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Etiology of Skeletal Muscle Lipotoxicity and Insulin Resistance and Type 2 Diabetes

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Abstract: **Skeletal muscle is the significant site for disposal of consumed glucose in lean healthy normal glucose tolerance (NGT) individuals. Following a meal, approximately one third of ingested glucose is used up by the liver and the rest by peripheral tissues, mainly skeletal muscle by means of an insulin dependent system. This review was aim to overview and discuss the role of skeletal muscle fat accumulation, lipotoxicity and in fact muscle insulin resistance and especially the most central role in the pathophysiological events leading to T2DM. We performed an electronic search through medical databases; PubMed/Midline, Embase for all these relevant studies that were published up to December 2016, in English language and containing only human subject. we then searched the references found in identified articles for relevant studies concerning, skeletal muscle lipotoxicity and insulin resistance. Insulin resistance in skeletal muscle appears by decreased insulin-stimulated glucose uptake and results from impaired insulin signaling and multiple post-receptor intracellular flaws consisting of impaired glucose transportation, glucose phosphorylation, and decreased glucose oxidation and glycogen synthesis. Insulin resistance is a core problem in type 2 diabetes, it is also related to obesity and the metabolic syndrome.**

Keywords: **T2DM, lipotoxicity, PubMed/Midline, Embase, Etiology of Skeletal Muscle.**

1. INTRODUCTION

Skeletal muscle is the significant site for disposal of consumed glucose in lean healthy normal glucose tolerance (NGT) individuals. Following a meal, approximately one third of ingested glucose is used up by the liver and the rest by peripheral tissues, mainly skeletal muscle by means of an insulin dependent system. Obesity is a major international health problem with increasing occurrence [(1)]. Several metabolic conditions and diseases including insulin resistance and T2D most often accompany weight problems. T2D pathophysiology is related to an increased fat mass [(2)], and insulin resistance correlates with weight problems even within the normal range [(3, 4)]. The adipose tissue plays a crucial function in managing energy balance via lipid storage and secretion and by being an active endocrine organ secreting adipokines that affect systemic metabolism [(5)]. It is popular that weight problems is related to increased plasma levels of totally free fatty acids (FFA) due to increased lipolysis and therefore FFA release from the fat and/or due to a reduced FFA clearance rate. Raised plasma FFA levels hinder the antilipolytic result of insulin resulting in a further increased release of FFA into the circulation. The relationship in between distributing FFA and insulin resistance is being disputed. Research studies have actually both offered evidence of insulin resistance and T2D in the existence of regular flowing levels of FFA [(6)] as well as elevated FFA levels without concomitant insulin resistance, therefore questioning the causal role of FFA in T2D pathophysiology [(7)]. Insulin resistance is a trademark feature of T2D preceding the start of overt disease by years. Given that the research studies by Sir Philip Randle recording substrate competitors in between fat and glucose oxidation, the 'glucose fat cycle' likewise referred to as the 'Randle Cycle' has actually been a central principle explaining the advancement of insulin resistance [(8)].

Skeletal muscle is the significant site of glucose uptake in the postprandial state in human beings. Under euglycemic hyperinsulinemic conditions, ~ 80% of glucose uptake occurs in skeletal muscle [(9)]. In insulin resistance states, such as T2DM and weight problems, insulin-stimulated glucose disposal in skeletal muscle is considerably impaired [(10,11,12)]. The

decreased insulin-stimulated glucose uptake is due to impaired insulin signaling and multiple postreceptor intracellular defects consisting of impaired glucose transport and glucose phosphorylation, and minimized glucose oxidation and glycogen synthesis [13,14] (**Table 1**). The specific system that leads to the development of insulin resistance in skeletal muscle is not yet totally comprehended, an increased intramyocellar fat material and fatty acid metabolites have actually been revealed to play a pivotal role in the development of insulin resistance in skeletal muscle [15,16,17]. The current studies have actually reported the existence of a problem in mitochondrial oxidative phosphorylation in skeletal muscle in insulin resistance states [18,19] and suggest that this mitochondrial defect adds to the increased intramyocellar fat content. In this paper we will sum up the evidence that supports the existence of insulin resistance in skeletal muscle, the cellular mechanism(s) that result in the development of insulin resistance, and the clinical effects of insulin resistance in skeletal muscle [20].

Table 1: Defects in Glucose Metabolism in Insulin Resistant Conditions. [14]

Insulin signaling	(1) Reduced insulin receptor tyrosine phosphorylation
	(2) Decreased IRS-1 tyrosine phosphorylation
	(3) Decreased PI3-kinase activation
Glucose transport	(1) Impaired GLUT4 translocation
	(2) Impaired GLUT 12 translocation
Glucose metabolism	(1) Decreased glucose phosphorylation
	(2) Decreased glucose oxidation and glycolytic FLUX
	(3) Impaired glycogen synthase

This review was aim to overview and discuss the role of skeletal muscle fat accumulation, lipotoxicity and in fact muscle insulin resistance and especially the most central role in the pathophysiological events leading to T2DM.

2. METHODOLOGY

We performed an electronic search through medical databases; PubMed/Midline, Embase for all these relevant studies that were published up to December 2016, in English language and containing only human subject. we then searched the references found in identified articles for relevant studies concerning, skeletal muscle lipotoxicity and insulin resistance

3. RESULTS

- ***Normal Skeletal Muscle Metabolism:***

Skeletal muscle utilizes both glucose and complimentary fatty acid (FFA) as fuel sources for energy production. Throughout the postabsorptive state, the plasma insulin concentration is low. Since the plasma insulin concentration is the primary factor that limits lipolysis in adipocytes [21] and promotes glucose uptake in skeletal muscle, throughout the fasting state, muscle glucose uptake is low and the plasma FFA concentration is elevated. Therefore, under fasting conditions, FFA functions as the principal fuel source for energy production in skeletal muscle, while the brain exclusively utilizes glucose [21].

Following glucose ingestion, the increase in plasma glucose concentration promotes insulin secretion from the beta cell and the resultant hyperinsulinemia suppresses lipolysis, resulting in decrease in plasma FFA concentration and subsequent decrease in the rate of lipid oxidation. Simultaneously, insulin stimulates glucose uptake in skeletal muscle, and the increased glucose flux into skeletal muscle, together with the activation of essential enzymes in glucose metabolic process by insulin, leads a marked increase in muscle glucose oxidation (**Figure 1**) [22,23]. Thus, under postprandial conditions, for instance, mixed meal, muscle energy metabolism changes from predominant oxidizion of fat during the fasting state, to primary oxidizion of glucose [24]. The capability of skeletal muscle to change from fat oxidation during the fasting state to glucose oxidation throughout the postprandial state has actually been described as metabolic flexibility [25].

After glucose is transported into the myocyte via the GLUT4 transporter, it is instantly phosphorylated by hexokinase, and the phosphorylated glucose either is converted to, and stored as glycogen, or goes into the glycolytic pathway for oxidation. Roughly 90% of glucose entering the glycolysis is oxidized and the staying 10% is launched as lactate. At low plasma insulin concentration, for example, fasting state, glycogen synthase, and glucose oxidation contribute equally to glucose disposal. With increasing plasma insulin concentration, glycogen synthase is activitaed by insulin and glycogen synthesise predominate (70% of glucose disposal) [26].

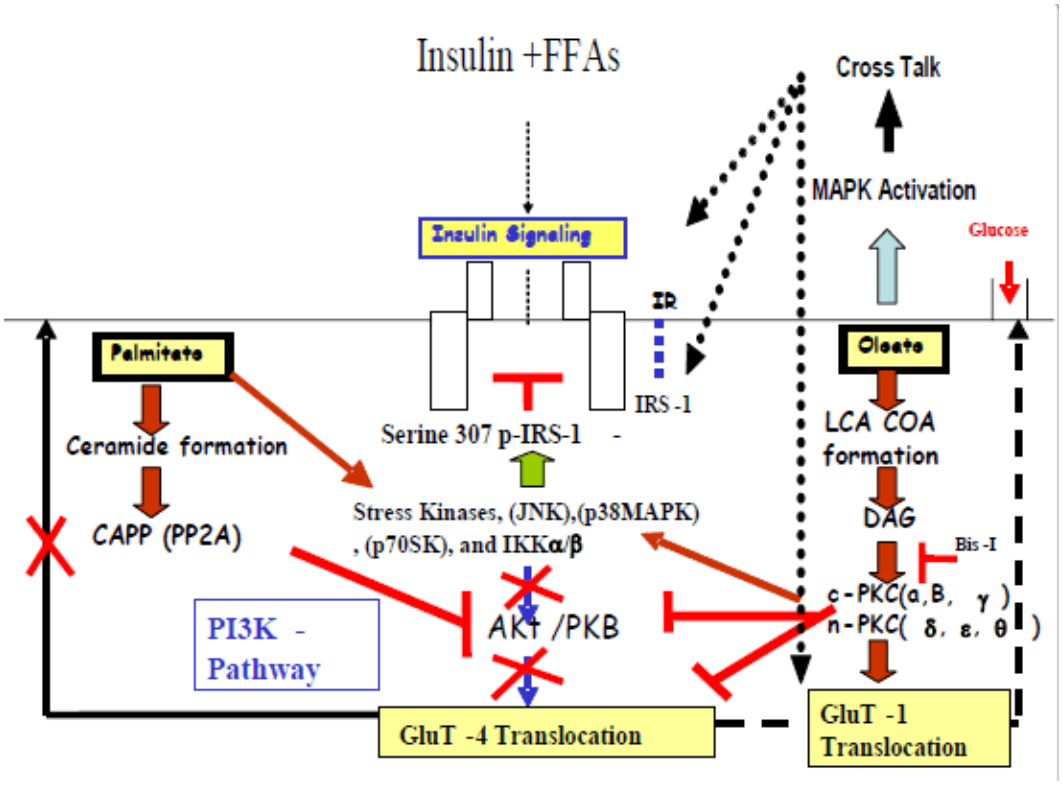

Figure1: Hypothetical scheme to explain changes in the insulin signaling upon treating the C2C12 skeletal muscle cells with different species of FFAs [22]

- ***Insulin Resistance in Skeletal Muscle:***

The term insulin resistance describes an impairment in insulin action in insulin-target tissues, such as skeletal muscle, adipocytes, and liver. With respect to skeletal muscle, the primary action of insulin is to stimulate glucose uptake and metabolic process [1,2,3]. In lean healthy individual's insulin promotes glucose uptake into skeletal muscle in a dose-dependent way, with a half-maximal effect (EC50) at a plasma insulin concentration 60 U/mL [21]. In insulin resistant states, insulin-stimulated glucose uptake is significantly decreased in skeletal muscle (**Figure 2**) [21].

Himsworth and kerr [27], using a combined oral glucose and intravenous tolerance test, were the first to demonstrate that tissue level of sensitivity to insulin is diminished in T2DM patients. In 1975, Ginsberg et al. [28], using the insulin suppression test, provided more proof that the ability of insulin to promote tissue glucose uptake in T2DM was significantly reduced. The most conclusive documentation for increased insulin resistance in skeletal muscle in lean, in addition to overweight T2DM subjects, has been offered by DeFronzo and coworkers [29,30] and Butterfield and Whichelow [31]. Using the gold basic euglycemic hyperinsulinemic clamp technique to measure insulin-stimulated glucose uptake, they demonstrated that both lean and obese T2DM topics have marked reduction (50%) in whole body glucose disposal throughout the insulin clamp.

Although glucose disposal throughout the insulin clamp represents insulin-stimulated glucose uptake by all peripheral tissues, the terrific bulk of this glucose uptake take place in skeletal muscle. Under euglycemic conditions studies, using the insulin clamp in combination with femoral artery and vein catheterization [3] has actually shown that roughly 80% of total body glucose uptake happens in skeletal muscle. In reaction to a physiologic increase in plasma insulin concentration (80 - 100 U/mL), leg muscle glucose uptake increases progressively in healthy topics and reaches a platue value of roughly 10 mg/kg leg wt min. On the other hand, during the last hour of the insulin clamp research study, the rate of

glucose uptake is decreased by 50% in lean T2DM subjects. Thus, the dosage action curve relating insulin-stimulated glucose uptake and the plasma insulin concentration shifts to the right with a boost in EC50 (to 120 - 140 U/mL) in subjects with T2DM (**Figure 2**) [21]. In addition, the beginning of insulin action in skeletal muscle in T2DM subjects is markedly delayed. Even though the insulin infusion is continued for an additional 60 minutes in subjects with T2DM to enable insulin to more totally reveal its biologic action, glucose uptake stays blunted. These research studies indicate that insulin resistance in skeletal muscle in topics with T2DM is manifested, not only by a decrease in the magnitude of insulin action, however likewise by s delayed onset of insulin action to stimulate glucose uptake [32].

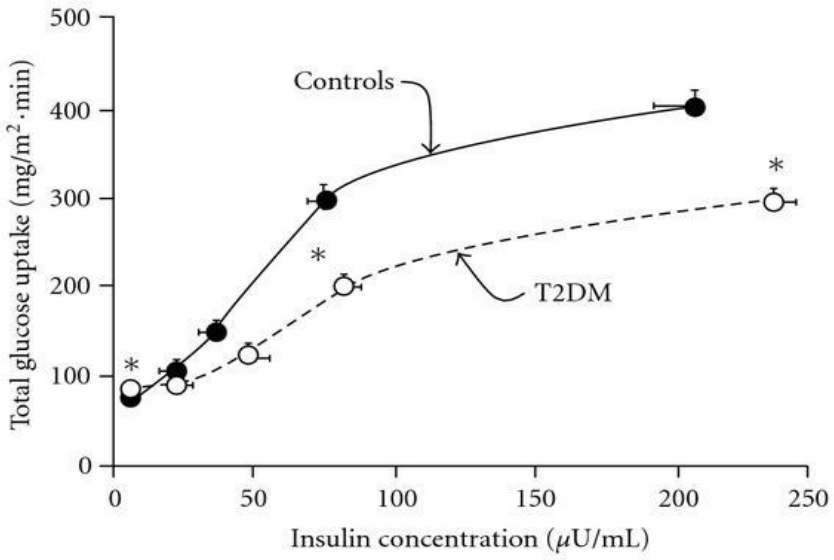

Figure 2: Dose-response curve relating the plasma insulin concentration to the rate of insulin mediated wgole body glucose uptake in controls and type 2 diabetic subjects. [21]

- ***Lipotoxicity and insulin action in skeletal muscle:***

Infusion of lipids in different dosages has actually been used in numerous studies to mimic the state of lipid oversupply as can be seen in obesity and T2D. In healthy people, severe elevation of plasma FFA by lipid infusion produces acute insulin resistance of the skeletal muscle tissue [33]. It has been shown that increased levels of plasma FFAs cause insulin resistance by preliminary inhibition of glucose transport/phosphorylation and consequently by the disability of the proximal insulin signaling pathway, followed by a reduction in both the rate of muscle glycogen synthesis and glucose oxidation [34, 35]. The molecular mechanisms underlying this disability is currently not totally understood, and information are somewhat opposing. Belfort et al. revealed that an increase in plasma FFA caused a dosedependent inhibition of insulin-stimulated glucose disposal and insulin signaling in skeletal muscle of lean, healthy people. The repressive result of plasma FFA was already substantial after a modest boost in plasma FFA and established at concentrations within the physiological variety [36]. Kruszynska et al. have reported comparable results on insulin signaling [37]. On the other hand, when lipids are instilled to currently insulin-resistant obese individuals, physiological elevation of plasma FFA levels led to lipid-induced metabolic modifications, which could not be described by decreased proximal insulin signaling in skeletal muscle [38]. Lipid infusion studies can clearly cause reactions different from what would have been observed if a dietary intervention was applied since consumption of food evidently affects different hormonal agents and pathways, which are not triggered during lipid infusion. Hence, lipid infusion research studies might be synthetic and needs to be interpreted with that in mind. Studies on the impacts of high-fat feeding on insulin signaling in human subjects are doing not have; however, rat research studies have actually reported defective insulin-induced activation of glucose transport in the high-fat-feeding model of insulin resistance [39, 40]. Intramyocellular lipids Accumulation of poisonous lipids types as intramyocellular lipid (IMCL) might occur as a result of increased fats uptake due to sustained lipid overload and/or as a result of a minimized rate of fatty acids oxidation [41] and might be a primary consider the advancement of insulin resistance [42, 43]. IMCL is the common measure for any type of lipid types that is located within the myocyte and kept in lipid droplets, primarily through triglyceride (TG) but in some cases, as lipid intermediates such as longchain fatty acyl-CoAs, DAG and ceramides. It is well known that IMCLs have a physiological function as an important energy source that drives muscle fat oxidation, and data from early studies suggested that IMCL could be utilized as a source of fuel during

workout as muscle TG was discovered to be depleted after prolonged workout [44], and throughout exercise, big amounts of flowing FFAs are directed into muscle cells for energy [44]. Research studies have shown a strong association in between high IMCL material and skeletal muscle insulin resistance in obese topics [45], in lean non-diabetic offspring of T2D topics [46] and in T2D subjects [43]. In addition, a research study has actually revealed that, a diet high in fat and intravenous lipid infusion increase the amount of IMCL and simultaneously decrease insulin level of sensitivity [20]. The association between IMCL and insulin resistance is additional supported by research studies revealing reduced IMCL concentrations and corresponding enhanced insulin sensitivity in action to weight reduction [42]. It has been shown that under conditions of lipid oversupply the content of signifying molecules (intermediates), including long-chain acetyl CoA, DAG and ceramides is increased in skeletal muscle, which can activate protein kinase C (PKC), resulting in a serine phosphorylation of the insulin receptor substrate-1 (IRS-1), impairing its ability to relate to the insulin receptor and interfering with PI3K activation and insulin signaling [47].

4. CONCLUSION

Insulin resistance in skeletal muscle appears by decreased insulin-stimulated glucose uptake and results from impaired insulin signaling and multiple post-receptor intracellular flaws consisting of impaired glucose transportation, glucose phosphorylation, and decreased glucose oxidation and glycogen synthesis. Insulin resistance is a core problem in type 2 diabetes, it is also related to obesity and the metabolic syndrome. The molecular and cellular mechanisms triggering muscle insulin resistance are not fully comprehended. The majority of research studies concur that it is not the total quantity of IMCL per se that triggers insulin resistance, however rather the build-up of the lipid intermediates as well as the cellular localization of the lipids. Finally, numerous studies do agree that a inefficient or overloaded adipose tissue and metabolic consequences hereof have been seen in prediabetic phenotypes including individuals subjected to suboptimal fetal environment, suggesting that lipotoxicity could be potentially more damaging to particular 'at-risk' groups of the population.

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