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Skeletal Muscle And Diabetic Treatment

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Introduction

Diabetes Melitus (DM) is a common health problem worldwide. International Diabetes Federation (IDF) count 90% among all the DM subjects is type 2 diabetes mellitus (T2DM). Still, 79% of all T2DM patients are in low-middle income country [1]. Therefore, accurate treatment strategy is needed to reduce major complication and decrease healthy cost for T2DM treatment.

T2DM is a chronic disease characteristically by peripheral resistance of insulin, marked by increased glucose circulating in bloodstream and glucose intolerant appeared [2]. The primary target of insulin in peripheral tissue and can act as insulin-mediated glucose uptake major organ is skeletal muscle [3,4]. Up to 80% glucose in hyperinsulinemia-clamp state uptake by skeletal muscle [4,5]. Hence, higher muscle mass correlated with higher glucose disposal rate in human[6]. Muscle strength also correlated with blood glucose, proven by lower blood glucose during muscle contraction[7]. Glucose transporter (GLUT) dan Sodium dependent glucose transporter-2 (SGLT-2) play a key role in blood glucose disposal into skeletal muscle[8], and their translocation into sarcolemma was increase in exercised muscle. Conversely, they will decreased in unhealthy muscle[9], include in T2DM[10]. In terms of muscle mass, higher skeletal muscle index (muscle mass/body weight x 100%) associates with lower incidence of T2DM, as high as 96% in men and 121% in women[11]. Synergistically, each SD higher muscle strength associated with 13% lower risk of T2DM [6,12].

Muscle Metabolism and Nutrition

Glucose uptake mechanism through GLUT-4 in skeletal muscle can be in two ways, there are insulin-mediated involving phosphatidylinositol-3kinase-Akt (PI3K/Akt) signaling pathway[13] and contraction or hypoxia-mediated involving AMPK pathway[14]. Binding of insulin by its receptors in sarcolemma activate PI3-K and serin/threonine kinase Akt/PKB, then induce translocation of GLUT-4 transporter from intracellular matrix into sarcolemma and let glucose entered intracellular matrix through GLUT-4 to increase glucose disposal rate[15]. Activation of PI3K/Akt pathway play as a key role in insulin-stimulated GLUT-4 translocation. Disturbance in this cascade will perturb glucose uptake into skeletal muscle and cause insulin resistance leading to T2DM [13,16]. Hypoxia-stimulated glucose uptake is

dependent on AMPK activation, which not significantly different between insulin resistance subject with healthy subjects [13,17]. AMPK is energy sensor molecule activated when AMP/ATP ratio was increased in muscle cell, for example in resistance training or cellular stress [18]. Activation of AMPK will increasing oxidative metabolism and produce ATP as a main energy source. Exercise-induced AMPK activation will regulate GLUT-4 translocation in to sarcolemma and increase glucose disposal from bloodstream [18]. Otherwise, glucose intake, exercise duration and intensity also regulate GLUT-4 translocation by AMPK pathway [19]. Therefore, insulin resistance will surely decrease glucose uptake, inhibit oxidative metabolism and ATP production. Insulin resistance is very important issue due to for β-cell dysfunction catalyst, increased hepatic glucose production, and progression of the disease [13]. Insulin resistance was the main cause of feeding-stimulated hyperglycaemia [20]. Unfortunately, In T2DM glucose uptake by skeletal muscle reduced by 60% than healthy muscle [21]

Muscle Mass Regulation

Skeletal muscle is major organ which can gain (hypertrophy) dan reduced (atrophy) in accordance with mechanical and metabolic condition. Skeletal muscle has a satellite cell and its microenvironment with myogenic characteristic [22], which its population and efficacy will decreased along with aging [23]. Hypertrophy stimulus such as exercise or muscle damage will stimulate satellite cell to proliferation forms myonuclei and induce hypertrophy [24]. Satelite cell's proliferation capacity in men is higher than women, it may be there are more myogenin contained in men's muscle than women [25,26] This higher capacity also can caused by testosterone-stimulated proliferation [26] which not found in women. This condition evidenced by other previous in vivo study with decreased satellite cell number and size by testosterone-knockout condition [27]. Nutrition intake will improve insulin or insulin-like growth factor respond in order to stimulates protein synthesis by activate PI3K-Akt-mTOR pathway and stimulate satellite cell proliferation and regeneration along with suppression of protein degradation in skeletal muscle [28,29].

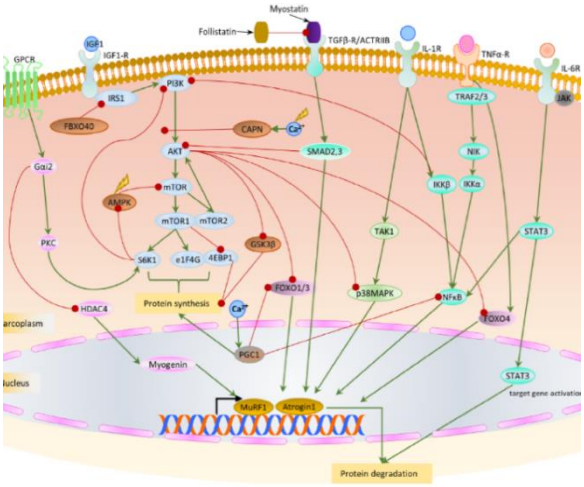

Figure. Hypertrophy and Atrophy Signaling Pathway in Skeletal Muscle [18]

Muscle hypertrophy characteristically by increasing both muscle number (hyperplasia) and muscle size[18]. Muscle hypertrophy can occur in stimulated healthy muscle such as exercised muscle (e.g. aerobic can induce muscle hypertrophy) [30] or pathology like myotonia congenita [31]. IGF-Akt/PKB-mTOR signaling play as main pathway in protein synthesis regulation [18,32]. Binding of IGF ligand to IGF receptor (IGF-R) will activate PI3K, followed by phosphorylation PIP2 to PIP3. Then PIP3 activates Akt that will increase protein synthesis through mammalian target of rapamycin (mTOR) activation. mTOR positively regulates its downstream target S6K1 dan inhibit 4EBP1. Those two effect leading to increased protein synthesis. Other downstream pathway of Akt is inhibition of glycogen synthase inhibition 3b (GSK3β) and forkhead box O (FoxO) transcription factor. Inhibition of both will reduce inhibiton of protein synthesis through PGC-1 and eIF2b [18]. Increased stimulation of IGF-Akt/PKB-mTOR pathway also induce satellite cell activation and proliferation leading to muscle hypertrophy. Other than those classical pathway, hypertrophy also induced due to satellite cell activation via G protein coupled receptors (G-PCR) in Gαi2 subunit [33]. Gαi2 can bypass Akt and directly regulates S6K1 and GSK3β resulting increased protein synthesis. These can occur both in PKC-dependent or HDAC4-dependent pathway [33].

While, if degradation rate was higher than synthesis of any stimuli, skeletal muscle will reduced in size (atrophy). Many stimuli that can induce muscle atrophy are infection [34,35], pathology condition of muscle [36,37], and immobilization [38]. Ubiquitin proteasome system (UPS) and autophagy-lysosomal system coordinate to worsen protein degradation and inhibit protein synthesis resulting muscle wasting [39,40]. Ubiquitin proteasome system (UPS) plays a “master role” in protein degradation through activation FoxO transcriptional factor which also under control of Akt [18,41]. Phosphorylation and translocation of FoxO in nucleus causing protein breakdown by its downstream molecules, Atrogin-1 and muscle-specific ring finger (MuRF) that were part of E3 ligase ubiquitin of UPS. In in vivo study with mice, mRNA encoding atrogin-1 and MuRF-1 expression was increase in many study with atrophy stimuli, like long-time use of glucocorticoid [42,43], TNFα exposure [44,45], starvation [46], denervation [47], malignancy [48], or other pathologic condition like ALS, COPD, or tetraplegia [49]. Downstream targets of FoxO can induce muscle atrophy, such as Foxo1 will increase Atrogin-1 expression through inhibition of IGF indirectly [50,51], Foxo3a increase atrogin’s promotors in glucocorticoid exposure, and Foxo 4 increase atrogin-1 expression through TNF-α exposure [52]. Increase Interleukin-6 (IL-6) in bloodstream also induce muscle atrophy, by activate STAT pathway. Phosphorylation of STAT will activate JAK/STAT pathway and increase catabolic rate [53] or by ataudapat pula melalui NFκB-dependent pathway [54]. Therefore, given IL-6 inhibitor will promotes muscle regeneration in muscle atrophy condition [55,56].

Pathophysiology of Diabetes Mellitus

T1DM is hyperglycaemichypoinsulinaemia caused by mostly autoimun attack pancreatic β-cell [57]. Without its optimal condition in producing insulin, impossible for body to maintain blood glucose in normal range. As a main organ in glucose disposal, healthy skeletal muscle can uptake glucose in non-insulin mediated [58]. Despite of β-cell destruction, in T1DM also there is mitochondrial dysfunction in skeletal muscle marked by decreased oxidative gene expression in mitochondrial DNA. It will worsen glucose control in hypoinsulinaemia condition in T2DM [59]. In contrary with T1DM, in T2DM hyperglycemia result from peripheral insulin resistance followed by hypersecretion of insulin by

pancreas as a compensatory manner resulting euglycemia hyperinsulinemia condition[60]. This compensation will be followed by insulin deficiency as β-cell become fatigue and destructed by inflammatory reaction as primary factor of T2DM [61]. Insulin resistance on liver allow gluconeogenesis keep going although hyperglycemia progressed [60], while insulin resistance on skeletal muscle will decrease glucose uptake rate [62]. Suppressed insulin secreation in T2DM also caused by decrease of intestinal insulin regulators such as gluagon-like peptide-1(GLP-1) by L-cell in ileum [63]. Directly, insulin can act as negative feedback in glucagon secretion, lower insulin flux will increased glucagon to cause hyperglicaemia[60].

Impaired of Muscle Function in T2DM

It's clearly understood that T2DM altered skeletal muscle regeneration and performances [64-67]. In T2DM, skeletal muscle mass decrease as high as 6% per decade [68], and poor glycaemic control associated with lower muscle mass [69]. Other than mass, muscle strength in T2DM subjects 7-8% weaker than healthy subjects [66,70-73]. Even with same muscle mass, muscle strength in upper and lower extremity of T2DM subjects is linear with higher HbA1c and disease duration [74,75] and decreased muscle quality in T2DM is strongly correlated with mortality [70]. In T2DM, extensor and flexor muscle strength of knees and ankles was impaired compared with those without diabetes [72]. Still, compared with those without T2DM, people with T2DM seems to walk slower, in shorter steps, and show more gait variability inlinear of turn path, despite of without neuropathy [76,77]. Muscle tremor was significantly greater in T2DM people, indicating deficits of central motor control [77].In T2DM with neuropathy complication, postural stability, length of sway, and balance was impaired, especially in men than women [78,79]. In previous in vitro study, molecular mechanism of muscle atrophy in T2DM patients is complex and involve many molecules inhibiting protein synthesis, stimulate degradation and impair cell quality [80]. Even though, paradoxical findings found that skeletal muscle mass in hyperinsulinemia T2DM patient was indifferent with healthy subjects [81,82], which probably caused by inhibition of TP53INP2, a molecule for protein degradation, by insulin resistance [83]. However, insulin resistance will cause marked disturbances in protein synthesis and muscle regeneration [84]. Other than directly caused by insulin deficiency, decrease in muscle mass and quality also caused by hyperglycaemia in T2DM as many population study [74,85,86]. Moreover, hyperglycaemia perturbing atrophy muscle for recovery [87]. In T2DM skeletal muscle, there is impaired mitochondrial content and function following insulin resistance result in perturb AATP production essentials for protein synthesis [88-90-], as mitochondria is the most affected organelles [91-93]. In low glucose level, normal muscle will switch ATP production using fatty acid instead of glucose (metabolic flexibility). But in T2DM muscle, metabolic flexibility was impaired and ATP production decreased [64,90,94]. Lower of fatty acid utilization will let fat to accumulate and infiltrate into skeletal muscle and definitely reduce muscle strength in elderly subjects [95]. High fat and glucose environment will disturbing satellite cell proliferation and muscle regeneration, linear with Fitzpatrick et al [96] and Aguiari et al [91], respectively.

Mass Regulatory Molecular changes in T2DM Muscle

T2DM-induced muscle atrophy due to oxidative stress and inflammation which disturbing protein metabolism [67,97]. Study of atrophy signaling genes in T2DM is still preliminary. In T2DM, PI3K/Akt/mTOR

pathway is the most suppressed pathway that cause muscle atrophy [80,97]. Suppression of Akt in T2DM caused by any depletion of insulin by insulin resistance or decreased activators like IGF-1 and increased upstream inhibitor like TNF-α, IL-6, etc. due to inflammation and oxidative stress [98,99] Reduction of these proinflammatory cytokine kan attenuates muscle atrophy signaling in insulin-independent manner as described previously [100]. Activation of Akt by insulin regulates its downstream regulator of autophagy, such as FoxO as transcriptional regulator and Unc-51 Like Protein Activating Kinase 1 (ULK-1) as nontranscriptional regulator, which receive their inhibitory signal from mTOR and stimulatory signal from AMPK [011,102]. In T2DM muscle, insulin resistance and proinflammatory cytokines will suppress protein synthesis was by decreased Akt signaling and along with e1F4G and S6K1 as downstream targets of mTOR for protein synthesis was decreased in T2DM muscle [103,104]. Suppression of Akt signaling will induce suppression of FOXO3a phosphorylation which can lead to increase activation of Atrogin1 and MuRF1 as components of E3 ligase UPS and promotes protein degradation [105-107]. Besides stimulate protein synthesis, mTORC1 also stimulates insulin secretion by β-cell [108]. Even so, sustained activation of mTORC1 such in high dose insulin-treated T2DM will cause beta cell exhaustion of their insulin secretion capacity and deteriorate glucose metabolism in T2DM [109]. There are two major pathway yang play a role in protein degradation of skeletal muscle, they are UPS and autophagy system. The UPS play about 50% of protein degradation [83,110]. In healthy state, insulin will suppresses autophagy signaling through Atg1/Ulk1 inhibition by mTORC activation [111] and inhibition of FoxO3 transcription factor by Protein Kinase B-mediated phosphorylation [112]. But in hyperglycemic state as T2DM, expression of UPS was elevated along with elevated number of apoptotic myocyte[113], and expression of FoxO1 was 60% higher in T2DM [97]. Phosphorylation of Ulk1 as a marker of autophagy in skeletal muscle tended to increase in hyperglycemic state such uncontrolled diabetes [114].

Role of Diabetic treatment in skeletal muscle

Sulfonylurea

Sulfonylurea is antidiabetic drug acting in closure of ATP-sensitive K channel (KATP)[104]. In pancreatic β-cell, it will increase insulin secretion. Although, KATP closure can cause β-cell apoptosis and reduced β-cell mass, especially by glibenclamide[115,116]. In skeletal muscle, administration of glibenclamide in rat in vivo study may activate atrophic signaling pathway through either caspase dependent or independent [117]. But in another in vitro study conducted by Mele et al, there is decreased skeletal muscle protein content after 24 hours incubation in sulfonylurea and glinid that may cause skeletal muscle atrophy. Among the sulfonylureas, glibenclamide act as the most potent atrophic agent and more effective in fast-twitch oxidative fiber than in glycolytic fiber, while Glimepirid has less potent atrophic agent. For glinid, the most potent atrophic agent is repaglinide[118]. In Database of Food and Drug Administration Adverse Event Reporting System (FDA-AERS), there are 0.27% human experienced muscle atrophy with gibenclamide use, while no atrophy reported in glimepiride and glinid[118].

Biguanide

Metformin as a insulin-sensitizer improve insulin sensitivity and its potentials in skeletal muscle [119]. By stimulate mitochondrial biogenesis, metformin can preserve oxidative fiber muscle [120]. But it contrastwith Wessel et al stated metformin give negative effect on skeletal metabolism by perturb

mitochondrial function [121]. Metformin as the most used biguanides, act as activators of AMPK[122]. An in vitro study revealed, activation of AMPK can induce muscle atrophy by activating autophagy signaling pathway, such activation of FoxO transcription factor followed by increase expression of atrophic genes, MuRF1 and Atrogin1[123] and inhibition of mTOR, essential molecule for protein synthesis in cultured skeletal muscle[124]. An opposite result stated in an in vivo study of obesity-induced muscle atrophy in rat, metformin can ameliorated muscle atrophy, may be due to regulation of PGC1α-FoxO3 pathway [125] and control oxidative stress in rat T2DM muscle [126]. But still, There is limited in vivo study for metformin-induced muscle atrophy.

Thiazolidinedione (TZD)

Thiazolidinedione is antidiabetic drug as a synthetic ligand of peroxisome proliferator-activated receptors (PPARs). It can improve insulin sensitivity by repair PI3K/Akt pathway and reduce caspase-3 pathway as stimulator of protein degradation [127,128]. Theoretically, TZD can improve muscle metabolism by reduce muscle fat content and improve lipid metabolism [129]. But there are controversial result of in human study, weight-loss in nondiabetic subjects pioglitazone has no effect in muscle loss. Resistance training can improve muscle loss instead of pioglitazone only [130]. But combination of the two give better result in women [131]. In another study, compared to nondiabetic men, diabetic men given pioglitazone has no differences in total lean mass loss in 3.5 years follow up [120]

DPP IV inhibitor

Dipeptidyl peptidase IV (DPP-IV) inhibitor has beneficial effect on skeletal and heart muscle. DPP-IV inhibitor can upregulates translocation of GLUT-4 in skeletal muscle and thus decrease blood glucose level. Many studies has been conducted to reveal beneficial effect of DPP-IV inhibitor, such as lower inflammatory parameters, enhanced GLP-1 secretion, and improve sarcopenic parameters (Fat-free mass, SMI, muscle strength, gait speed) [132,133]. In an in vivo study, DPP IV knockout mice show better glucose tolerance, enhanced insulin secretion, and reduced incretin degradation [134,135]. Moreover, long period of DPP IV inhibitor administration can prevent glucose intolerance, obesity, and T2DM in diabetogenic streptozotocin-induced mice [136]. Because of strong relation between reduced DPP IV and GLP-1 activation, it is currently unknown whether beneficial effect of DPP IV inhibitor is direct or indirect (through GLP-1 activation) manner [104]

GLP 1 RA

Glucagon-like Peptide 1 (GLP-1) and incretin is an intestinal hormones to increasing insulin sensitivity and β-cell anti-apoptotic hormone[137,138]. Increase of GLP-1 associates with increase of β-cell density and pancreatic mass in animal model [138]. Therefore, GLP-1 receptor agonist has many beneficial effect in attenuate T2DM progression, lower body weight by decreased gastric emptying[139], and improve insulin resistance[140] in skeletal and heart muscle. In an in vivo study, GLP-1 agonist can stimulate insulin extraction and increase oxygen delivery in a way by increase capillary recruitment via nitric oxide (NO)-dependent manner in rat skeletal muscle, improving insulin resistance condition[141,142]. In in vitro study of cultured human [143] and rat [141]muscle, GLP-1 agonist increase GLUT-4 expression and glucose disposal which this condition worsen by hyperglycemia in T2DM.

SGLT-2 Inhibitor

Sodium/Glucose cotransporter 2 (SGLT-) inhibitor act by prevents reabsorption of glucose in kidney inducing glucosuria insulin-independently [104]. It has many advantages in preserve cardiovascular and kidney function, so it recommended for T2DM patients with cardiovascular or kidney dysfunction [144]. Insulin-mediated glucose uptake by skeletal muscle increase approximately 18% after 2 weeks-dapagliflozin treatment [122]. In skeletal muscle, it seems SGLT-2 inhibitor has bad effect, this showed in several study of diabetes-induced sarcopenia, such chronic use of SGLT-2 inhibitor induced proteolysis [145], decline SMI after 1-year use of dapagliflozin [146], worse insulin resistance, and significantly higher of free fatty acid, ketone bodies and HDL-cholesterol, and decreased SMI [147,148]. But opposite result showed in several study, such asimproved hand grip strength on T2DM after administration of SGLT-2 inhibitor, due to reduced chronic inflammation and adipokine balance [149], reduced body weight and fat mass without affecting skeletal muscle mass [150,151]. However, further study of in vitro needed to prove effect of SGLT-2 inhibitor in skeletal muscle mass.

Insulin

Insulin known as potentials agent for protein synthesis in skeletal muscle, as long as insulin sensitivity is preserved. Insulin can activate anabolic signaling through PI3K/Akt/mTORC pathway and suppress autophagy signaling. Insulin-mediated protein synthesis occur in young adults, but not in older adults, may be due to insulin resistance of aging process [152] or reduced blood flow and glucose utilization in elder people [153]. But in a human study, insulin can attenuates progression of sarcopenia in T2DM marked by higher skeletal muscle index (SMI) compared to non insulin-treated group [154]Even so, sustained activation of mTORC in high dose insulin-treated T2DM will cause beta cell fatigue and deteriorate glycation control in T2DM [109]. Over-suppression of autophagy by high dose-insulin also can disturb repairment capacity and worsen muscle disease by alter gene expression [103].

Summary

T2DM known to be the most high impact metabolic disease globally, such its progression, molecular changes, daily life quality, and healthy cost consumed for the treatment. Regulation of glucose play a key role to maintain disease progression and health quality. One of the most important organ for blood glucose regulation is skeletal muscle. High blood glucose impair its proliferation and regeneration, while impaired muscle metabolism will inhibit glucose disposal from bloodstream, reciprocally. In T2DM, high blood glucose caused by insulin resistance let muscle to glucose “starving” and perturb ATP production, while its hyperglycemia environment and inflammatory respond make essentials molecular changes result in inhibit protein synthesis and stimulate protein degradation by suppressing PI3K/Akt/mTOR pathway and ubiquitination or autophagy activation, respectively. All those mechanisms will result in reduced both muscle cell number and size. Therefore, its important to maintain blood glucose in normal range and inhibit inflammatory respond to minimize muscle atrophy in T2DM.

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