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Muscular response and adaptation to diabetes mellitus

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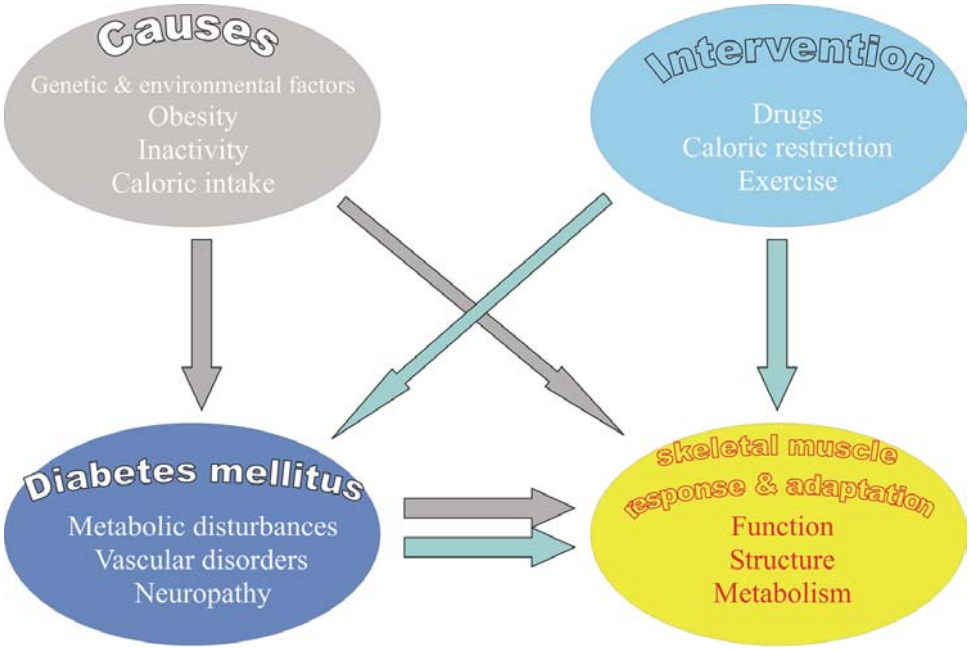

Figure 1. Schematic overview of etiology, muscular responses and the mechanisms involved as well as possible measures for intervention.

1. ABSTRACT

Diabetes mellitus (DM) is an epidemic medical challenge that threatens the health and life quality of people worldwide. DM impairs metabolic, neural and vascular function and thus has profound impacts on different systems and organs in the body. Though continuous endeavour has been made to study its etiology and mechanisms, no cure for DM has yet been found. DM development may be multi-factorial. The skeletal muscle is one of the most important systems, involved in the development of DM, and affected by insulin. DM induces diverse functional, metabolic, and structural changes in the skeletal muscle. DM reduces the functional capacity of skeletal muscle leading to muscle weakness, causes metabolic disturbance characterized by reduced cellular glucose uptake and fatty acid oxidation, and structural changes with muscle atrophy, augmented lipid deposition, decreased mitochondria as well as muscle fiber transformation. DM-induced changes in the skeletal muscle seem to be dependent on types and severity of DM as well as on muscle fibers. The central mechanism underlying these changes is impaired insulin action in the skeletal muscle.

2. INTRODUCTION

Diabetes mellitus (DM) is a common and costly disease. It is the sixth leading cause of death. DM shortens the average lifespan by up to 15 years and is the main cause of new cases of blindness, kidney failure and amputations (1). According to the reports of WHO, the worldwide prevalence of diabetes mellitus was 171,000,000 in 2000 and will be 366,000,000 in 2030. DM can be divided into four classes: type 1, type 2, gestational and other specific types secondary to different causes like pancreatitis. Type 2 DM is the most common and is characterized by insulin resistance.

The main pathological defects in DM consist of excessive hepatic glucose production, peripheral insulin resistance, and impaired beta-cell secretion function (2). Although the etiology of DM, especially type 2 DM, remains unclear, it is well-documented that DM is associated with a variety of factors including genetic and environmental circumstances, obesity, physical inactivity and caloric intake (3, 4)(Figure 1). The pivotal pathology of DM is impaired cellular glucose uptake that leads to persistent hyperglycaemia. Thus, DM is a systemic disorder involving almost all organs, especially the skeletal muscle.

Skeletal muscle accounts for up to 40% of human body mass and is the most important system for glucose uptake. On the one hand, the skeletal muscle is the major periphery in glucose utilization and therefore has profound impact on the development of DM. On the other hand, the pathophysiological mechanisms of DM cause tremendous changes in the skeletal muscle with regard to muscle atrophy, dysfunction, metabolic disturbance and structural changes (5-7)(Figure 1). It has been shown that the diabetic skeletal muscle undergoes an atrophic process which includes reduced muscle mass and muscle fiber diameters or cross-sectional area and a proportional shift of muscle fiber composition (6, 8, 9). Along with the structural changes, there are functional changes including reduced muscle strength and endurance capacity. A number of studies have shown that the changes occurring in the diabetic skeletal muscle are linked to DM-associated metabolic influences (10, 11), hemodynamic and vascular impairments (12, 13), as well as DM complications (14).

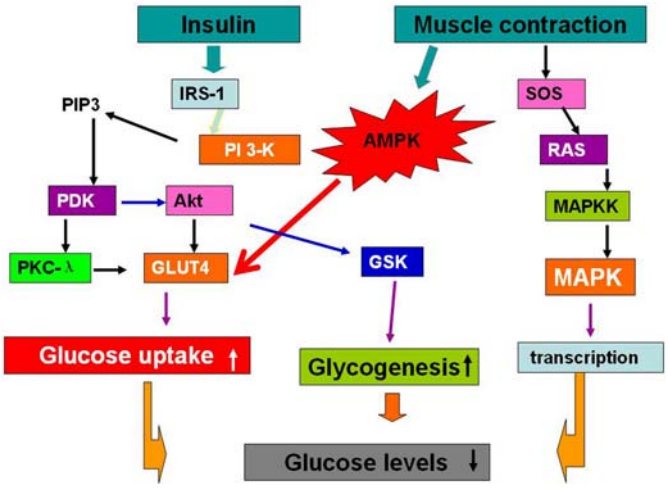

Figure 2. Illustration of molecular mechanisms involved in glucose uptake in the skeletal muscle. Insulin-stimulated glucose uptake is regulated through insulin action signaling pathways in which insulin receptor substrate (IRS), phosphatidylinositol-3-kinase (PI-3K), protein kinase C (PKC) and glucose transporter 4 (GLUT4) are involved. There are also insulin-independent pathways that include AMP-activated protein kinase (AMPK) and mitogen-activated protein kinase (MAPK), and GLUT4.

The mechanisms underlying the muscular response to DM are far from completely understood (15-17). The possible mechanisms may involve changes in insulin/adrenal receptors and glucose transporters (18-20), oxidative stress (21, 22), impaired endothelial function (23-25), mitochondrial dysfunction (26-28), and disturbed signal transduction (20, 29).

Although progress has been continuously achieved in the treatment of DM, especially type 1 DM with insulin (30, 31), handling DM (especially type 2 DM) is still a critical issue (32) because the etiology and mechanisms of DM development are not fully understood. Two principal problems still exist: how to cure DM and how to lower the prevalence of DM by primary and secondary prevention. In addition to pharmaceutical therapy (33-35), major effort has been made in the management of factors associated with DM (36-38). Studies have demonstrated that glucose tolerance can be significantly improved through caloric restriction and physical activity (36, 39). It is interesting to observe that exercise without weight loss can have positive effect on DM (40). Indeed, physical exercise may be the most important measure in the management of DM (36, 41, 42). Effective preventive intervention for DM has been pursued but the outcome has yet to be validated (43-45).

This review presents an overview of the factors associated with the development of DM and the mechanisms underlying insulin resistance with emphasis on muscular response and adaptations, especially in type 2 DM. Furthermore, this review also updates the newly emerging data on the effects of interventional measures on the skeletal muscle in terms of DM management and prevention.

3. PATHOPHYSIOLOGY OF DIABETES MELLITUS

The pathophysiology of DM is very complex and has not been completely elucidated. The principal pathophysiological disturbance in DM is defect of insulin action, which can manifest as reduced glucose tolerance or increased insulin resistance. The pathophysiology of DM with regard to the skeletal muscle involves glucose and lipid metabolism and protein turnover, blood supply and neural control, along with changes in muscular function and structure.

3.1. Physiological functions of insulin

Insulin is a 51-amino acid peptide, synthesized and secreted by β-cells of the islets. Its original peptide is removed from the endoplasmic reticulum and packaged into secretion vesicles in the Golgi. It is then folded to its native structure, and locked in this configuration by the formation of two disulfide bonds. A specific protease that cleaves the center third of the molecule allows the amino terminal B peptide disulfide to bind to the carboxy terminal A peptide.

Physiologically, insulin directly or indirectly affects the function of virtually all tissues in the body. Most insulin actions are directed to the metabolism of carbohydrates, lipids, and proteins.

3.1.1. Metabolic action of insulin

Glucose metabolism plays a pivotal role in energy turnover. The major biological action of insulin is regulation of the blood glucose level. It counters the concerted action of a number of hormones that can elevate blood glucose level. Insulin stimulates cellular glucose uptake and glycogenesis, inhibits glycogenolysis and gluconeogenesis (Figure 2). The action of insulin on glucose uptake in the skeletal muscle and adipose tissue is initiated by activation of the insulin receptor tyrosine kinase. This induces subsequent phosphorylation of insulin receptor substrate-1 (IRS-1), binding and activating phosphatidylinositol 3-kinase (PI-3K) and the serine kinase phosphoinositide-dependent kinase-1, which in turn

phosphorylates and activates Akt and protein kinase C (PKC)-λ, which subsequently leads to translocation of glucose transporter 4 (GLUT4) to the cell surface (46). A number of studies have shown that defects of insulin action on glucose metabolism can lead to impaired glucose tolerance and development of DM (46, 47).

In addition to its role in the regulation of glucose metabolism, insulin also has profound impacts on lipid metabolism by stimulating lipogenesis and inhibiting lipolysis, which decreases plasma fatty acid concentrations. It has been reported that insulin increases lipoprotein lipase activity in fat, stimulates fatty acid and triacylglycerol synthesis, attenuates fatty acid oxidation and augments triglyceride uptake into fat (48). Defects of insulin action on lipid metabolism cause accumulation of lipid in the cells, which worsens insulin resistance (49, 50).

Insulin also has distinct impact on protein metabolism. Insulin stimulates protein synthesis and lowers blood amino acid levels by increasing the rate of protein synthesis and facilitating transport of some amino acids into muscle, adipose tissue, liver and other cells. Insulin also inhibits protein degradation by lowering proteolysis activity in muscle. Insulin action defect can result in disturbed protein metabolism, i.e. decreased protein synthesis rate and increased protein degradation, in the skeletal muscle (51, 52).

3.1.2. Vascular action of insulin

The vascular system controls the delivery of nutrients and hormones to muscle, and the insulin action on metabolism is attributed to its effect on muscular blood supply (53). Insulin can cause vasodilatation, increase total blood flow and regulate capillary recruitment in skeletal muscle. It has been reported that insulin has a physiological role in dilating skeletal muscle vasculature in humans, and this effect occurs in a dose-dependent fashion within a half-maximal response of approximately 40 mU/ml (23, 24). Therefore, defects of insulin action have been demonstrated to be linked to the development of hypertension (54, 55). Though there is still controversy with regard to the vascular effects of insulin, it is generally accepted that insulin-stimulates glucose uptake which affects the vascular function (56). Studies have shown that capillary recruitment in the skeletal muscle may serve as an important mechanism for an early insulin action (57, 58). Increasing evidence suggests that vasodilatation by insulin is mediated by activation of endothelial nitric oxide synthase (eNOS) (59). Through this pathway, insulin can stimulate the production of NO in vascular endothelium. In this context, insulin stimulates NO production, leading to vasodilatation and increase in blood supply to the skeletal muscle (60), which can contribute to an augmentation of glucose uptake.

3.1.3. Neural action of insulin

Insulin is expressed at a high level in many areas of the brain and in different neural cells, including glial and neuronal cells (61). Cerebral insulin receptors play an important role in the regulation of energy homeostasis and neural degeneration (62). Insulin action inhibits tau hyperphosphorylation and thus may block the formation of neurofibrillary tangles. Loss of insulin receptor in nestin-positive neurons leads to mild insulin resistance and hypertriglyceridemia (63). Evidence derived from clinical and basic research has shown that insulin receptor is associated with cognitive function, including learning and memory. There is also evidence that signaling via IRSp58/53 may define a synapse-specific role for insulin in the brain (64).

As on the central nerve system, insulin has distinct impacts on the peripheral nerve system. Insulin action defects may be an important mechanism for the development of diabetic complications such as diabetic neuropathy and muscle weakness (65-67). It is suggested that a decrease in Na^+-K^+ pump concentration in nerve cells may be due to atrophy of the axons (68). In an animal experiment, Lesniewski *et al.* found that in streptozotocin (STZ)-induced muscle weakness in mice, the relative loss of torque via nerve stimulation (-43%) was greater ($P = 0.02$) than the force loss in the directly-stimulated muscle (-24%), indicating a functional neural deficit (69). This suggests that excitation-contraction uncoupling may contribute to the loss of muscle strength. It has been reported that changes in the presynaptic compartment of the neuromuscular junction may contribute to the muscle weakness (70). Further studies have shown that proximal and distal segments of peripheral nerves are affected equally in the early stages of experimental diabetic neuropathy (14). The insulin action on the nerve system may be attributed to its impact on the regulation of nerve growth factor (NGF), since it is evident that NGF plays an important role in maintaining nerve function and insulin action defect can affect NGF expression in different tissues (67, 71, 72).

3.2. Factors associated with diabetes mellitus

Although the etiology not completely clear, DM is generally considered as a multi-factorial disease. Genetic predisposition and environmental aspects as well as physical inactivity, caloric intake and obesity are the most important factors involved in the development of DM.

3.2.1. Genetic factors

Genetic factors are shown to be associated with development of DM (73). A number of epidemic studies have demonstrated a high concordance rate in monozygotic twins (74-76), familial clustering of the disease (77) and high morbidity in some races (78). Such data suggest a strong genetic component in the pathogenesis of type 2 DM (79, 80). Investigations in first-degree relatives of type 2 diabetic patients have also shown that the risk of hyperglycemia is increased about fourfold (81, 82). Furthermore, it was found that there is increased risk of diabetes in some races, for instance, the risk was 1.43 times that of Caucasians for Asians, 1.76 for Hispanics, and 2.18 for African-Americans (83).

The genetic influence on insulin action or insulin resistance is involved at different levels through the signal transduction pathway of insulin action. It has been reported that an altered expression of insulin receptor types A and B

in the skeletal muscle is related to insulin resistance (84, 85). It is evident that polymorphisms in the genes encoding IRS 1 and 2, peroxisome proliferator–activated receptors (PPARs), and GLUT4 glucose transporter may lead to severe insulin resistance and type 2 DM (86-90). PPARs are members of the nuclear hormone receptor family of transcription factors, and are involved in adipocyte differentiation and gene expression. Tavares *et al.*, for instance, found that Ala12 allele of the PPAR-γ2 gene was associated with lower fasting plasma insulin levels and higher insulin sensitivity in type 2 diabetic patients (91). In addition, positional cloning studies have mapped type 2 DM susceptibility to CAPN10, which encodes the intracellular cysteine protease, calpain 10 (92). However, the mechanisms for these defects have not been thoroughly elucidated. Several genes are found to be associated with DM. These genes include subtypes of maturity-onset diabetes of the young (93) and maternally-inherited diabetes with deafness caused by mitochondrial mutations (94).

3.2.2. Environmental factors

DM is probably a result of the interaction between genetic disposition and environmental effects, and the term "environment" has broadened in the past 40 years to include knowledge generated from sequencing genes (3).

Retrospective studies showed that low birth weight was associated with insulin resistance and type 2 diabetes in adulthood, which may result from a metabolic adaptation to poor fetal nutrition (95, 96). This seems to be supported by another study showing that low birth weight was associated with an odds ratio of 2.3 for diabetes, 1.8 for impaired glucose tolerance, and 3.3 for impaired fasting glucose control, especially in men with low birth weight and family disposition (97). It is considered that poor prenatal nutrition impairs the pancreas' ability to secrete enough insulin and induces permanent damage (98). Underlying mechanisms also include reprogramming of the hypothalamic-pituitary-adrenal axis, islet development, and insulin signaling pathways. Emerging data suggest that oxidative stress and mitochondrial dysfunction may also play a critical role in the pathogenesis of type 2 DM (99).

There is a study showing that the risk of type 2 DM is increased in current smokers, and those who have smoked for 20-39 years have significantly higher risk than non-smokers (100). This may be due to the fact that smoking can increase abdominal fat distribution without increasing weight, release oxygen-free radicals and reduce insulin sensitivity (101).

3.2.3. Obesity

The relationship between obesity and type 2 DM is well established (102). Although there are other risk factors for type 2 DM, a number of studies have shown that obesity, especially its visceral form, is a well-established risk factor for type 2 DM (103-105). In a longitudinal study on 4479 subjects, it was found that general obesity and high waist-to-hip ratio were associated with an increased odds ratio of developing diabetes by 2.4 and 2.6, respectively (106). The fact that obesity and type 2 DM are frequently associated suggests that these two conditions share a susceptibility gene (107). For instance, disrupted lipid metabolism due to mitochondrial dysfunction may lead to insulin resistance through inhibition of tyrosin phosphorylation of IRS-1 (46, 108). It seems likely that obesity is associated with low-grade inflammation of white adipose tissue resulting from chronic activation of the innate immune system, and this can subsequently lead to insulin resistance, impaired glucose tolerance and even DM (102). An increased availability of free fatty acids (FFAs) is of particular importance for the liver and skeletal muscle. The role of FFAs in type 2 DM is most evident in obese patients who have several abnormalities in FFA metabolism. Because of a mass effect, the release of FFAs from the total adipose tissue depot to the blood stream is increased in obese subjects and the high concentration of circulating FFAs impairs muscle glucose uptake by competitive inhibition (109). In upper-body obesity, which predisposes individuals to type 2 diabetes, the rate of lipolysis is accelerated in visceral adipose tissue (110). This results in a selective increase in FFA mobilization to the portal vein, which conducts visceral fat to the liver. A high 'portal' FFA concentration has undesirable effects on the liver, resulting in dyslipidaemia, hyperinsulinaemia, hyperglycemia and hepatic insulin resistance (109). In this context, FFAs may play an important role as "second signal" in the development of DM (110).

3.2.4. Physical inactivity

Type 2 DM can be considered as a disease of physical inactivity (111, 112). Physical inactivity is probably the principal mechanism responsible for obesity, which results from a mismatch between energy intake and expenditure (113). Physical inactivity seems to be an independent factor associated with the development of DM, the relationship between physical inactivity and type 2 diabetes can be independent on body weight (112). It is also evident that benefits of exercise can be achieved regardless of obesity (114). A lack of contractile activity by skeletal muscle is associated with less GLUT4 protein in the sarcolemma and a lower glucose uptake into the muscle. Muscle contraction-induced signal pathway in increased glucose uptake differs from insulin signaling, but is remarkably similar to that stimulated by hypoxia (3). It is evident that physical inactivity is significantly associated with impaired glucose tolerance and directly contributes to the cascade of events that lead to the expression of the 'exercise-deficient phenotype' associated with insulin resistance and type 2 DM (115, 116). Numerous studies have shown that physical exercise can restore insulin sensitivity (42, 117-119).

3.2.5. Caloric intake

Diet is an important environmental factor associated with insulin resistance or diabetes. Exposure of infants to dairy products (especially cow's milk and the milk protein β casein), high nitrates in drinking water, and low vitamin D consumption are linked to increased risk of type 1 DM. Type 2 DM is strongly associated with physical inactivity and malnutrition. It is known that an increased consumption of corn syrup with concomitantly reduced fiber intake seems to increase the risk of type 2 DM (120).

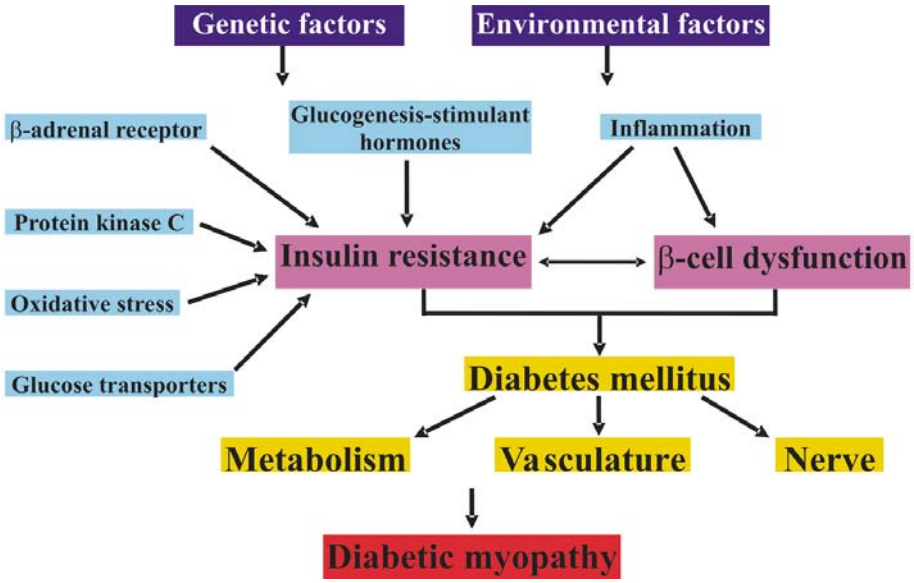

Figure 3. Factors and possible mechanisms responsible for insulin resistance and development of type 2 diabetes mellitus.

In an experimental study, fat feeding induced insulin resistance in liver and adipose tissue prior to metabolic changes in skeletal muscle, which caused an oversupply of energy substrate to skeletal muscle (121). An oversupply of energy is critical for development of diabetes. It is observed that diet with caloric restriction induced weight loss, reduced glycaemia and increased plasma ketone concentrations along with up-regulated gene expression of insulin signal pathways (122). It is evident that lipid deprivation selectively depletes intramyocellular lipid stores and promotes a normal metabolic state (in terms of insulin-mediated whole-body glucose disposal, intracellular insulin signaling, and circulating leptin levels) despite a persistent excess of total body fat mass (123). Though weight loss by caloric restriction improves insulin sensitivity, the effects on fatty acid metabolism are less conspicuous (124). One of the mechanisms of caloric intake responsible for development of diabetes may be the effect on glycogen metabolism, since a chronic caloric restriction alters activity of glycogen synthase and glycogen phosphorylase (125). Additionally, an oversupply of energy-induced disturbance of lipid metabolism can be related to insulin resistance because of lipotoxicity (50, 126).

3.3. Mechanisms of insulin resistance

The term "insulin resistance" adopted in clinical and experimental settings underscores the inability of insulin to promote normal glucose homeostasis. The mechanisms underlying insulin resistance are very complex and poorly understood. To date, several hypotheses have been raised. These include glucotoxicity (127), lipotoxicity (50, 128), mitochondrial dysfunction (46, 129, 130), and inflammation (102, 131).

In general, the mechanism responsible for insulin resistance is involved in the signal transduction pathways of insulin action (20, 132). The causes of acquired insulin resistance include glucotoxicity and lipotoxicity resulting from hyperglycemia and elevated FFA levels. Elevated levels of glucose and lipids increase oxidative stress, advanced glycation end products, flux through the hexosamine biosynthetic pathway, activation of PKC and proinflammatory pathways in skeletal muscle, and these changes have been shown to lead to insulin resistance (Figure 3).

3.3.1. Glucogenesis-stimulant hormones

Blood glucose level is a product of glucose intake, gluconeogenesis, glycogenolysis, glycolysis and glycogenesis. Insulin is a unique hormone to lower blood glucose level, which is counteracted in the regulation of blood glucose level by a variety of hormones termed glucogensis-stimulant hormones, including growth hormone, stress hormones like glucorticoide and adrenal cortical steroid as well as sex hormones (118). Glucagon, for instance, is an opposite hormone counteracting the insulin effect on glucose metabolism. Hyperglucagonemia and increased hepatic FFA oxidation are thought to be responsible for the increased hepatic gluconeogenic efficiency in diabetes (133). It has been shown that glucagon may be significant in the pathogenesis of muscle wasting in metabolic stresses such as diabetes and starvation (134).

Under stressful conditions (e.g. hypoglycemia, trauma, vigorous exercise), increased secretion of other hormones such as adrenaline, cortisol and growth hormone, and increased activity of the sympathetic nervous system, can affect glucose metabolism (135). It has been shown that glucocorticoid-induced insulin resistance probably reflects postreceptor defect(s) in the muscle (136). Glucocorticoids may also regulate the supply of gluconeogenic substrates through permissive effects on the lipolytic action of catecholamines and other hormones in adipose tissue and on the glycogenolytic action of catecholamines on skeletal

muscle, and through permissive effects on the stimulation of gluconeogenesis in the liver by glucagon and epinephrine (137).

In a previous animal study, it was shown that ß-adrenal receptor blocker (propanolol) could partly prevent insulin resistance by reducing plasma concentration of FFAs. This suggests an indirect effect of catecholamines on the development of insulin resistance in the skeletal muscle (138). Epinephrine increases hepatic glucose production and inhibits insulin secretion and glucose uptake (139).

Finally, the relationship between excessive secretion of growth hormone-induced insulin resistance and diabetes is well established (140-142). An over-expression of growth hormone can lead to the development of diabetes (141). The mechanisms responsible for growth hormone-induced insulin resistance may be attributed to the interaction between insulin and insulin-like growth factor-1 at the receptor level and signal transduction (143, 144) or common transcriptional programs (145).

3.3.2. β_3-adrenal receptor

The β_3-adrenergic receptor (β_3-AR) plays an important role in the regulation of lipid metabolism and glucose homeostasis. Through β_3-AR, adrenaline and noradrenaline stimulate lipolysis in human fat cells and increase glucose uptake in skeletal muscle. Therefore, the polymorphism of the β_3-AR gene may be associated with obesity and related type 2 DM, coronary heart disease and hypertension (146). It has been demonstrated that the adrenergic system regulates energy balance through the stimulation of both thermogenesis and lipid mobilization in brown and white adipose tissues in humans and animals (147, 148). It was shown that an increased component in visceral adipose tissue could be responsible for the enhanced delivery of FFAs into the portal vein, which may contribute to the development of insulin resistance as observed in abdominal obesity (149). A number of pharmacological studies have confirmed highly-selective β_3-AR agonists as potent agents to treat both obesity and DM (150), probably through affecting the expression of glucose transporters (146, 151). It has been suggested that abnormalities of sympathetic activity, including disturbances of leptin and β_3-AR, cause obesity and impaired glucose tolerance in rodents and humans (139, 146).

The defect of β_3-AR-induced insulin resistance may be related to leptin mechanism since it was found that a knockout of leptin receptor induced insulin resistance along with changes in β_3-AR gene expression (152). Indeed, the identification of leptin in 1994 led to great advances in understanding the regulation of energy balance in rodents and humans, and the progress in understanding central and peripheral leptin receptor signaling is stimulating the development of anti-obesity and anti-diabetic drugs (153). Leptin and insulin have opposite effects on lipid metabolism, with leptin favoring lipid oxidation and insulin favoring lipid storage as triglycerides (154). However, there might be a cross-talk in intracellular signaling stimulated by both leptin and insulin (155). Recently, it has been reported that phosphorylation of Ser-318 of IRS-1 mediates the inhibitory signal of leptin on the insulin-signaling cascade in obese subjects (156). It is reported that a knockout of adrenal receptor in animals leads to insulin resistance along with leptin resistance (157).

3.3.3. Protein kinase C

The PKC family is composed of at least 11 isoforms, which are categorized into three groups (conventional PKCα, ßI, ßII, and γ; novel PKC δ, ε, η and θ; and atypical PKC ζ and λ/ι) according to their structure and mechanisms of activation (158-160). PKC can be activated by insulin and can modulate insulin signaling by regulating the kinase activity of insulin receptor (Figure 2). PKC serves downstream of insulin receptor and PI-3K, and therefore, plays an important role in signal transduction of insulin action. Generally, activation of PKC has a negative regulatory effect on insulin-mediated response, and therefore, is associated with insulin resistance (161).

It is shown that chemical agents leading to insulin resistance decrease insulin receptor gene expression along with a decrease in phosphorylation of PKCζ and Akt/PKB (162). Defect in PKC activation in muscle leads to insulin resistance in skeletal muscle (163). Distribution of different PKC isoforms may serve as an important mechanism in regulating insulin action (159). Certain PKC isoforms (e.g., ζ and λ) have been identified as downstream targets of PI-3K activation, while diacylglycerol-sensitive PKCs (e.g., ϕ and ε) have negative regulatory effects on insulin signaling (159).

3.3.4. Glucose transporters

Decreased insulin-stimulated glucose transport, especially the major insulin-responsive glucose transporter, GLUT4, in skeletal muscle is a major contributing factor to insulin resistance in patients with type 2 diabetes and obesity (47). GLUT4 transporter proteins are located in cytosol under basal conditions. As postprandial glucose levels rise, the subsequent increase in circulating insulin promotes glucose transport in skeletal muscle and adipose tissue by stimulating the translocation of GLUT4 from intracellular storage vesicles to the plasma membrane, thereby increasing the rate of glucose uptake and maintaining blood glucose at a normal level (164). This insulin-induced redistribution of GLUT4 protein is achieved through a series of highly organized signal transduction pathways, at least two independent insulin receptor signals, one leading to the activation of PI-3K (46) and the other to the activation of AMP-activated protein kinase during hypoxia and contraction in skeletal muscle (159).

GLUT4 is the primary effector molecule for insulin-mediated glucose disposal. A number of studies on rats have shown that increased expression of GLUT4 using transgenic model results in increased whole-body glucose uptake and improves glucose homeostasis, while knockout of the GLUT4 gene causes impaired insulin tolerance and defects in glucose metabolism in skeletal muscle (20). An over-expression of GLUT4 can reverse insulin resistance

(165, 166). GLUT4 expression is up-regulated by exercise training and thyroid hormone treatment and is down-regulated by fasting, STZ-induced diabetes, obesity, high-fat diet, and denervation. However, it is also observed that no significant difference in muscular GLUT4 expression level was found between the diabetic and non-diabetic subjects, this suggests that a disturbed translocation of GLUT4 may have more impact on glucose uptake.

3.3.5. Oxidative stress

When caloric intake exceeds energy expenditure, the increased citric acid cycle activity generates an excess of mitochondrial NADH and reactive oxygen species (ROS). When excessive NADH cannot be dissipated by oxidative phosphorylation (or other mechanisms), the mitochondrial proton gradient increases and single electrons are transferred to oxygen, leading to the formation of free radicals, particularly superoxide anion (148). The cells normally have a protective mechanism for maintaining homeostasis of ROS. Uncoupling proteins (UCP), for instance UCP3, play an important role in the protective mechanism (167, 168). Studies have shown that oxidative stress alters the intracellular signaling pathway of insulin action and therefore is associated with insulin resistance (169). The state of oxidative stress may mediate insulin resistance during the development of DM (17). Oxidative stress- induced mitochondrial damages are attributed to the pathogenesis of insulin resistance (46, 170). Fatty acids are particularly prone to oxidative stress, resulting in the formation of lipid peroxides, which are cytotoxic, highly reactive and lead to oxidative damage to proteins and DNA. It is evident that oxidative stress in mitochondria is increased in UCP3 knockout mice, indicating that these mice are more prone to oxidative stress than wild type mice (46). In contrast, antioxidants like vitamin C and alpha-tocopherol can improve diabetes-induced muscle dysfunction (171, 172). Furthermore, the response of heat shock proteins, which serve as an important antioxidative mechanism in the cells, is clearly attenuated in diabetes (173-175).

3.4. Mechanisms of impaired insulin secretion

Although peripheral insulin resistance is one of the hallmarks of type 2 diabetes, insulin resistance alone is not sufficient to cause type 2 DM in the absence of a β-cell defect and the development of diabetes is based on the β-cell dysfunction (176). This includes defects in insulin secretion, proinsulin conversion to insulin, and amyloid deposition in the islet. Failure to produce insulin secretion (relatively or absolutely) is the major mechanism in the development of DM. Therefore, defects in pancreatic islet β-cell function play an important role in the development of DM. Numerous studies have demonstrated that treatment with STZ leading to β-cell destruction can induce DM (8, 177). Type 1 diabetes is caused by destruction of pancreatic β cells, and type 2 DM represents a heterogeneous disorder characterized by multiple defects in both insulin secretion and β-cell mass.

3.4.1. Genetic factors

Experimental studies on knockout mice have demonstrated that a mutation in insulin signaling may be responsible for the defect in insulin secretion (87), which appears to be a genetically-determined tendency to β-cell dysfunction. In transgenic mice, islet amyloid deposits and hyperglycemia during amyloid fibril formation lead to an initial defect in early insulin secretion and insulin action (178). Subjects with genetically-disposed insulin resistance and beta-cell insufficiency seem prone to developing type 2 diabetes (73). Further evidence supporting the genetic role in insulin deficiency is the presence of an autoantibody against insulin (179, 180). However, insulin deficiency is also thought to be non-genetic in nature. Studies show that defect in insulin secretion in overt non-insulin-dependent diabetes is dysfunctional: beta-cell mass is reduced by 20-40% in patients with long-standing diabetes, and the insulin secretion deficit is progressively worsened with more severe hyperglycemia and recovers considerably with improvement in glycemic control. These observations indicate that part of the insulin deficiency is an acquired abnormality in diabetes (181).

3.4.2. Inflammation

Inflammation leads to destruction of β-cells and thus results in insulin deficiency. A typical clinical case is acute pancreatitis (182, 183). Another typical example of inflammation leading to insulin deficiency is immune-mediated inflammation through insulin autoantibody (179, 180).

Diabetes is also associated with a systemic chronic inflammatory response characterized by altered cytokine production and activation of inflammatory signaling pathways (184). Chronic hyperglycemia can result in a reaction between glucose and the free amino acids and other large biological molecules, leading to formation of advanced glycation end products. These products are known to cause tissue damage through activation of inflammatory mediators such as IL-1ß, IL-6, and TNF-α, which are linked to impaired insulin secretion (185). It has been shown that TNF-α inhibits insulin-induced phosphorylation of the receptor tyrosine kinase in several cell types (186). Diabetes susceptibility is associated with an increase in intestinal inflammatory activity (187). It was found that the circulating monocytes were activated in newly-diagnosed type 1 diabetes (188). Furthermore, it is evident that anti-inflammatory treatment provides protection and enhances beta-cell function (189, 190).

3.4.3. Immune disorders

In type 1 DM, insulin deficiency results from autoimmune pancreatic β-cell destruction, possibly triggered by environmental factors. The pathogenesis of autoimmune destruction of β-cells involves interactions among susceptibility genes, auto-antigens, and environmental factors. Genetic susceptibility to type 1 diabetes in non-obese diabetic mice involves at least 17 Idd loci and has been mapped to the major histocompatibility complex (191). In non-obese mice, early antigen-presenting cell recruitment to islet lesions was temporally coincident with progressive T-cell infiltration. The auto-antigens include glutamic acid decarboxylase, insulinoma-associated protein, islet cell autoantibodies and other proteins in β

cells (191). It is thought that these proteins are exposed or released during normal β-cell turnover or β-cell injury, activating a cell-mediated immune response resulting in β-cell destruction (192). In the "Diabetes Prevention Trial", 3.7% of relatives of type 1 diabetic patients were individuals presenting islet cell auto-antibodies, and a high-risk cohort could be identified on the basis of insulin auto-antibodies and diminished first-phase insulin response to intravenous glucose (191).

Trials in gene therapy directed to autoimmune and inflammatory disorders have been conducted (193). Approaches delivering inflammatory cytokine inhibitors (anti-cytokines), or anti-inflammatory cytokines, such as transforming growth factor-1β, have protective effects against experimental autoimmune diseases (194).

4. MUSCULAR RESPONSE AND ADAPTATION TO DIABETES MELLITUS

As a systemic disorder, DM has profound impact on different systems in the body. The skeletal muscle is the most important system for insulin action, and thus insulin action disturbance can cause a variety of changes in the skeletal muscle including functional, structural, and metabolic changes.

4.1. Functional changes in diabetic muscles

DM may have profound effects on the function of the skeletal muscle. Studies have shown that DM leads to muscle weakness and exercise intolerance (10, 195, 196). Diabetes-induced muscle weakness results not only from changes in muscle mass and structure, but also from the functional changes in the skeletal muscle.

4.1.1. Oxygen uptake and muscle contraction in diabetic patients

Diabetic patients show a reduced exercise tolerance, which is certainly associated with the diabetes-induced metabolic disturbance. It has been reported that the working capacity in diabetic individuals is decreased in comparison with non-diabetic individuals (197). In comparison with non-diabetic women (overweight or lean), the maximal oxygen consumption (VO_{2max}) and oxygen uptake kinetics are significantly lowered in diabetic women (198). The lowered exercise capacity is associated with diabetic complications like retinopathy or nephropathy (199), however, reduced exercise capacity was also observed in diabetic patients without complications (200). At maximal exercise, for example, diabetic patients had a 24% lower maximal walking time and 20% lower VO_{2max} than controls (both $P < 0.05$), while hemodynamic measures did not differ between the groups (200).

Insulin-stimulated glucose uptake is important for muscle contraction, and therefore, impaired insulin function in DM can lead to disturbance of muscle contraction. It was shown that there was a 15-29% reduction in sciatic motor and sensory saphenous nerve conduction velocity in diabetics (201). The diabetes-induced changes in muscle contraction differ between muscle fibers. For example, in soleus (a muscle composed of mainly slow muscle fibers), there was a slowing of twitch times both for contraction and relaxation and a reduction of maximum tetanic relaxation rate (6). There was little effect on strength assessed by maximal tetanic tension production. In the fast muscle, twitch times were relatively unaffected, but maximum tetanic relaxation rate was reduced (6).

It is known that the Na^+/K^+-pump plays an important role in controlling muscular contraction (202). In STZ-induced diabetic rats, activities of Na^+/K^+ -ATPase and the Na^+ -pump are altered (204). There were significant increases in alpha 1- and alpha 2-levels and a detectable, though not statistically significant increase in beta 1-levels in diabetic skeletal muscle (203). This seems consistent with the observation by Nishida *et al.*, of a decrease in muscle Na^+/K^+-ATPase activity along with a compensatory increase in its alpha 2 subunit gene expression (204). The diabetes-induced muscle contraction impairment can also be associated with altered sarcolemmal Ca^{2+}-transport activity in skeletal muscle (205).

4.1.2. Changes in muscle strength in DM

Muscle weakness is one of several diabetic complaints. Complications in type 2 diabetes cause significant functional impairment (206). Andersen *et al.* reported that there was a significant decrease in muscle strength (determined with isokinetic dynamometry) of ankle flexors (by 17%) and ankle extensors (by 14%) in patients with 11-year diabetes (207). This muscle weakness may be the direct result of diabetic complications (208). Recently, a follow-up study on muscle strength has shown that, weakness of ankle plantar and dorsal flexors is progressive in patients with symptomatic diabetic neuropathy and changes with the severity of neuropathy (209).

It seems that not only diabetic complications but also diabetes itself can lead to muscle weakness (210). Muscle weakness was already observed at an early stage of diabetes with impaired glucose tolerance (211). Heimer *et al.* reported that the respiratory muscle was lacking in strength and endurance in patients with diabetes compared to non-diabetic controls (212).

It is likely that muscle weakness is not only a result of diabetes, but also a factor triggering the development of DM, since muscle weakness can precede the diabetes (213). The causality of diabetes-induced reduction in muscle strength may be multi-factorial. For instance, it was observed that the lipid content in skeletal muscle is related to muscle weakness (214).

4.1.3. Changes in endurance capacity in diabetic individuals

The endurance capacity in diabetic patients is reduced due to impaired energy metabolism. It is reported that aerobic fitness is related to metabolic parameters (215). Epidemiological studies have shown that lack of physical activity and physical fitness leads to an increased incidence of DM (216). It is evident that the time to exercise exhaustion was significantly lower in type 1 diabetic patients than in non-diabetic subjects (217). Similar results

were documented in type 2 diabetic patients (218). Lau *et al.* found that oxygen consumption and gas exchange efficiency at anaerobic threshold were significantly reduced in type 2 DM patients compared to controls (219). Furthermore, it has been reported that oxygen uptake was lower in diabetic men than in controls at the anaerobic threshold (15.0 ± 0.8 vs. 18.8 ± 1.0 ml·min^{-1}·kg^{-1}, $P < 0.01$), and the aerobic exercise capacity was related to hyperglycaemia (220).

The diabetes-induced decrease in exercise endurance capacity may be attributed to at least two mechanisms: the disturbance in energy metabolism, and changes in muscle structure (see below).

4.2. Structural changes in diabetic muscles

The skeletal muscle is an extremely heterogeneous system in structure and function (221, 222). The skeletal muscle is composed of muscle fibers which can be classified into different types based on their functional and biological characteristics (221). However, the fiber constitution of a muscle is not fixed, and responds to stress with a so-called muscle fiber transition (221, 223, 224) that serves as an important and fine mechanism for muscular adaptation. Muscle fiber transition is determined by transformation of myosin isoforms like myosin heavy chain (MHC) (225, 226). It is well-known that the response of skeletal muscle to cellular stress is also heterogeneous (227, 228). Therefore, the response of skeletal muscle to cellular stress in DM may involve muscle atrophy, vascular changes, neural changes, muscle fiber transition, and ultrastructural changes.

4.2.1. Muscle atrophy

A number of studies have shown that the skeletal muscle in DM undergoes an atrophy process which leads to muscle mass loss (195). Sexton *et al.*, for instance, found that STZ-induced DM resulted in a weight reduction by about 50% in the hindquarters of diabetic rats because of marked muscle atrophy (196). In this study, plantaris muscle weight was 41% less than that in control rats (174 ± 9 vs. 293 ± 11 mg; $P < 0.001$), and morphometric analysis revealed that the cross-sectional area of muscle fiber was reduced 39% in DM rats. A further study has shown that there is increased protein degradation activity along with decreased protein synthesis rate in chemically-induced DM (229), which may be responsible for the diabetic muscle atrophy. This seems to be supported by the evidence that degeneration and necrosis of myofibers take place in the diabetic skeletal muscle (9, 230). Furthermore, the degrees of muscle atrophy occurring in diabetic muscle were different with regard to muscle fiber types, so that a decreased area percentage of slow fibers and an increased area percentage of fast fibers of the whole muscle cross section were found (231). In a human study, it was found that the weight of appendicle skeletal muscle was significantly lower in DM patients than in controls (230). However, the prevalence of sarcopenia does not correlate with obesity or diabetes (5). This result may be attributed to the fact that DM is not necessarily the unique cause of muscle loss and imply that the major cause of sarcopenia in this study is physical inactivity. Recently, it has been demonstrated that the myofiber diameter of the extensor digitorum longus and rectus femoris muscles is reduced in STZ-diabetic rats (8).

4.2.2. Vascular changes in diabetic muscles

Insulin has distinct action on hemodynamics (23). Multi-focal infarction of skeletal muscle has been reported in advanced DM (232). Indeed, DM-induced angiopathy may serve as the most important mechanism for the common complications of DM like retinopathy (233), and nephropathy (234). Diabetic angiopathy is a collective term for conditions specific to the diabetic state, and angiopathy produces calcification of the media of larger arteries, but its major effects are on the microcirculation (235). The major vessel alterations in DM include thickened capillary basement membrane and atherosclerosis (233, 235, 236). Multiple factors, including altered levels of vasoactive substances, altered vasomotor responsiveness, chronic plasma volume expansion, and tissue hypoxia, contribute to a state of generalized microvascular vasodilatation in early insulin-dependent DM (237, 238). Although the mechanism of DM-induced angiopathy has not been completely elucidated yet, it is likely that the persistent vasodilatory action of insulin with the consequent elevation in capillary pressures and flows may be the initiating mechanism leading to both renal and extrarenal diabetic microangiopathy (233, 238, 239). It is known that endothelial dysfunction is an integral aspect of the insulin resistance syndrome, independent on hyperglycemia (24).

Studies have shown that insulin exerts a stimulant effect on activity of nitric oxide (NO) synthase and production of NO that mediates vasodilatation, and the impaired NO-mediated vasodilatation in DM may be responsible for the development of microangiopathy (131, 240-242). The other possible mechanism responsible for DM-induced angiopathy is an abnormally enhanced myogenic response of the skeletal muscle arterioles. This seems to be independent of the impaired endothelial function and likely due to the increased activity of voltage-dependent Ca^{2+} channels and/or up-regulation of PKC in arteriolar smooth muscle (243). Additionally, changed capillary permeability may be attributed to microangiopathy in DM (238). Whereas Leinonen *et al.* showed an increase in permeability of diabetic capillaries for clearance of ^{133}xenon in an earlier study (244), Gudbjornsdottir *et al.* found a significantly-reduced trans-capillary passage in type 2 diabetic subjects (245). Therefore, the contribution of DM-induced capillary permeability to angiopathy needs to be further clarified.

4.2.3. Diabetic neuropathy

Neuropathy is one of the most important and common complications of DM (69, 246). Even in a seldom reported case of cylindrical spirals (abnormal uniform membranous inclusions in skeletal muscle) in a 60-year-old man, a coincidence of slowly-progressing polyneuropathy confirmed by electrophysiological findings and DM was observed (247). It is well-known that neural function has determinant effects on muscle structure, nutrition and function (248, 249). Thus, DM-induced neuropathy may play an important role in the muscle response and

adaptation to DM. DM causes significant reduction in sciatic motor and sensory saphenous nerve conduction velocity, and these changes can be prevented by essential fatty acid diet supplement (201). This may indicate an involvement of abnormal fatty acid metabolism in the etiology of diabetic neuropathy.

Diabetic neuropathy includes sensory and motor neuron involvement. It was shown in an experimental study that neurotrophin-3 was significantly down-regulated (by about 70%) in hind-limb muscle of DM rats, and this down-regulation could be prevented by insulin (250). This suggests that, changes in sensory neurons were involved in the DM-induced neuropathy, since neurotrophin 3 acts as a target-derived neurotrophic factor for large caliber sensory neurons and plays a role in the maintenance of the adult phenotype of proprioceptive and mechanoreceptive fibers. The changes in moto neurons were observed in DM-induced neuropathy by Lesniewski *et al.* (69). In their study, the relative loss of torque via nerve stimulation (-43%) was greater than the force loss in the directly stimulated muscle (-24%), indicating a functional neural deficit in the experimental diabetes. Several studies have shown that DM-induced neural impairments are involved in the neuromuscular junction. In a previous study, Kjedsen *et al.* observed a reduction in Na^+-K^+ pump in the peripheral nerve in diabetic skeletal muscle (68). Fahim *et al.* found that nerve terminals showed less synaptic vesicles in STZ-induced diabetes and had degenerated mitochondria. Furthermore, disorganization of microtubules and neurofilaments was observed in the intramuscular nerves (66).

4.2.4. Muscle fiber transition in diabetic muscles

The skeletal muscle is composed of muscle fibers (222), with three types of muscle fibers known in mammalian skeletal muscle, i.e. type I, type IIa and type IIb (221). Single fiber analysis has shown that the composition of muscle fiber types is not fixed, but changeable in response to stimuli. In general, increased neuromuscular activity, such as electro-stimulation and exercise training, leads to a shift from fast fiber type to slow type, whereas decreased neuromuscular activity, like physical inactivity, denervation and treatment with thyroid hormone, can cause a shift from slow type to fast type (221). This fiber transition is determined by myosin isoforms, and there may be different myosin isoforms (hybrid fibers) even in the same single fiber. For MHC, there are four isoforms in rodent muscle (MHC I, MHC IIa, MHC IIx and MHC IIb, respectively) and in human skeletal muscle there are three (MHC I, MHC IIa and MHC IIx, respectively) (222). MHC isoform transition may serve as a fine mechanism for muscular adaptation to cellular stresses. A number of studies have shown that different MHC isoform transitions can be observed in response to different cellular stress (225, 226, 251, 252).

DM-induced muscle response is associated with the etiology of DM in a muscle fiber-specific manner. In an early study on the muscle of insulin-dependent DM, it was shown that hypoinsulinism had different effects on the 3 fiber types in heterogeneous rat skeletal muscle, and that slow-twitch fibers were least affected by the diabetic condition (253). This is supported by a further study by the same research group reporting that compensatory muscle hypertrophy was significantly reduced in fast-twitch muscle fibers in DM, whereas the slow-twitch fibers were capable of responding to the chronic overload condition (254). It is evident that hypoinsulinism causes morphological alterations in proximal skeletal muscle fibers that are similar to those of neurogenic myopathy, i.e., changes in the distribution of oxidative enzyme reactions, type I fiber hypertrophy, and type II fiber atrophy, which was greater in type IIB than in type IIA (255). These results seem to be in accordance with those of Stephenson *et al.*(256). Furthermore, it has been demonstrated that net glutamine uptake in fast-twitch fibers was decreased 75%-95%, but enhanced more than 2-fold in slow-twitch muscle from diabetic animals compared to non-diabetic controls (257). This result suggests fiber-specific effects of DM on skeletal muscle. The fiber-specific muscular response may be attributed to the fiber-specific defects in insulin signal transduction to glucose transport in diabetes (258).

The muscle responses in non-insulin dependent DM or type 2 DM, characterized by insulin resistance, seem different from those in insulin-dependent DM. In type 2 DM, there was a significant reduction in density of glucose transporter GLUT4 in slow muscle fibers compared to that in fast fibers, and at the same time there was a 75% reduction in slow fiber fraction (259). Thus, a reduction in the fraction of slow-twitch fibers, combined with a reduction in GLUT4 expression in slow fibers, may contribute to muscle insulin resistance in type 2 diabetes. A subsequent study showed that a reduced skeletal muscle type I fiber population was one component of a multi-factorial process involved in the development of insulin resistance (260). In a more recent study, muscle fiber composition and fiber type-specific glycolytic and oxidative enzyme activities were measured in slow oxidative, fast oxidative glycolytic, and fast glycolytic fibers (261). The authors demonstrated a 16% reduction in slow fiber fraction along with a 49% increase in fast fiber fraction, which may indicate that reduced oxidative enzyme activity in type 2 diabetic patients is most likely due to a reduction in slow oxidative fibers.

4.2.5. Ultrastructural and molecular changes in diabetic muscles

In animal experiments, the ultrastructural damage caused by diabetes is associated with the severity and duration of the disorder. At an early stage, single fiber atrophy was noted (262). With prolongation of the disorder, extensive damage was observed in the white muscle fibers, characterized by the atrophy and wide separation of myofibrils, irregularity, and thinness of myofilaments and massive glycogen deposition. The damage in the myofibril itself, however, was less pronounced in red and intermediate fibers, and these fibers had mitochondria that were more abnormal. Morphological changes vary in the three types of fibers. In diabetic animals, the mitochondria of fast oxidative glycolytic and slow oxidative fibers showed a loss of cristae and an increase in electron-dense granules (263). There was also an increased number of lipid

droplets close to the mitochondria and the nuclei, and a separation of individual muscle nuclei from satellite cells in slow oxidative fibers. The fast glycolytic fibers showed some disorientation of the T-tubular system. All these results suggest that STZ-diabetes has differential effects on the fine structure of the three fiber types of rat skeletal muscle (263). This seems to be supported by a further study showing different abnormal myofibers, muscle fiber degeneration, signs of denervation, and necrosis (264). The STZ-induced diabetic myofibers revealed excessive lipid accumulations and abnormal mitochondrial arrangements along with a significant shift in fiber type profile (53.6% type IIA and 46.4% type IIB). An ultrastructural study on muscle biopsies from the tongue and soleus muscle of diabetic Chinese hamsters showed the presence of excessive lipid droplets within the muscle fibers (265). These droplets were often found in the cytoplasm near mitochondria, sometimes surrounded by one or more mitochondria. However, few ultrastructural studies on skeletal muscle have been performed in human subjects. One study with electron microscopy showed that skeletal muscle mitochondria were smaller in type 2 diabetic and obese subjects than in normal volunteers (9).

An insulin receptor defect is an important issue in DM. Knockout of the insulin receptor gene can cause metabolic changes similar to those of type 2 DM (266). Studies have shown that changes in expression of insulin receptor isoforms occur in the diabetic muscle. In comparison with non-diabetic muscle, the expression of insulin receptor-B is up-regulated in diabetic muscle. This can be responsible for insulin resistance, since this isoform of receptor has lower affinity to insulin (267-269). However, there are also controversial results derived from an animal study that showed no altered expression of the two insulin receptor isoforms in the skeletal muscle (270).

It has been shown in rats that expression of GLUT4 at the protein level correlates with plasma glucose (271). Diabetes-induced changes in GLUT4 expression in the skeletal muscle seem to be muscle-fiber specific. Gaster *et al.* found that GLUT4 density was significantly higher in slow fibers than in fast fibers from both lean and obese subjects, while GLUT4 density was significantly lower in slow fibers than in fast fibers in type 2 diabetic subjects (259).

Another significant alteration in the diabetic skeletal muscle is an impaired response of stress protein or heat shock protein (Hsp), and studies on Hsp response in diabetic muscle have been reported (144, 272). Bruce *et al.* showed that intramuscular Hsp70 and heme oxygenase-1 (a kind of small Hsp) mRNA were reduced in patients with type 2 DM (174), and the data provided new evidence that the pathogenesis of type 2 DM involved perturbations to the antioxidant defense mechanism within skeletal muscle. This result is consistent with that reported by Kurucz *et al.* who demonstrated that Hsp70 mRNA was lowered in type 2 diabetes and the Hsp70 mRNA level correlated with the glucose uptake rate (175). Interestingly, 8-week endurance exercise training can modulate Hsp70 response in diabetics (173), so that endurance training may offset some of the adverse effects of diabetes by up-regulating tissue Hsp expression. However, in that study, endurance training induced activation and expression of transcriptional regulatory heat shock factor-1 only in non-diabetic controls. Thus, diabetes may impair Hsp response, possibly via transcriptionally- mediated mechanisms.

In addition, diabetes-induced changes in insulin signal transduction have been extensively studied with respect to molecular changes in the skeletal muscle, (see section 3: pathophysiology of diabetes mellitus).

4.3. Metabolic changes in diabetic muscles

4.3.1. Changes in energy metabolism

Skeletal muscle is strongly dependent on oxidative phosphorylation for energy production and characterized by the ability to switch easily between glucose and fat oxidation in response to energy challenge (173). The manifestations of insulin resistance in type 2 diabetes and obesity include reduced glucose transport and phosphorylation and reduced rates of glycogen synthesis, whereas abnormal fatty acid metabolism entails increased accumulation of triglycerides and other lipid metabolites as well as dysregulation of lipid oxidation during fasting and insulin-stimulated conditions (173).

It was observed that the overall capacity for energy turnover in diabetes was reduced (273), and the maximal oxygen consumption as well as oxygen kinetics were reduced (198). The reduced capacity of oxygen consumption is probably an early phenomenon of diabetes-induced energy metabolism disturbance (274). A previous study showed that the diabetes-induced changes in energy metabolism were muscle-fiber specific (275)(see below).

Multiple factors can be involved in the impairment of the metabolic flexibility in diabetic muscles. An impaired functional capacity of mitochondria, which are the primary site of fuel metabolism and ATP production in the skeletal muscle, is one factor leading to dysregulation of oxidation enzyme, and thereby perturbed metabolism of both glucose and fatty acids (276). Maternally-inherited defects in mitochondrial DNA with functional defects have been shown to cause an insulin deficiency, and insulin resistance in type 2 diabetes is reportedly associated with reduced muscle mitochondrial DNA copy numbers and mitochondrial protein synthesis rate (276).

4.3.2. Glucose metabolism

The skeletal muscle accounts for the majority of insulin-stimulated glucose uptake (277). Therefore, impaired insulin function in diabetes may have profound impact on glucose metabolism in the skeletal muscle and be responsible for the hyperglycemia.

It is reported that the store of glycogen in the diabetic skeletal muscle is significantly reduced (278), which is associated with decreased glycogen synthase activity. It is evident that glycogen synthase I activity, and glucose 6-phosphate (G-6-P) content in skeletal muscle were significantly increased after insulin injection in non-diabetic rats, while a blunted reaction was observed in

diabetic rats (277). The first step in glucose uptake in skeletal muscle is the phosphorylation of glucose to G-6-P by hexokinase. It has been shown that the activity as well as gene expression of hexokinase in the diabetic skeletal muscle is decreased (279, 280). For healthy subjects, 31% of the glucose dose given was utilized in direct glycogenesis and this was decreased to 15% in diabetics (281). In diabetes, both oxidative and glycolytic pathways in the skeletal muscle are altered in a fiber type-dependent manner. A 'glucose-fatty acid cycle' in skeletal muscles was observed 5 days after the administration of a single injection of streptozotocin (275). This cycle is more important in fast-oxidative-glycolytic and slow-oxidative fibers than in fast-glycolytic fibers. It was observed that blood lactate was increased and diabetes-induced hyperlactatemia was not associated with changes in monocarboxylate transporter expression but with alterations of oxidative and glycolytic enzymes (282). Furthermore, the blood lactate level in diabetics was higher after exercise than that in non-diabetic subjects (283).

4.3.3. Lipid metabolism

Although insulin resistance refers primarily to the insulin function on glucose metabolism, the underlying mechanisms seem to be "shifted" from the traditional "glucocentric" to a "lipocentric" viewpoint (284). Based on the physiological function of insulin on lipid metabolism, insulin resistance-induced hyperinsulinemia can stimulate synthesis of fatty acids and bring about disturbance of lipid metabolism.

The basic disturbances of lipid metabolism in type 2 diabetes include increased adipose tissue stores, increased triacylglycerol excess, impaired uptake and/or oxidation of fatty acids during post-absorptive conditions (285). Studies have shown that there is a blunted breakdown in lipid dynamics in skeletal muscle of individuals with insulin resistance, manifested by elevated levels of circulating FFAs (146), decreased rates of lipid oxidation (286), and excess accumulation of intramyocellular triacylglycerol (9, 287). In a study on transgenic mice over-expressing apoA-II, an elevated level of both FFAs and triglycerides was observed, which suggests a link between the apoA-II gene locus and plasma FFA levels in type 2 diabetes (146). The disturbed lipid metabolism in diabetes is also reflected by the close relationship between diabetes and hyperlipidemia (288). An augmented fatty acid uptake in type 2 diabetes may be an important factor leading to increased fatty acid storage within the muscle (16). In severe defects of insulin action, as seen in uncontrolled diabetes, cell starvation leads to increased ketone body production in the muscle which can account for as much as 25% of total ketone production in the body (289). The diabetes-induced disturbance of lipid metabolism is at least partly responsible for obesity development in diabetic patients (109).

4.3.4. Protein metabolism

The skeletal muscle proteins are constantly under synthesis and degradation, and the anabolic effect of insulin on protein metabolism is blunted in diabetes. Generally, the diabetic effect on skeletal muscle protein metabolism is negative in terms of nitrogen balance. Therefore, as described above, diabetes can lead to muscle atrophy. The other aspect of diabetic effect on protein metabolism is attributable to disturbed energy metabolism, in which, a part of proteins is switched to energy turnover due to reduced glucose uptake and utilization as well as to fatty acid oxidation.

Studies have shown that there is an increase in both protein breakdown and protein synthesis during insulin deprivation. Because the magnitude of the increase in protein breakdown is greater than that in synthesis, there is a net protein loss during insulin deprivation (290). A previous study showed that though insulin decreases whole-body protein breakdown in splanchnic and leg tissues in type 1 diabetes, defects of insulin action can selectively decrease protein synthesis in splanchnic tissues, which accounted for the observed decrease in whole-body protein synthesis (291). There are studies demonstrating a substantial increase in leucine transamination during insulin deprivation, which contributes to leucine catabolism in type 2 diabetes (292). In dialysis patients, the presence of diabetes showed a potential to increase body protein losses and muscle wasting (292), and no significant difference was found between diabetic and non-diabetic patients in terms of protein synthesis. Thus, diabetes leads to significantly higher negative net protein balance in diabetic patients. Previous studies on whole-body protein turnover have shown that insulin deficiency in diabetic skeletal muscle causes marked reduction in protein synthesis rates (293, 229) as well as diminished nitrogen repletion and increased amino acid oxidation. These effects can be reversed by insulin treatment (292). However, it was reported that acute insulin deprivation affected neither the synthesis rate nor the ratio of MHC to mixed muscle protein in type 1 diabetic subjects. The fractional synthesis rates of MHC and mixed muscle protein during insulin treatment are similar to those of control subjects (292).

5. MANAGEMENT OF DIABETIC MUSCLES

As shown in Figure 1, diabetes is linked to multiple factors, especially genetic factors, lifestyle and physical inactivity, and the pivotal mechanism responsible for DM is insulin action defect in the skeletal muscle. Therefore, the management of diabetic muscle includes a number of measures involving pharmacological therapies, caloric restriction and physical activity (Figure 1). All the measures aim to substitute or restore insulin action, minimize or correct the factors associated with diabetes, especially insulin resistance, prevent hyperglycemia, and reestablish muscle structure and functions.

5.1. Pharmacological strategy

Pharmacological therapy, including gene therapy, oral anti-diabetic drugs and insulin, contributes greatly to the advanced management of DM. It is well documented that pharmacological therapy can significantly improve metabolism, especially glucose control, and reduce diabetic complications. However, there has not been any systematic study on effect of pharmacological therapy on muscular function and structure in diabetes.

5.1.1. Gene therapy

Genetic factors are involved in the initiation and development of DM (73). Thus, gene therapy may serve as an important and promising measure to treat diabetic muscle (294).

Studies have shown that stem cell therapy can effectively improve insulin action and metabolism in diabetes (295). An electrotransfer-enhanced DNA injection in muscle could lead to release of biologically-active insulin, restoration of basal insulin levels, and lowering of fasting blood glucose level with increased survival in severe diabetes (296). Because GLUT4 is dysregulated in skeletal muscle in non-insulin-dependent diabetic patients, it is an attractive target for gene therapy. Studies have shown that an over-expression of GLUT4 in muscle results in augmented glucose uptake and metabolism, and prevents development of insulin resistance in transgenic mice (20), whereas genetic ablation of GLUT4 results in impaired glucose tolerance and defects in glucose metabolism in skeletal muscle. However, it is evident that insulin resistance is associated with disturbed GLUT4 translocation rather than GLUT4 expression (297-300). Thus, the over-expression of GLUT4 to restore the impaired glucose uptake seems not to be an ideal measure in treating insulin resistance.

Further study has also shown that a synergic action can be achieved in skeletal muscle between the insulin produced and the increased glucose phosphorylation by glucokinase in double-transgenic mice using adeno-associated viral 1 vectors (for insulin and glucokinase) (301). Therefore, the joint action of basal insulin production and glucokinase activity may generate a "glucose sensor" in skeletal muscle that allows proper regulation of blood glucose in diabetic animals and thus prevents secondary complications (301).

Although gene therapy sounds quite rational, the major problem with gene therapy may be technical. Gene therapy requires an effective transfer of the assigned gene *in vivo* resulting in high-level and long-term transgenic expression, all in the absence of significant toxicity or inflammatory responses (302), and a clear identification of the interactions of the gene defects involved in diabetic patients.

5.1.2. Oral anti-diabetic agents

A number of anti-diabetic agents have been proven effective in treating diabetes, especially type 2 diabetes. Based on their mechanisms of action, oral anti-diabetic agents are classified as stimulating insulin secretion, reducing glucose production, or increasing insulin sensitivity.

As the most commonly-prescribed oral anti-diabetic drug, metformin can decrease blood glucose by reducing hepatic glucose production, enhancing skeletal muscle glucose uptake and glycolysis, reducing lipid synthesis, and increasing oxidation of fatty acids, thereby improving insulin sensitivity and insulin-stimulated glucose uptake (303). It is proposed that the molecular basis of metformin action in skeletal muscle involves the translocation of glucose transporter proteins from an intracellular compartment to the plasma membrane (304).

Thiazolidinediones like rosiglitazone represent a new class of agents that reduce insulin resistance and improve insulin sensitivity and are thus widely used in type 2 diabetes (305). It is evident that treatment of insulin-resistant C2C12 cells with thiazolidinediones leads to increase in insulin-stimulated muscle glucose transport and glucose uptake by activating tyrosine phosphorylation of the insulin receptor and PI-3K (276).

The sulphonylureas and glinides are another two groups: one selectively inhibits beta cell sulphonylurea receptors (SUR1), and the other blocks cardiovascular and skeletal muscle sulphonylurea receptors (SUR2) (306). The mechanism of drug action is inhibition of the ATP-sensitive K^+ channels, which leads to depolarization of the cells and insulin secretion.

5.1.3. Insulin substitution

Insulin substitution is a very important and sometimes a key approach to DM for improving glucose control and reducing the risk of diabetic complications, especially in treatment of type 1 diabetes (30, 31). However, insulin therapy is still a critical issue for type 2 diabetes (32). Since diabetes is considered as an insulin insufficiency (absolute or relative), insulin substitution should be considered as the initial therapy, particularly in lean individuals or those hospitalized or acutely ill (176).

It is shown that islet transplantation fully corrected the diabetes-induced changes in protein tyrosine phosphorylation and PI- 3K activity and normalized IRS-1 and IRS-2 protein content in both skeletal muscle and myocardium (307). A study has shown that insulin therapy can normalize blood glucose level and improve insulin-stimulated glycogen synthesis in type 2 diabetes (30). It is evident that insulin therapy can improve or restore the signaling of insulin action on glucose uptake in the skeletal muscle (30, 308).

5.2. Lifestyle intervention

As stated above, lifestyle factors are associated with the incidence and development of diabetes. Thus, measures to alter lifestyle, such as diet control, exercise and weight loss, are cornerstones of diabetes management to improve blood glucose control, reduce/prevent muscle wasting and abnormality (309). Numerous studies have shown that lifestyle intervention produces profound effects on the incidence and progression of DM (310), and therefore plays an important role in DM prevention and treatment (45).

Studies have shown that weight loss, especially through physical exercise, can bring about improvement in insulin resistance, enhanced basal metabolism and activity levels as well as counteract age- and disease-related muscle wasting (311). Different mechanisms may be involved in the effect of weight reduction on diabetic muscle, and they depend on the measures leading to weight loss, such as

caloric restriction and physical activity (see below). Weight loss can reduce intramuscular lipid accumulation that serves as an important mechanism responsible for insulin resistance (312). It was observed that body weight loss resulted in a decrease of postprandial IL-6 release from skeletal muscle (313). In a study with dynamic positron emission tomography imaging, it was shown that a 4-month weight loss program led to significant improvement in glucose transport and phosphorylation (314).

5.3. Caloric restriction

Caloric intake is an important factor associated with the incidence and development of DM, caloric restriction is thus crucial for treating diabetes. Its beneficial effects on optimal metabolic outcomes include weight loss, reduced glycaemia and lipid mass, altered ectopic fat accumulation in muscle along with up-regulated gene expression of insulin signal pathways (122). A previous study showed that energy restriction caused metabolic improvement in the pre-diabetic and diabetic state (44). A further study demonstrated that caloric restriction induced a decrease in lipid peroxidation, improvement in the antioxidant defense systems and restoration of the redox status in the liver (125).

There is evidence that low-carbohydrate diets (restricting total carbohydrate to <130 g/day) in the management of obese patients with type 2 diabetes significantly improved glycemic control, weight loss and anti-hyperglycemic effect (315). However, it is not recommended in the treatment of diabetes because the long-term effects of these diets are unknown (317). An average amount of carbohydrate recommended for patients with diabetes is 55 to 60% of the total caloric intake (316) as suggested for the normal population.

A disturbance of lipid metabolism induced by energy over-supply can be related to insulin resistance because of lipotoxicity (50, 126). It was demonstrated that normal intake of fat should be limited to a maximum of 30% of the total caloric intake for treating diabetes (121). It has been shown that lipid deprivation selectively depletes intramyocellular lipid stores and induces a normal metabolic state (in terms of insulin-mediated whole-body glucose disposal, intracellular insulin signaling, and circulating leptin levels) despite a persistent excess of total body fat mass (123).

Diabetic patients have similar protein requirements to those of the general population — about 0.86 g/kg per day (317). To maintain muscle mass and energy expenditure, protein intake should make up 30% of total daily calorie intake (315). It is evident that nutritional supplementation with oral amino acid mixture significantly reduced fasting and postprandial blood glucose, HbA1c in elderly subjects with type 2 diabetes (117). It is likely that increased amino acid antagonizes muscle catabolism by means of increased endogenous protein synthesis. However, excessive protein intake should be avoided as it may contribute to the pathogenesis of diabetic nephropathy (117).

Although the effects of caloric restriction on DM in terms of energy metabolism and glucose control are quite certain, the impact of caloric restriction on diabetic skeletal muscle remains unclear.

5.4. Physical exercise

As depicted in Figure 1, multiple factors are involved in the development and progression of DM. Physical exercise can counteract many of these factors, and therefore exerts beneficial effects on diabetic patients, especially on diabetic muscle. Studies has demonstrated that physical exercise improved diabetic outcome and glucose metabolism, reduced diabetic complications, as well as restored functional and structural changes in the skeletal muscle.

5.4.1. General effects of exercise on DM

Regular exercise provides multiple health benefits, such as improved sense of wellbeing and protection against all-cause mortality in DM patients. Numerous studies have shown that physical exercise increases insulin sensitivity (42, 117-119), improves blood glucose control (318) and lipid profile (117) and lowers body weight (316). Physical exercise stimulates expression/translocation of glucose transporters and glucose uptake (319-321). There is evidence that endurance training improves the lipid profile in already physically active type 1 diabetic men, and this effect could be independent on body composition or glycemic control (322). In a prospective cohort study, it was shown that walking at least 2 hours per week led to a reduction in the incidence of premature death by 39%–54% from all causes and by 34%–53% from cardiovascular disease among patients with diabetes (323). In elderly diabetic patients, physical exercise improves both insulin sensitivity and quality of life (324).

Epidemiological studies have suggested that physical exercise substantially reduces the incidence of type 2 diabetes in high-risk individuals, indicating the importance of regular physical activity for the primary prevention of type 2 diabetes (325). It has been shown that an increase of 500 kcal in energy expenditure each week was accompanied by a 6% decrease in diabetic incidence (326).

5.4.2. Effects of exercise on diabetic muscles

DM can cause a series of pathological changes in the skeletal muscle, including impaired muscular function, disturbed metabolism, and altered muscle structure. Physical exercise is proven to be an effective measure in the management of DM, and has profound impact on the skeletal muscle with respect to function, metabolism, and structure.

5.4.2.1. Exercise effects on diabetic muscle function

Muscle function is impaired in diabetic patients and the functional impairments involve muscle strength and muscle endurance capacity. Studies have shown that physical exercise restores or improves muscle function in DM. It is evident that physical exercise can significantly improve physiological parameters (total mass, fat mass,

grip strength, peak flow, flexibility, and VO_{2max}) after a 12-week program (327). In elderly diabetic patients, strength training can increase skeletal muscle volume and strength (324).

Reduced endurance capacity is a typical muscle functional impairment caused by DM. A previous study showed that an endurance training program for 10 - 15 weeks led to an improvement in maximum aerobic capacity as well as endurance capacity by 10%, along with an 80% increase in intramuscular glycogen store in middle-aged type 2 diabetic patients (328). An 8-week combined aerobic and resistance exercise training showed a significant increase in exercise test duration along with increase in peak oxygen uptake (329). Recently, the benefit of physical exercise has been discussed in terms of different forms, such as strength training or endurance training (330). Interestingly, resistance training alone can also lead to an increase in endurance capacity along with an improvement of glucose metabolism in diabetic individuals (331). It seems that both of these training forms are beneficial to the diabetic muscle. It has been reported that resistive exercise training led to a significant increase in leg and arm strength (332). The maximal leg and arm strength could be distinctly increased through progressive resistance training (333). Furthermore, resistance training for 4-6 weeks could improve quadriceps strength by 16%, although the maximal oxygen uptake remained unchanged (334).

5.4.2.2. Exercise effects on diabetic muscle metabolism

DM-caused metabolic disorders are involved in different aspects, depending upon diabetic causes, severity, and types. Studies have shown that physical activity can counteract diabetes-induced metabolic disorders (335, 336). It is known that impaired oxygen uptake kinetic response to exercise is associated with diabetes-induced limited oxygen consumption (337). In comparison with non-diabetic women, diabetic individuals benefited more from an exercise-training program for 3 months by augmenting oxygen uptake kinetics (198).

Numerous studies have demonstrated that physical exercise can improve glucose metabolism in DM (338). A long-term training program could provide beneficial effects on blood glucose level and HbA1c in type 2 diabetic patients (339). Dela *et al.* observed that one-legged exercise training (10 weeks) could significantly improve the insulin-stimulated muscle glucose clearance in diabetic muscle (340). A previous study showed that neither aerobic nor resistive training altered muscle glycogen synthase total activity, glycogen content, or levels of PI-3K. However, the fractional activity of glycogen synthase in response to insulin stimulation in vastus lateralis muscle could be increased significantly by aerobic training (332), suggesting an exercise-induced improvement in insulin sensitivity. In an animal study, the skeletal muscle derived from diabetic rats showed decreased oxidation and increased release of lactate, which could be distinctly affected by sciatic-nerve stimulation (341), suggesting that muscle contraction has an impact on lactate oxidation in diabetic skeletal muscle.

As stated above, fatty acids that are taken up by muscle and not oxidized may increase triacylglycerol storage in muscle, which is associated with skeletal muscle insulin resistance in DM (287). A previous study showed that in comparison with resting values, plasma FFA oxidation was significantly elevated by exercise (2.13 ± 0.51 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ at rest versus 8.10 ± 1.44 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ during exercise), and plasma FFA oxidation is not impaired during exercise in non-obese type 2 diabetic patients (342). There is a study demonstrating that the decreased rate of fatty acid oxidation in obesity could be significantly augmented by exercise on cycle ergometer (343). It is indicated that the fatty acid translocase is the major fatty acid transporter and plays an important role in insulin-induced increase of muscle fatty acid uptake and utilization during exercise (344). A further study showed that exercise combined with weight loss enhanced post-absorptive fat oxidation in skeletal muscle (345). The exercise effects on lipid metabolism in skeletal muscle seem to be muscle-fiber specific. It is evident that exercise training improved the total GLUT4 protein expression ($P < 0.01$), decreased the intramuscular triglyceride concentration, increased the fatty acid oxidation capacity, and the number of capillaries around type I fibers, whereas no significant alteration was observed around type II fibers (346).

However, the reported correlation between intramuscular triglyceride content and insulin resistance does not represent a functional relationship, since it has been reported that a greater storage of intramuscular triglyceride was observed in both well-trained athletes and diabetic individuals (347). The former represents an adaptive response to endurance training, allowing a greater contribution of the intramuscular triglyceride storage pool as a substrate source during exercise, while the latter, in contrast, seems to be secondary to a structural imbalance between plasma FFA availability, fatty acid storage and oxidation in DM.

The effect of exercise on protein metabolism in diabetic muscle has not been extensively investigated. Biochemical pathways that control protein synthesis are complex and include a series of cellular processes. In diabetic muscle, there is a reduced protein synthesis rate. In mild or moderate diabetes, exercise training can induce a higher rate of protein synthesis (348, 349) whereas this could not be observed in severe diabetes (350). A previous animal study showed that exercise caused an increase in muscle mass along with augmented protein synthesis (351). To date, there seems to be a lack of studies dealing with the effect of exercise training on protein degradation in diabetic muscle.

5.4.2.3. Exercise effects on diabetic muscle structure

DM causes a series of changes in muscle structure and functions. Physical exercise is probably the most potent measure to restore or improve these changes. However, there seems to be a lack of studies dealing with exercise effects on structural changes in human diabetic muscle. In an animal study, it was shown that chronic endurance exercise (12 weeks) did not cause significant

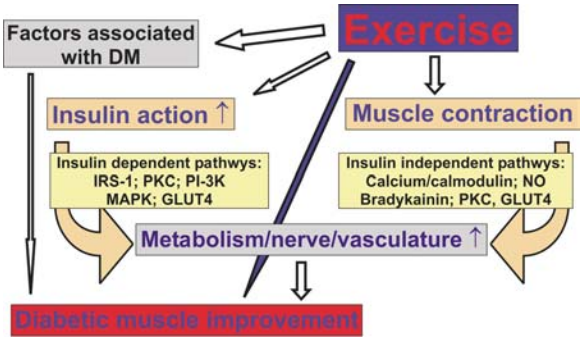

Figure 4. Possible mechanisms involved in effects of physical exercise on diabetic skeletal muscle (for detailed explanation see text). DM: diabetes mellitus; IRS-1: insulin receptor substrate 1; PKC: protein kinase C; PI-3K: phosphatidylinositol-3-kinase; MAPK: mitogen-activated kinase; GLUT4: glucose transporter 4; NO: nitric oxide.

changes in the diabetic muscle in terms of composition of MHC isoforms (352). It was found in a further animal study that endurance exercise-induced increase in GLUT4 expression was not accompanied by change in muscle fiber type composition (353). It is reported that strength training interventions may be a powerful tool in the prevention of age-associated sarcopenia (354). A 16-week training program could lead to an increase in the ratio of capillary to muscle fiber by 15% in insulin-dependent diabetic patients (355), although the capillary density was unchanged. Recently, it is found that 16-week strength training in addition to standard diabetic care can significantly improve muscle quality and increase muscle fiber cross-sectional area (356) along with reduced insulin resistance in the muscle.

The effects of exercise on diabetic muscle have also been observed at the ultrastructural level. Toledo *et al.* found that intervention with aerobic exercise training and dietary restriction led to an increase in percentage of myofiber volume occupied by mitochondria from 3.70 ± 0.31 to 4.87 ± 0.33% (357), and this is consistent with an improvement in insulin resistance. Exercise was found to significantly attenuate the diabetes-induced changes in collagen fibrils, cytoplasmic area, and level of mitochondrial disruption (358). It is evident that exercise combined with diet could clearly reduce intramuscular lipid contents (359), and this effect seemed to be attributable to a reduction in lipid droplet size within the muscle (360).

5.4.3. Possible mechanisms of exercise effects on diabetic muscles

Mechanisms underlying the effects of exercise on diabetic skeletal muscles are complex and not completely understood.

Exercise has profound impacts on the factors associated with the etiology and development of diabetes. A number of studies have shown that physical exercise can effectively reduce body weight, improve energy turnover, decrease blood and muscular lipid level, augment substrate oxidation, and counteract the negative effect of physical inactivity on diabetic skeletal muscle (45).

Exercise effects on diabetic skeletal muscle might be attributed to two major mechanisms, one is improvement of insulin action, and the other is muscle contraction-related glucose transport. A previous study showed that physical training increased insulin secretion along with an improvement in glucose tolerance in type 2 diabetes (361). Exercise can effectively modulate the signal transduction pathway of insulin action and therefore stimulate cellular glucose uptake and utilization (42, 118, 362).

Additionally, exercise can facilitate glucose transport into muscle cells in an insulin- action independent pathway, i.e. muscle contraction pathway that might be attributed to calcium/calmodulin, PKC and nitric oxide/bradykanin (362).

In response to exercise, a number of molecular mechanisms may play an important role in the diabetic skeletal muscle. A previous study showed that exercise could modulate the response of heat shock proteins (173), and it is known that heat shock proteins play a pivotal role in cellular adaptation to stress (363). Furthermore, studies have shown that physical exercise significantly affects inflammatory and oxidative cytokines, which are associated with insulin resistance and diabetic development (115, 364-366).

In brief, mechanisms responsible for effects of physical exercise on diabetic skeletal muscle are multi-factorial, as depicted in Figure 4. Clarification of the mechanisms would help us understand the management of diabetic skeletal muscle.

6. PERSPECTIVES

Although studies on DM are continuously emerging, the diabetic skeletal muscle remains a critical issue in terms of etiology and mechanisms responsible for diabetic myopathy and effective measures in handling the diabetic muscle.

DM is an epidemic disease. The major difficulty in handling this problem includes the complex nature, multiple risk factors associated with DM and as yet unclear mechanisms. Clinical trials have demonstrated effects of interventional measures on prevention as well as prognosis of DM; however, there is still a lack of knowledge on diabetic muscle. As the skeletal muscle is an important issue in DM, studies on diabetic muscle would be valuable in helping DM prevention and treatment.

In the management of diabetic muscle, gene therapy sounds quite promising, however, to date there are limited studies on gene therapy for diabetic muscle, either function or structure. Physical exercise is certainly an important measure in treating diabetic muscle, which not only improves insulin sensitivity in the skeletal muscle, but also acts through insulin-independent pathways. However, mechanisms responsible for the effects of physical exercise on diabetic muscle have not been completely elucidated, especially, the interaction among insulin signaling

pathways and other cellular/molecular mechanisms including heat shock protein response, oxidative stress, apoptosis. Trials with gene therapy are mainly carried out in animals, and thus the effects of gene therapy on human DM and especially on human diabetic muscle, remain unclear. Since lifestyle plays an important role in DM development and changes in diabetic muscle, studies on human diabetic muscle seem to be of special interest in this respect.

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