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Pathogenic Features of Insulin Resistance and Critical Organ Damage in the Liver, Muscle and Lung

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1. Introduction

1.1 Overall pathogenic features of insulin resistance

Over the last two decades, type 2 diabetes and metabolic syndrome (MetS) have been increasing worldwide in concert with an increasing obesity pandemic [Grundy, 2005; Kopelman, 2007; Dixon, 2010]. In particular, abdominal obesity predisposes to development of type 2 diabetes and MetS through the pathogenic feature of insulin resistance, mostly accompanied by hyperinsulinemia to compensate for impairment of insulin action, especially in the early stage of these diseases [Bartnik, 2007]. In addition to genetic background, generally unfavorable lifestyles, such as smoking, infrequent exercise, sedentary working, overeating, and unbalanced nutrition provoke insulin resistance and cause progress in cooperation with obesity [Grundy, 2005; Kopelman, 2007; Bartnik, 2007; American Diabetes Association, 2010]. Once excess abdominal obesity is present, numerous cytokines, chemokines, and free fatty acids (FFA) are secreted from hypertrophic visceral fat as well as trunk subcutaneous fat, leading to deterioration of such pathogenicity [Capeau, 2008; Meshkani, 2009; Gustafson, 2010]. Type 2 diabetes and MetS have emerged as major public health problems as comorbid conditions not only with microvascular disease but also with macrovascular disease [Grundy, 2005; Kopelman, 2007; Dixon, 2010; Bartnik, 2007; American Diabetes Association, 2010]. Because insulin resistance and resultant hyperinsulinemia are a pivotal pathophysiology, these etiologies simultaneously contribute to hypertension, dyslipidemia (increased triglycerides and decreased high-density lipoprotein cholesterol), and hyperuricemia in a complex manner, in addition to causing abnormal glucose metabolism [Grundy, 2005; Kopelman, 2007; Dixon, 2010; Bartnik, 2007; American Diabetes Association, 2010].

Currently, insulin resistance is not limited to traditional insulin-sensitive tissues and organs such as skeletal muscle; it also affects other critical organs such as the kidney [Kubo, 1999; Chen, 2003; Guarnieri, 2010] or possibly the lung [Kaparianos, 2008; Klein, 2010; Fimognari, 2010], which are involved in the development of cardiovascular diseases and impaired quality of life. In addition, glucose and FFA as fundamental energy substrates are closely related to each other; this relationship was originally conceptualized as the "glucose-fatty acid cycle" by Randle et al. half a century ago [Randle, 1963]. Therefore, clinicians in different fields, including cardiology, lipidology, and hepatology, and clinical scientists should be aware of the pathophysiology of insulin resistance, extending far beyond the narrow range of clinical diabetology, for the prevention, care and improvement of critical diseases comprising microvascular and macrovascular diseases, and organ damage.

1.2 Effect of hyperinsulinemia

It is unknown whether the insulin resistance exerts similar effects in all tissues and organs. Hyperinsulinemia per se has substantial effects on many tissues and organs because in addition to precise regulation of glucose metabolism, insulin has pleiotropic actions. These actions are mostly anabolic properties, leading to storage of lipids and glucose substrates, and increased protein synthesis and cell proliferation and growth, which are activated via the MAP kinase pathway [Meshkani, 2009; Godsland, 2009]. However, these often result in adverse outcomes such as vascular endothelial thickening, polycystic ovary syndrome, and provoking latent cancers as well as acanthosis nigricans, a skin lesion characterized by thickened and hyperpigmented plaques around the neck [Harwood, 2007; Higgins, 2008]. Furthermore, insulin has been shown to have antinatriuretic actions (Na^+ reabsorption by the kidney and circulating volume retention) and enhanced sympathetic nervous system activation, eventually resulting in elevated blood pressure, which is one of the components of MetS. Notably, chronic hyperinsulinemia in turn deteriorates insulin resistance in tissues originally sensitive to insulin because the insulin receptor is downregulated by a feedback mechanism or is degraded along with insulin [Capeau, 2008].

1.3 Progression of insulin resistance

As shown in **Figure 1** [Laakso, 2003], the amount of circulating insulin, i.e., hyperinsulinemia, normal insulinemia, or hypoinsulinemia, can interfere with the effects of insulin resistance in the progression of type 2 diabetes and MetS, with varying degrees of glucose toxicity and/or lipotoxicity. However, insulin resistance will continue to progress unless the individual improves an unhealthy life style and abdominal obesity, regardless of an irreversible and progressive decline in insulin secretion.

Type 2 diabetes has a strong genetic component [American Diabetes Association, 2010]. Of note, the prevalence of impaired glucose tolerance is high in many Asian countries [Sharma, 2010]. Therefore, a strong gene-environmental interaction may be one of the causes for the rapidly increasing rate of diabetes, especially in Asians, who are now becoming accustomed to an unhealthy lifestyle [Sharma, 2010]. Among the Asian peoples, particularly the Japanese, they show a lower insulin secretory capacity after glucose loading, suggesting a smaller potential for pancreatic beta cell function than in Western people [Kaku, 2010]. Furthermore, most Asians also have a genetic background of the "thrifty gene", including specific polymorphisms of peroxisome proliferator-activated receptor (PPAR), beta 3-adrenagic receptor, and ucp- 1 [Hara, 2000; Kahara, 2002].
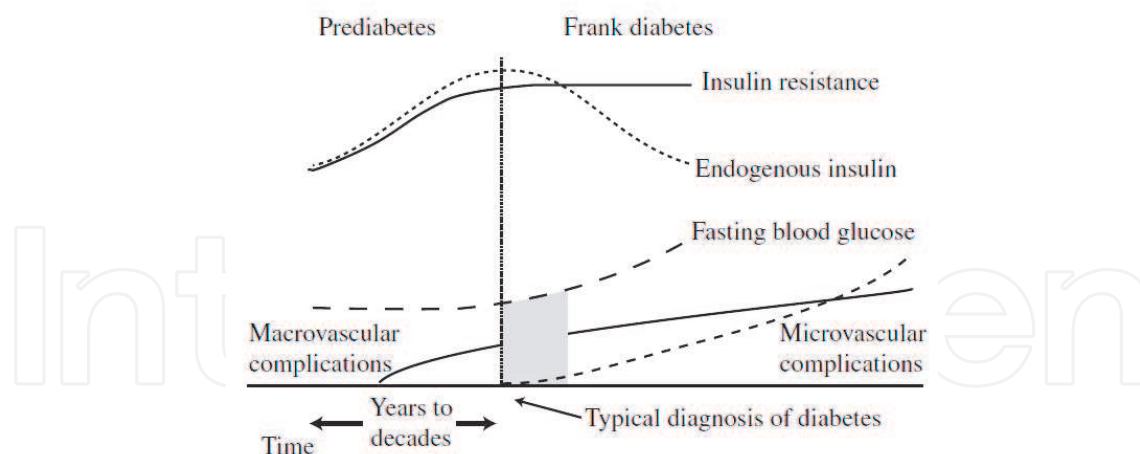
Fig. 1. Insulin resistance, impaired insulin secretion, and fasting glucose in relation to micro- and macrovascular diseases (Laakso, 2003).

Worldwide, it is unknown which factor factors occur first, insulin resistance or insulin deficiency. People with type 2 diabetes probably have both conditions in varying degrees. In this chapter, we discuss the pathophysiology of insulin resistance and organ damage (liver, muscle, and lung) particularly in the stages of hyperinsulinemia with mild glycemia, where restrict more stringent glucose control soon after diagonosis of diabetes is important for the so called "legacy effect" long-term legacy effect that is known as long-term reduction of myocardial infarction and all-cause mortality in intensive treatment cohort as compared to the standard arm after further 10-years follow up UKPDS [Chalmers, 2008; Murray, 2010].

1.4 Common mechanisms of multiple organ damage in relation to insulin resistance

Common mechanisms of organ damage that relate to insulin resistance appear to be dyslipidemia, abnormal glucose metabolism, subtle inflammation, oxidative status, low blood flow systemically as well as locally because of reduced nitric oxide (NO) synthesis, and hypertension, most of which enhance the renin-angiotensin-aldosterone system (RAAS) and Rho/Rho kinase signaling, which attenuate microvessel function in many organs [Capeau, 2008; Meshkani, 2009; Gustafson,2010; Lastra, 2010; Choi, 2010]. Several animal and cellular studies have shown that activation of the RAAS as well as Rho/Rho kinase signaling is associated with impaired insulin signaling and insulin resistance in most organs, including the liver, muscle, and kidney [Choi, 2010; Lastra, 2006].

Regarding abnormal glucose metabolism, euglycemia or mild hyperglycemia with resultant hyperinsulinemia is observed in the early stage of type 2 diabetes, whereas reduced insulin secretion and chronic hyperglycemia with lasting insulin resistance is still observed in advanced stages [Bartnik, 2007; American Diabetes Association, 2010]. Specific mechanisms according to organs (liver, muscle, and lung) are described in the following sections. The effects of insulin on cell metabolism are mediated by binding of insulin to its receptor on the cell surface, leading to phosphorylation of tyrosine residues, followed by the activation of phosphatidylinositol 3-kinase (PI 3-kinase) [Liu, 2010; Tatoń, 2010; Tarantino, 2010]. The main receptor is insulin receptor substrate (IRS), which has four isoforms (IRS1-4). Many organs and tissues have both IRS-1 and IRS-2 with different actions [Tatoń, 2010; Tarantino, 2010]. IRS-3 is mainly involved in adipocytes and IRS-4 is involved in the kidney/thalamus. Insulin resistance appears to occur at the receptor level by the inhibition of receptor tyrosine

kinase activity, although a relatively reduced number of insulin receptors on the cell surface may also affect insulin resistance. Because a comprehensive description of insulin resistance in all organs is beyond the scope of this review, we will highlight major organ damage (liver and muscle) as well as the emerging field of the lung.

2. Insulin resistance and liver and skeletal muscle

It is now commonly accepted that in addition to critical immune functions such as natural killer cells and digestive function such as formation of bile acid as well as actions of detoxification, the liver plays a central role in regulating systemic metabolism, including protein, carbohydrate, and lipid metabolism, all of which are under close control by a series of hormones secreted from various organs [Tarantino, 2010]. Of these hormones, in particular, circulating insulin substantially interferes with these hepatic functions and systemic metabolism [Capeau …] 2008; Meshkani, 2009; Gustafson, 2010; Lastra, 2010; Choi, 2010; Liu, 2010; Tatoń, 2010; Tarantino, 2010; Samuel, 2010].

Originally, simple steatosis, i.e., fatty liver, was thought to remain benign throughout life. However, currently, fatty liver or so called non-alcoholic fatty liver disease (NAFLD) and its worsened condition, non-alcoholic steatohepatitis (NASH), have been emerging as one of the conditions that cause critical organ damage in the general population, mostly accompanied by type 2 diabetes and MetS [Capeau, 2008; Meshkani, 2009; Liu, 2010]. Similar to other lifestyle-related diseases, most people with NAFLD remain untreated with few or no symptoms until a blood test or abdominal ultrasound are conducted in the clinical setting. Generally, serum hepatic enzymes, especially alanine aminotransferase, are often elevated beyond the normal range [Schindhelm, 2006; Chang, 2007; Ghouri, 2010]. However, these hepatic enzymes occasionally remain within the normal ranges [Chang, 2007] and are overlooked until an abdominal ultrasound test is performed. Importantly, NASH may occasionally progress to cirrhosis (10-15%) and rarely to hepatic cancer after several decades [Estep, 2010]. NAFLD generally follows the presence of abdominal hypertrophic fat cells in clinical practice. Plausible main causes are direct influx via the portal vein of FFA (long chain FFA), glycerol, and proinflammatory cytokines comprising tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1 from visceral and upper body fat, which follow insulin resistance at visceral fat tissues by activating hormone sensitive lipase and adipose tissue triacylglycerol lipase [Capeau, 2008; Meshkani, 2009; Gustafson, 2010; Nakajima, 2010].

2.1 FFA metabolism in hepatic cells

Chronically elevated fatty acids can impair the function of pancreatic β-cells [Bollheimer, 1998]. In addition, elevated fatty acids enter hepatic cells via fatty acid transporter protein CD 36 and fatty-acid-binding protein [Makowski, 2004], providing a major amount of FFA, which are converted into triglycerides (TG) and secreted by the liver in the form of very low density lipoprotein (VLDL). FFAs from lipolysis of adipose fat account for approximately 60% of the total FFA in the liver [Donnelly, 2005]. In contrast, chylomicron, an exogenous triglyceride-rich lipoprotein synthesized from the diet in the intestine, enters the circulation via the thoracic duct after being absorbed into the lymph duct, and eventually is taken up through remnant receptors by the liver, and this accounts for 15% of the total FFA in the liver. The rest of the FFAs are those newly synthesized by the liver. Therefore, theoretically, a substantial improvement of NAFLD and NASH would not occur until body fat is substantially reduced. FFA has lipotoxic effects and exerts hepatic injury, whereas TG

formation, which may be less toxic, is protective in hepatic cells [Capeau, 2008; Tarantino, 2010; Cnop, 2001]. These FFAs do not develop significant metabolic disturbances as long as they are successfully oxidized in well-functioning mitochondria in target tissues. Consistently, in the early stage of NAFLD, fat accumulation in the form of TG with intact β-oxidation is considered to be rather benign and is called the "first hit" stage. However, excess β-oxidation increases reactive oxygen species (ROS), and this is considered to provoke the so called "second hit" process to NASH [Gentile, 2008; Tessari, 2009]. Insufficient action of superoxide dismutase, which neutralizes superoxide free radicals, may contribute to increased ROS in the cytosol [Faraci, 2004; Miao, 2009]. Increased ROS in turn activates the immune system and hepatocytes and stellate cells, followed by increased collagen synthesis and transforming growth factor secretion, resulting in development and progression of hepatic fibrosis [Gressner, 2008; Matsuzaki, 2009].

2.2 FFA metabolites and impairment of insulin signaling

Excess long-chain fatty acyl CoAs, diacylglycerol (DAG), and FFA metabolites cause IRS-1 serine phosphorylation via protein kinase C (PKC), thereby inhibiting the PI 3-kinase pathway [Shulman, 2000]. In this situation, inhibition of FOXO1 via Akt does not occur, resulting in increased glyconeogenesis and reduced glycogen synthesis [Sharma, 2010], because glucose enters the liver through glucose transporter GLUT2, which is always present at the cell membrane, independent of insulin action. TNF–α inhibits insulin signal transduction by activating Jun kinase and IKKβ, which cause serine phosphorylation of IRS [Gustafson, 2010; Shulman, 2000; Popa, 2007].

With regard to glucose metabolism, the liver appears to play a pivotal role because liver IRS knockout mice show systemic insulin resistance, whereas muscle IRS knockout mice do not have insulin resistance, regardless of increased fat mass and circulating fatty acids [Brüning, 1998; Kim, 2000]. Nevertheless, controversy still remains because extra-hepatic IRS2-dependent mechanisms may be involved in the regulation of glucose homeostasis [Simmgen, 2006].

Under most conditions, hepatic insulin resistance and peripheral insulin resistance progress in parallel, although the clinical relevance and mechanisms have not been fully elucidated. Under conditions of hepatic insulin resistance, glucogenolysis and gluconeogenesis are stimulated because of decreased suppression by insulin, resulting in hyperglycemia, especially in the fasted state, and the storage of glycogen in the liver is reduced.

The liver has both IRS-1 and IRS-2 with different actions [Capeau, 2008; Meshkani, 2009, Taton, 2010; Morino, 2006]. Kubota et al. showed that IRS-2 mainly functions during fasting and immediately after refeeding, and IRS-1 functions primarily after refeeding [Kubota, 2008]. Furthermore, liver-specific IRS-2-knockout mice display insulin resistance during fasting but not after refeeding. Therefore, IRS-2 may be involved in the fasting state via limitation of hepatic glucose production by controlling phosphoenolpyruvate carboxykinase and glucose 6-phoshatase [Capeau, 2008; Haeusler, 2008]. Thus, insufficient amount of hepatic IRS-2 during fasting due to insulin resistance may result in abnormal glucose metabolism with postprandial hyperglycemia [Kubota, 2008].

2.3 Insulin resistance and abnormal lipogenesis

There is a paradoxical mechanism in the lipogenic metabolism of hepatocytes in subjects with insulin resistance. Although the mechanism has not been fully elucidated yet, de-novo

lipogenesis is activated by sterol regulatory element- binding protein (SREBP)-1c, which is insulin sensitive and is enhanced by elevated insulin [Eberlé, 2004; Ferré, 2007]. Alternatively, such lipogenesis is partially explained as a result of endoplasmic reticulum stress, activating the cleavage of SREBP-1c [Ferré, 2007; Ferré, 2010].

The three SREBP isoforms, SREBP-1a, SREBP-1c and SREBP-2, have different roles in lipid synthesis. Animal studies using transgenic and knockout mice suggest that SREBP-1c is involved in FFA synthesis and glucose metabolism, whereas SREBP-2 is relatively specific to cholesterol synthesis [Eberlé, 2004; Ferré, 2007; Ferré, 2010]. The SREBP-1c isoform appears to be mainly regulated at the transcriptional level by insulin. Indeed, SREBP-1c knockout mice are likely to have high plasma glucose during a carbohydrate feeding period [Liang, 2002], suggesting that SREBP-1c expression is involved in the pathophysiology of type 2 diabetes and MetS. Although extensive studies have been limited to animal studies, liver X receptor, which is a nuclear hormone receptor highly expressed in the liver and it responds to oxysterol, enhances fatty acid synthesis by activating SREBP-1c, which in turn activates lipogenesis as well as VLDL assembly and secretion [Liang, 2002; Okazaki, 2010]. Therefore, there is a complicated relationship between glucose metabolism and lipid metabolism, which includes many transcriptional factors

The liver can store extra fat that should be originally accumulated in adipose tissue or skeletal muscle. However, such fat accumulation eventually aggravates organ function. Ectopic fat deposition, especially as triglycerides, in the liver may be a rough hallmark of insulin resistance, particularly in adipose tissue. However, organ damage does not occur yet, although impaired insulin signaling is imminent. Excess fat accumulation and their metabolites may provoke a second stage. Therefore, NAFLD and NASH may be more severe clinical conditions than simple obesity regardless of the visceral or subcutaneous type. Tarantino et al. [Tarantino, 2010] suggested that hepatocytes are the last type of cell to store fat when other cell types are full with fat. Therefore, lifestyle intervention and possible treatments should be initiated at simple steatosis instead of overt steatohepatitis.

2.4 Possibility of pharmacological treatment

Recently, it has been shown that a relatively long time (1-2 years) of treatment with vitamin E and thiazolidinediones improves NAFLD and NASH [Aithal, 2008; Duvnjak, 2009; Sanyal, 2010; Musso, 2010], suggesting that anti-oxidative agents and PPAR-γ agonists may improve the pathophysiology of the liver as well as clinical variables in patients with NASH and NAFLD. PPAR-γ, which belongs to the nuclear hormone receptor family, is mainly expressed in adipose tissues [Anghel, 2007] and exerts substantial actions such as adipocyte differentiation and fibroblast differentiation into mature adipocyte types [Anghel, 2007; Mandrup, 1997]. Therefore, improvement of NASH and NAFLD may be predominantly caused through improvement of the etiology in the visceral tissue or upper subcutaneous fat, although the precise underlying mechanism is unknown. Considering the discrepancy between the site of PPAR-γ expression and that of the pharmacological effects, the plausible mechanism is that thiazolidinediones restore fat accumulation from the liver or muscle into adipose tissues and confine it in adipose tissue at the long term expense of adipose cells [Samuel, 2010]. Mayerson et al. [1997] showed that treatment with rosiglitazone results in a significant reduction of hepatic triglyceride content along with successful suppression of adipocyte lipolysis. Unexpectedly, there is also increased intramyocellular fat as triglycerides accompanied by improved insulin sensitivity in muscle. This suggests that

intramyocellular fat alone is unlikely to reflect insulin resistance, similar to triglyceride accumulation in the liver and the "first hit" stage in the second hit theory of NASH.

Such apparent improvement in insulin resistance often results in adverse outcomes, such as an increase in the amount of adipose cells by differentiation of adipose cells, eventually leading to weight gain and systematic edema [Duvnjak, 2009; Sanyal, 2010], which in turn loads the heart and aggravates latent heart failure. Long-term treatment of thiazolidinediones, in which pioglitazone may be better than rosiglitazone in terms of less side effects [Tang, 2006; Tzoulaki, 2009], can result in intolerance for some people with diabetes because of these adverse effects, regardless of whether they provoke heart failure. Likewise, the safety and efficacy of long-term treatment with vitamin E has not been established yet in the clinical setting. Metformin (biguanide), an insulin-sensitizer, is considered as the first choice for type 2 diabetes because it has fewer side effects and a mild lipid-lowering property. However, the outcomes of clinical trials are conflicting [Duvnjak, 2009]. Therefore, it is not recommended to treat NAFLD patients with metformin unless they have abnormal glucose metabolism.

In contrast, 3-hydroxy-3-methyglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) do not seem to be an effective treatment for NASH, with conflicting outcomes [Nelson, 2009; Kimura, 2010]. Statins are used in clinical practice to improve lipid metabolism, particularly low density lipoprotein-cholesterol. In addition, they have a pleiotropic effect including anti-inflammatory actions [Davignon, 2004] in which proinflammatory cytokines, such as C-reactive protein (CRP) and TNF-α, are substantially reduced by the use of statins. Notably, although CRP and TNF-α are related to insulin resistance and metabolic abnormalities, statins are unlikely to improve the histology of NALD and NASH. This finding might be related to the fact that statins are associated with deterioration of glucose metabolism [Sattar, 2010; Koh, 2010]; however, further in depth studies are required.

2.5 Liver cirrhosis and insulin resistance

Liver cirrhosis causes hepatic insulin resistance, resulting in hyperinsulinemia and diabetes because of both decreased insulin clearance and increased secretion of insulin from the pancreas [Petrides, 1994; Hickman, 2007; Garcia-Compean, 2009]. A substantial amount of patients with cirrhosis have glucose intolerance (~96%) and a relatively small amount of them may have overt diabetes (~30%) [Hickman, 2007; Garcia-Compean, 2009]. In patients with liver cirrhosis, particularly in the decompensated stage, substantial hyperglycemia as well as hypoglycemia occur as a result of a lack of glucose control because of lack glucose uptake in the postprandial state and glucose secretion by the liver in the fasting state. Such diabetes and abnormal glucose metabolism, which develop as a complication of cirrhosis, are known as "hepatogenous diabetes" [Garcia-Compean, 2009] and they worsen the clinical outcomes of patients along with malnutrition associated with advanced cirrhosis. Hepatitis C virus (HCV) and hemochromatosis are known to frequently accompany diabetes and insulin resistance [Hickman, 2007; Garcia-Compean, 2009]. Although underlying mechanisms between HCV infection and insulin resistance are not clearly known, HCV induces insulin resistance primarily because of TNF-α overproduction, regardless of obesity and hepatic fibrosis stage [Kawaguchi, 2010].

2.6 Skeletal muscle and insulin resistance

Skeletal muscle is a large organ that consumes a variety of nutrients including glucose, lipids, and proteins. After a meal, approximately one third of absorbed glucose is taken up

by the liver and the rest is mainly taken up by the skeletal muscle [Abdul-Ghani, 2010]. Therefore, skeletal muscle can substantially interfere with systemic glucose metabolism and alter peripheral insulin sensitivity as well as hepatic insulin sensitivity [Samuel, 2010; Turcotte, 2008]. Therefore, the pathogenic features of skeletal muscle need to be considered in relation to the liver and adipocytes. In liver and muscle, there are many common mechanisms of lipid and glucose metabolism. Ectopic fat accumulation in skeletal muscle is often observed in patients with type 2 diabetes and MetS. Such fat deposition is considered to be the cause of insulin resistance [Tarantino, 2010; Samuel, 2010; Abdul-Ghani, 2010]. However, while the amount of intramyocellular lipids can be used as a marker of insulin resistance in general, similar to the liver, these neutral triglycerides themselves are not thought to be harmful [Abdul-Ghani, 2010; Eckarde, 2011]. In addition, storage of carbohydrates as glycogen in muscle is impaired in people with insulin resistance [Samuel, 2010].

FFA metabolism and increased fatty acid metabolites such as long-chain acyl CoA, DAG, and ceramide, are likely to play a pivotal role in the development of insulin resistance in skeletal muscle [Samuel, 2010]. Accumulated DAG has a high affinity for PKC, which in turn cause a reduction of tyrosine phosphorylation of IRS-1, followed by reduced glucose uptake via GLUT4. A plausible reason why lipid intermediates accumulate in muscle cells is because of an unbalance between a higher rate of FFA uptake and a lower rate of FFA disposal, which is primarily performed by β–oxidation in the mitochondria. High circulating FFA may result from adipocyte lipolysis because of insulin resistance in adipose tissue. Because higher circulating FFA are correlated with a higher uptake of FFA by muscle, consequent high FFA in muscle may be related to insulin resistance in adipose tissue.

Muscle oxidation capacity is reduced in patients with type 2 diabetes and obesity, leading to increasing oxidative stress in skeletal muscle [Abdul-Ghani, 2010; Turcotte, 2008; Eckardt, 2011; Tsutsui, 2011]. Increased oxidative stress, such as ROS, in the muscle deteriorates exercise capacity [Tsutsui, 2011], resulting in muscle weakness and disuse muscle atrophy.

It is well known that favorable modulation of mitochondrial oxidative capacity in skeletal muscle by exercise training improves the oxidation of fatty acids, leading to effective insulin downstream signaling. It has been suggested that insulin resistance of muscle in the elderly may contribute to the development of sarcopenia [Volpi, 2004; Boirie, 2001], an unintended loss of muscle mass, strength, and function. In fact, when glucose is ingested with a regular meal, it is likely that increased insulin has a negative effect on muscle protein synthesis, particularly in older individuals [Volpi, 2004], suggesting that increasing muscle protein synthesis via insulin may be impaired in the elderly. It is unknown whether this negative effect is also observed in patients with type 2 diabetes; studies in relation to insulin effects on skeletal muscle are required to prevent "diabetes disability" in the elderly and people with insulin resistance.

Adiponectin, a hormone secreted by normal-sized adipocytes, stimulates AMPK activation, fatty-acid oxidation, glucose uptake, and lactate production in skeletal muscle [Yamauchi, 2002]. Adipocyte-myocyte crosstalk is an important modulator in the development of skeletal muscle insulin resistance [Havekes, 2010]. Accumulating evidence suggests that not only adipose cells but also skeletal muscle synthesize and secrete specific cytokines called "myokines" that modify metabolic crosstalk between organ systems. A substantial amount of IL-6 is released from skeletal muscle during and after exercise, i.e., contracting skeletal muscle, which is correlated with increases in AMPK activity in many tissues [Pedersen,

2007]. A slight to mild increase in serum IL-6 levels is often observed in obese people and individuals with type 2 diabetes, whereas a greater increase in IL-6 levels after exercise is considered as a facilitator of increased fuel metabolism, leading to adipocyte lipolysis and fat oxidation. Therefore, under certain conditions, IL-6 and other muscle-derived cytokines may play a role in preventing metabolic abnormalities such as type 2 diabetes [Pedersen, 2007] and damage to skeletal muscle.

3. The lung and insulin resistance

Complications of diabetes affect many tissues and organs, resulting in retinopathy, nephropathy, neuropathy, cardiovascular diseases, peripheral vascular diseases, stroke, and periodontal pathologies. Diabetes as well as MetS and hypertension, which are associated with insulin resistance and hyperinsulinemia, contribute to these complications and organ damage/failure. We discuss here impaired lung function in relation to the pathogenic features of insulin resistance.

Impaired lung function and lung diseases have been rarely discussed in terms of metabolic abnormalities. Although the diabetic lung was topically discussed in early human studies [Kaparianos, 2008; Klein, 2010], there have been limited investigations for metabolic abnormalities and impaired lungs.

With regard to respiratory function, respiratory diseases are generally divided into obstructive or restrictive lung diseases. To date, chronic obstructive pulmonary disease (COPD) is a leading cause of mortality in many countries and is increasing mainly because of the expanding number of smokers as well as the advancing age of the population. The association of COPD with all-cause mortality and cardiovascular events has been intensively studied in numerous prospective and cross-sectional studies [Fimognari, 2010; Rabe, 2007]. Molecular and cellular studies have explored the detailed mechanisms of COPD, which are considered to be related to local inflammation in the lung and systemic inflammation as assessed by elevated CRP and TNF-α levels [Fimognari, 2010; Rabe, 2007]. Although elevated CRP levels have been considered to be related to insulin resistance [Ndumele, 2006; Lu, 2010], metabolic abnormalities including type 2 diabetes and MetS have not been found to be involved in the etiology of COPD or an obstructive spirometric pattern [Fimognari, 2010]. Accumulating evidence is now questioning the association between the pathogenic features of insulin resistance and COPD because of elevated plasma adiponectin and the absence of either dyslipidemia, at least quantitatively [Basili, 1999], or insulin resistance [Fimognari, 2010] in COPD patients.

3.1 Restrictive lung disease and metabolic abnormalities

In recent years, some studies have addressed the association between low vital capacity, i.e., restrictive lung disease (RLD), and fatal and critical diseases. However, the magnitude of the increased mortality risk for RLD, e.g., the hazard ratio, appears to be comparable with that of mild-to-moderate COPD [Mannino, 2003a, 2003b; Purdue, 2007]. Although the etiology and cause of RLD are unknown, the prevalence of RLP is similar to that of COPD; it is approximately half to equal that in COPD or obstructive lung disease in some studies [Mannino, 2003a, 2003b; Purdue, 2007; Ford, 2004, Guerra, 2010].

In addition to earlier studies on the diabetic lung [Kaparianos, 2008], relatively recent cross-sectional studies and prospective studies, which investigated the relationship between

restrictive lung disease and cardiometabolic risks, have yielded almost uniform outcomes. They found that the restrictive pattern is associated with MetS (insulin resistance, dyslipidemia), type 2 diabetes, and inflammatory markers, especially CRP [Fimognari, 2010; Ford, 2004; Nakajima, 2008; Lin, 2006; Fimognari, 2007; Lee, 2008; Yeh, 2008; Chance, 2008]. Fimognari et al. [2007] revealed an association between RP and MetS in older persons in terms of insulin resistance. They observed that insulin resistance was much higher in the restriction group than that in the obstruction group and normal controls. Intriguingly, type 1 diabetes has been reported to be predominantly associated with features of RP [Schnack, 1996; Makkar, 2000; Boulbou, 2003]. Generally, type 1 diabetes is not accompanied by insulin resistance. Therefore, the results suggest a possible link between endocrine disorders, i.e., insufficient insulin action and impaired pulmonary function.

3.2 Determination of RLD in the clinical setting

Pulmonary function testing is often used and recommended for the assessment and management of impaired pulmonary function. However, spirometer-diagnosed COPD and RLD in such large studies could be equivocal because of controversy regarding the definitions and limitations in each facility. Furthermore, RLD may involve characteristics that reflect a restrictive pattern, some of which are caused by extrapulmonary impairment. This restrictive pattern includes various etiologies including classical RLDs such as interstitial lung diseases, respiratory muscle weakness, congestive heart failure, pneumonia, restrictive thoracic cage and, possibly, severe obesity. Theoretically, the determination of RLD should be assessed based on the reduction of total lung capacity (TLC) instead of a decline in vital capacity or forced vital capacity (FVC). According to the American Thoracic Society and the European Respiratory Society (ATS/ERS) task force [Pellegrino, 2005], a restrictive ventilatory defect is characterized by a reduction in TLC below the 5th percentile of the predicted value and a normal forced expiratory volume in 1 second (FEV_1)/vital capacity (VC). Therefore, it is not possible to accurately diagnose RLD using only an ordinary spirometer. However, measuring TLC is unfeasible in large studies as it is time consuming, expensive, and requires special facilities and trained technicians. It has been reported that a slightly increased FEV_1/FVC is often caused by submaximal inspiratory or expiratory efforts, or peripheral air flow obstruction [Pellegrino, 2005]. In our previous study, we showed that a stricter restrictive pattern was substitutively defined as a combination of low FVC assessed by lower limits of normal and relatively high FEV_1/FVC ($\geq 85\%$) [Nakajima, 2008].

Despite these limitations in the assessment of RLD, RLD and COPD have been associated with mortality and fatal incidents from cardiovascular disease [Mannino, 2003a, 2003b; Purdue, 2007; Hozawa, 2006, Guerra, 2010], but there is a lack of adequate understanding of the underlying mechanisms. Mannino et al. [2003b] reported that moderate and severe COPD were associated with an increased mortality risk in current and former smokers, but not in people who never smoked. In contrast, RLD was associated with an increased risk of mortality to a similar extent in all three smoking categories (current, former, and never smoked), suggesting that the mortality risk of COPD is mostly dependent on smoking status, whereas that of restrictive pattern is not. Likewise, in white people who have never smoked, the incidence of stroke is significantly increased along with reduced FVC, but not FEV_1/FVC [Hozawa, 2006]. Similar trends have also been recognized in other studies [Mannino, 2003a; Purdue, 2007] Therefore, factors other than smoking appear to deteriorate the fundamental pathogenesis of RLD.

3.3 Relation of RLD to cardiometabolic risks

Our laboratory and other investigators [Nakajima, 2008; Lee, 2008; Yeh, 2008, Klein, 2010] have reported that the mean FVC in persons with MetS or diabetes is reduced by approximately 6.0% compared with those without the diseases. In three studies [Nakajima, 2008; Lee, 2008; Yeh, 2008], the mean predicted FVC in persons with metabolic abnormalities, MetS, or diabetes (88-97%) ranges within the normal limit but it is higher in patients with a specific RLD, e.g., nonspecific interstitial pneumonia (59-83%) [Martinez, 2006]. The clinical relevance of a 6-7% decline in FVC within the normal range is unclear. Additional tests such as the 6-minute walk test and ventilation function test (carbon monoxide diffusion capacity) may give additional information on the features of the metabolic disorder-related restrictive lung pattern.

Regarding plausible underlying mechanisms between RLD and metabolic abnormalities, central obesity, particularly visceral fat and fatty liver diseases such as NAFLD, may physically impede the descent of the diaphragm, leading primarily to restrictive respiration impairment. However, a significant association between the restrictive pattern and type 2 diabetes and MetS remains, even after statistical adjustment for body mass index (BMI) and after stratification by BMI [Ford, 2004; Nakajima, 2008; Lin, 2006; Fimognari, 2007; Nakajima, 2010]. This suggests that for a given BMI, individuals with cardiometabolic abnormalities have a lower vital capacity than those without cardiometabolic abnormalities. Therefore, metabolic abnormalities and, possibly in part, mechanical limitation, may contribute to the development and progression of the restrictive pattern.

With regard to the cause of RLD, some prospective studies appear to suggest that restrictive patients are expected to develop metabolic abnormalities such as diabetes compared with subjects with normal spirometry. In the NHANES study [Ford, 2004], non-diabetes subjects with a restrictive pattern had an increased risk of developing diabetes in the follow-up. In the ARIC study [Yeh, 2008], low pulmonary function, defined as low forced vital capacity and low FEV_1, predicted the new onset of diabetes.

Metabolic abnormalities may cause impaired lung function. For example, insulin resistance may reduce the uptake of glucose by respiratory muscle, resulting in respiratory muscle weakness and poor ventilatory performance [Fimognari, 2010]. Nevertheless, regarding the cause-effect relationship, it has not been established which occurs first, the restrictive pattern or metabolic abnormalities. Alternatively other factor such as insulin resistance might cause both simultaneously.

3.4 Possible underlying mechanisms

Given that insulin resistance and related etiologies are the main cause of the restrictive lung, a plausible explanation for this is that several malignant cytokines, such as IL-6, CRP, TNF-α, and PAI-1, as well as decreased levels of adiponectin, which originate mostly from visceral and trunk subcutaneous adipocytes [Capeau, 2008; Meshkani, 2009; Gustafson,2010; Nakajima, 2010; Wannamethee, 2010], hyperglycemia, nonenzymatic glycosylation [Kaparianos, 2008; Chance, 2008], and diabetes-related growth hormones, such as insulin-like growth factor-I, insulin-like growth factor binding proteins, and transforming growth factor-β [Ezzat, 2008; Pilewski, 2005], may be related to histopathological alterations and functional abnormality because of oxidative and inflammatory processes. These molecules and resultant hyperinsulinemia, as well as ectopic fat deposition, leukocyte-endothelial cell adhesion, extracellular matrix deposition, fibroblast proliferation, pulmonary capillary leak,

pulmonary microangiopathy, and thickening of alveolar epithelia, may all converge into decreased lung compliance and diffusing capacity. Postmortem studies support the notion that the lung is a target organ for diabetic microangiopathy [Kaparianos, 2008; Klein, 2010]. Insulin resistance and resultant hyperinsulinemia may result in diastolic dysfunction of the lung via respiratory muscle weakness and functional failure by a similar pathology of skeletal muscle. Notably, lung-derived surfactant protein (SP)-A is associated with altered glucose tolerance and insulin resistance [Fernández-Real, 2008]. Fernández-Real (2008) found that SP-A levels in the blood were significantly higher among patients with glucose intolerance and type 2 diabetes than in those with normal glucose tolerance, even after adjustment for BMI, age, and smoking status. Additionally, SP-D, a lung-derived innate immune protein, is also associated with inflammation and metabolic abnormalities including insulin sensitivity [Fernández-Real, 2010]. Indeed, in the obese type 2 diabetes animal model, many qualitatively similar changes as in type 1 diabetes develop with extensive lipid deposition, altered alveolar type-2 cell ultrastructure and surfactant protein expression patterns [Foster, 2010]. Foster et al. (2010) recently reported in their study using obese diabetic rats that numerous lipid droplets were visible within alveolar interstitium, lipofibroblasts, and macrophages, particularly in subpleural regions, and that triglyceride content was higher not only in the liver but also in the lung. These findings suggest a definite relationship between metabolic abnormalities relating to insulin resistance and impairment of the lung. Potential histopathological features in the diabetic or metabolic abnormal lung are presented in **Figure 2**.
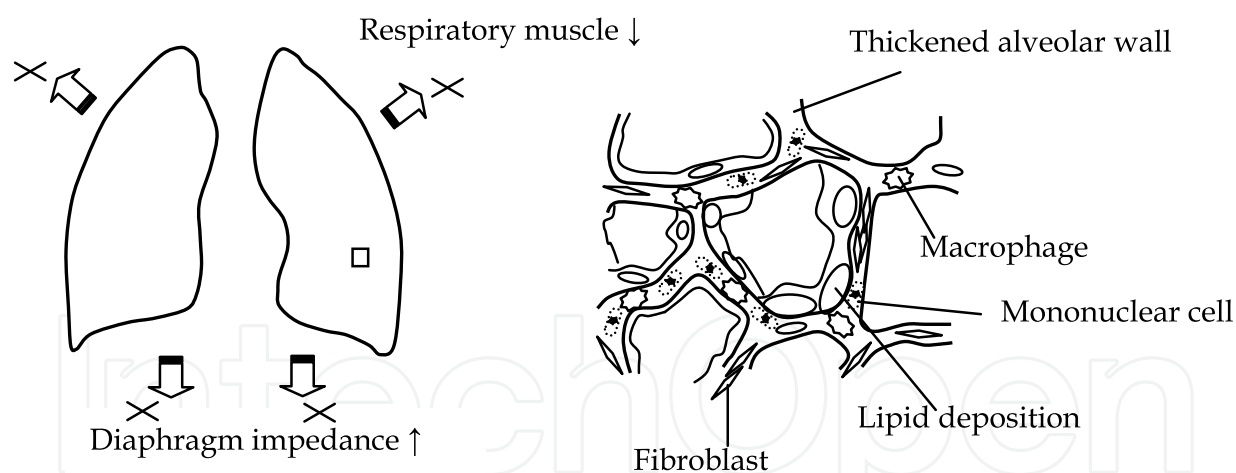

Fig. 2. A. Diastolic dysfunction of lung due to reduced respiratory muscle and increased diaphragm impedance. B. Histopathological features of alveolar space referring to Foster et al., 2010 and Klein et al., 2010. Lipid droplets are present in alveolar interstitium. Alveolar-capillary membrane is thickened with fibrotic changes.

3.5 Possible treatment for impaired lungs

The use of statins has been frequently discussed for patients with COPD [Fimognari, 2010; Dobler, 2009; Young, 2009], but their effect is unknown in RLD [Keddissi, 2007]. Statins prevent the decline in FEV_1 and FVC, irrespective of obstructive or restrictive disease

[Keddissi, 2007]. Considering that statins have a pleiotropic effect, this lung-protective effect may be because of the pleiotropic effect, including anti-inflammatory, anti-oxidant, anti-thrombogenic, and vascular function-restoring actions [Davignon, 2004]. Therefore, the mechanism underlying the association between metabolic disorders and RLD might be, at least in part, similar to that between cardiometabolic risk and cardiovascular disease. In addition, statin use is associated with slower rates of lung function decline in the elderly. These findings suggest a possible treatment for patients with impaired lung function and this possibility should be investigated further. However, lifestyle intervention is critical beyond any medications because insulin resistance and related etiologies develop and progress according to an unfavorable lifestyle.

3.6 Clinical perspective with respect to impaired lung function

Both types of impaired lung function, obstructive and restrictive lung disease, have been associated with an increased risk for high mortality and critical pathophysiology such as cardiovascular diseases probably because of chronic inflammation and oxidative stress. However, there is likely to be a difference in the underlying mechanism between obstructive and restrictive lung disease in terms of metabolic abnormalities.

Metabolic abnormalities, especially insulin resistance, and restrictive lung/reduced vital capacity belong to apparently unrelated fields. If there is a real association between insulin resistance and restrictive lung, it would be of substantial clinical interest and important for preventing possible synergic effects on the development and progression of fatal diseases. Although restrictive lung has been confirmed to be associated with increased mortality, particularly from diabetes, in recent studies [Fimognari, 2010, Guerra, 2010], it is unclear whether the restrictive pattern associated with metabolic abnormalities is a direct cause of mortality. Alternatively, RLD or the restrictive pattern might represent complications of longitudinal diabetes such as the three major complications of diabetes, because reduced lung volume and alveolar perfusion are correlated with extrapulmonary microangiopathy [Schnack, 1996]. Once RLD occurs in such patients, it may in turn worsen diabetes and metabolic abnormalities, resulting in aggravation of the pathogenesis. Intervention of the restrictive pattern by pulmonary rehabilitation or medication would clarify the cause-effect relationship between the restrictive pattern or RLD and cardiometabolic risks.

Further prospective as well as cross-sectional studies and clinical trials that address both fields are required to consider the potential importance of the subclinical restrictive pattern compared with obstructive lung, and to elucidate the complicated relationships between them.

4. Conclusion

Insulin resistance plays pivotal roles in all organs and tissues including the kidney and skin lesions. Ectopic fat deposition in the liver, muscle, and lung may be an initial hallmark of peripheral insulin resistance, particularly adipose tissue, which predominantly accumulates surplus energy as fat. If such conditions continue without proper treatment or intervention, second stages comprising oxidative stress, inflammation, and degeneration can occur and worsen organ function, along with impairment of insulin downsignaling in the cells of the target organ. Although some candidates have been considered for pharmacotherapy, these drugs may transiently improve the pathophysiology by redistribution of fat and change the direction of surplus lipids and carbohydrates, i.e., push back accumulated fat to original adipose tissues. Because of controversial clinical data concerning pharmacological therapies

as well as the cost and unknown adverse reactions, lifestyle interventions seem to be the only fundamental treatment for insulin resistance-related organ damage.

Further animal and human studies considering systemic organ damage and abnormal metabolism are required to explore the underlying complicated mechanisms and effective treatment and medications.

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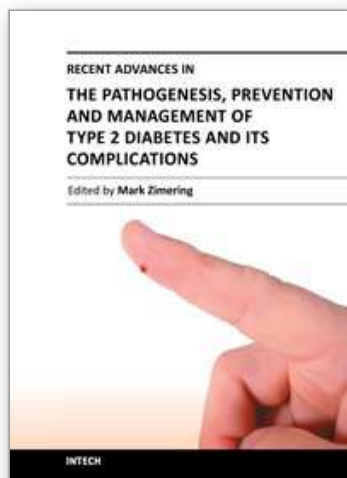
Recent Advances in the Pathogenesis, Prevention and Management of Type 2 Diabetes and its Complications
Edited by Prof. Mark Zimering

Type 2 diabetes "mellitus" affects nearly 120 million persons worldwide- and according to the World Health Organization this number is expected to double by the year 2030. Owing to a rapidly increasing disease prevalence, the medical, social and economic burdens associated with the microvascular and macrovascular complications of type 2 diabetes are likely to increase dramatically in the coming decades. In this volume, leading contributors to the field review the pathogenesis, treatment and management of type 2 diabetes and its complications. They provide invaluable insight and share their discoveries about potentially important new techniques for the diagnosis, treatment and prevention of diabetic complications.

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