellular lipids in human health. *Trends Endocrinol Metab*, 2012; 23: 391-398.
- 57) Kawaguchi M, Tamura Y, Kakehi S, *et al*: Association between expression of FABPpm in skeletal muscle and insulin sensitivity in intramyocellular lipid-accumulated nonobese men. *J Clin Endocrinol Metab*, 2014; 99: 3343-3352.
- 58) Cabinet Office, Government of Japan: Annual Report on the Ageing Society: 2018. https://www8.cao.go.jp/kourei/english/annualreport/2018/2018pdf_e.html (Last Accessed Jan. 28, 2020)
- 59) Chen LK, Liu LK, Woo J, *et al*: Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc*, 2014; 15: 95-101.
- 60) Cruz-Jentoft AJ, Bahat G, Bauer J, *et al*: Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2: Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing*, 2019; 48: 16-31.
- 61) Moon SS: Low skeletal muscle mass is associated with insulin resistance, diabetes, and metabolic syndrome in the Korean population: the Korea National Health and Nutrition Examination Survey (KNHANES) 2009-2010. *Endocr J*, 2014; 61: 61-70.
- 62) Kohara K, Okada Y, Ochi M, *et al*: Muscle mass decline, arterial stiffness, white matter hyperintensity, and cognitive impairment: Japan Shimanami Health Promoting Program study. *J Cachexia Sarcopenia Muscle*, 2017; 8: 557-566.
- 63) Hirsch CH, Fried LP, Harris T, Fitzpatrick A, Enright P, Schulz R: Correlates of performance-based measures of muscle function in the elderly: the Cardiovascular Health Study. *J Gerontol A Biol Sci Med Sci*, 1997; 52: M192-200.
- 64) Li R, Xia J, Zhang XI, *et al*: Associations of Muscle Mass and Strength with All-Cause Mortality among US Older Adults. *Med Sci Sports Exerc*, 2018; 50: 458-467.