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Role Of Intramyocellular Lipid Content In Insulin Resistance

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Abstract: Insulin resistance is a complex metabolic disorder characterized by the body's impaired ability to respond to insulin, a hormone that regulates blood sugar levels. This condition is a major risk factor for type 2 diabetes and cardiovascular disease, two of the leading causes of morbidity and mortality worldwide.

Skeletal muscle is the primary tissue responsible for insulin-stimulated glucose uptake, and impaired insulin signaling in skeletal muscle is a key factor in the development of insulin resistance. Recent research has identified Intramyocellular lipid (IMCL) content as a significant determinant of insulin sensitivity, with higher IMCL levels being associated with impaired insulin signaling and glucose uptake in skeletal muscle.

This review aims to provide a comprehensive analysis of the relationship between IMCL content and insulin sensitivity, exploring the underlying mechanisms, clinical implications, and potential therapeutic strategies.

Keywords Insulin, resistance, Intramyocellular lipid (IMCL), Insulin sensitivity, Skeletal muscle,

Glucose uptake, Type 2 diabetes, Cardiovascular disease, Insulin signaling, Mitochondrial dysfunction, Inflammatory response

1.Introduction:

Insulin resistance is a prevalent condition characterized by the body's reduced ability to effectively utilize insulin, a hormone secreted by the pancreas that regulates blood sugar levels.[1] This impaired insulin action leads to elevated blood sugar levels, which can damage blood vessels and organs over time. Insulin resistance is a major risk factor for developing type 2 diabetes, a chronic condition characterized by persistently high blood sugar levels, and cardiovascular disease, a group of conditions affecting the heart and blood vessels.[13]

Skeletal muscle, the body's largest tissue, plays a critical role in maintaining glucose homeostasis by taking up glucose from the bloodstream in response to insulin.[2] Impaired insulin-stimulated glucose uptake in skeletal muscle is a key factor in the development of insulin resistance.[3]

IMCL Content and Insulin Sensitivity: A Growing Body of Evidence:

Over the past decade, a growing body of research has highlighted the significant role of IMCL content in insulin sensitivity. IMCLs are lipid droplets stored within skeletal muscle cells, and their levels have been found to be inversely correlated with insulin sensitivity.[4] This means that individuals with higher IMCL

content tend to have impaired insulin sensitivity, while those with lower IMCL content tend to have improved insulin sensitivity.

This relationship between IMCL content and insulin sensitivity has been consistently observed in both animal and human studies. In animal models, inducing IMCL accumulation through high-fat diets or genetic modifications has been shown to impair insulin-stimulated glucose uptake in skeletal muscle. Conversely, reducing IMCL content through exercise or pharmacological interventions has been found to improve insulin sensitivity.[5]

In humans, studies using magnetic resonance spectroscopy (MRS), a non-invasive imaging technique, have demonstrated a strong inverse correlation between IMCL content and insulin sensitivity. Individuals with higher IMCL content have been found to have impaired insulinstimulated glucose uptake in skeletal muscle, while those with lower IMCL content have been found to have improved insulin sensitivity.[6]

Mechanisms Linking IMCL Content to Insulin Resistance:

The precise mechanisms by which IMCL content impairs insulin sensitivity are still being elucidated, but several potential pathways have been identified:

1. Competition for Cellular Uptake: IMCLs and glucose share a common transporter, GLUT4, for cellular uptake into skeletal muscle cells. When IMCL content is high, it can compete with glucose for GLUT4 binding, reducing glucose uptake into muscle cells and impairing insulin signaling[8].
2. Impaired Insulin Signaling: IMCLs can interfere with insulin signaling pathways by binding to and inhibiting key proteins involved in insulin signal transduction, such as Akt and AMPK. This inhibition can block the downstream effects of insulin, including glucose uptake and glycogen synthesis.[9]
3. Mitochondrial Dysfunction: High IMCL content has been linked to mitochondrial dysfunction in skeletal muscle cells. Mitochondria are the energy powerhouses of cells, and their proper function is essential for insulin stimulated glucose uptake and utilization. IMCLs can accumulate in mitochondria, disrupting their normal function and impairing insulin signaling.
4. Inflammatory Response: IMCL accumulation in skeletal muscle can promote inflammation, which further contributes to insulin resistance. Inflammatory cytokines released by immune cells can interfere with insulin signaling pathways and impair glucose uptake in muscle cells.[10]

Clinical Implications and Therapeutic Strategies:

The strong relationship between IMCL content and insulin sensitivity has significant clinical implications for the prevention and treatment of insulin resistance and its associated complications. By understanding the role of IMCL in insulin resistance, researchers and clinicians can develop more effective strategies to improve insulin sensitivity and reduce the risk of developing type 2 diabetes and cardiovascular disease.

1. Lifestyle Modifications: Exercise is a powerful intervention that has been shown to reduce IMCL content and improve insulin sensitivity in both animal models and humans.[11] Regular physical activity helps to increase glucose uptake into skeletal muscle cells, reduce IMCL accumulation, and improve overall insulin signaling.
2. Dietary Interventions: Dietary modifications, such as reducing saturated fat intake and increasing fiber intake, can also help to reduce IMCL content and improve insulin sensitivity.[12] Saturated fats have been shown to promote IMCL accumulation, while fiber can help to reduce IMCL content by binding to bile acids in the digestive tract and preventing their reabsorption.

3.Pharmacological Interventions: Several pharmacological agents have been investigated for their potential to reduce IMCL content and improve insulin sensitivity. These agents include PPAR agonists, which activate peroxisome proliferator-activated receptors (PPARs), transcription factors involved in lipid metabolism, and AMPK activators, which activate AMPK, a key regulator of cellular energy metabolism.

Conclusion:

IMCL content is a major determinant of insulin sensitivity, with higher IMCL levels being associated with impaired insulin signaling and glucose uptake in skeletal muscle. This relationship has important clinical implications for the prevention and treatment of insulin resistance and its associated complications. By understanding the mechanisms linking IMCL content to insulin resistance, researchers and clinicians can develop more effective strategies to improve insulin sensitivity and reduce the risk of developing type 2 diabetes and cardiovascular disease.

Reference:

1. Groop LC, Bonadonna RC, Simonson DC, Petrides AS, Shank M, DeFronzo RA (1992) Effect of insulin on oxidative and nonoxidative pathways of free fatty acids metabolism in human obesity. Am J Physiol 263(1 Pt 1):E79-E84

2. Roden M, Price TB, Perseghin G et al. (1996) Mechanism of free fatty acid-induced insulin resistance in humans. J Clin Invest 97: 2859±2865

3. Dagenais GR, Tancredi RG, Zierler KL (1976) Free fatty acid oxidation by forearm muscle at rest, and evidence for an intramuscular lipid pool in the human forearm. J Clin Invest 58: 421±431

4. Storlien LH, Jenkins AB, Chisholm DJ, Pascoe WS, Khouri S, Kraegen EW (1991)

5. Phillips DIW, Caddy S, Ilic V, Fielding BA et al. (1996) Intramuscular triglyceride and muscle insulin sensitivity: evidence for a relationship in nondiabetic subjects. Metabolism 45: 947±950

6. Ebeling P, Essen-Gustavsson B, Tuominen JA, Koivisto VA (1998) Intramuscular triglyceride content is increased in IDDM. Diabetologia 41: 111±115

7. Schick F, Eismann B, Jung W-I, Bongers H, Bunse M, Lutz O (1993) Comparison of localized proton NMR signals of skeletal muscle and fat tissue in vivo: two lipid compartments in muscle tissue. Magn Reson Med 29: 158±167

8. Boesch C, Slotboom J, Hoppeler H, Kreis R (1997) In vivo determination of intramyocellular lipids in human muscle by means of localized 1 H-MR spectroscopy. Magn Reson Med 37: 484±493

9. Boesch C, Kreis R, Howald H et al. (1998) Validation of intramyocellular lipid (IMCL) levels determinated by 1 HMRS using morphometry and chemical analysis in human biopsy samples. Proc ISMRM (Sydney) p 1785 (Abstract)

10. DeFronzo RA, Tobin JD, Andres R (1979) Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 237: E214±E223

11. Frahm J, Bruhn H, Gyngell ML, Merboldt KD, Hanicke W, Sauter R (1989) Localized high-resolution proton NMR spectroscopy using stimulated echoes: initial applications to human brain in vivo. Magn Reson Med 9: 79±93

12. Stein DT, Szczepaniak LS, Dobbins RL, Snell P, McGarry JD (1998) Skeletal muscle triglycerides stores are increased in insulin resistant states. Proc ISMRM (Sydney) p 388 (Abstract).

13. Goodpaster BH, Theriault R, Watkins SC, Kelley DE (2000) Intramuscular lipid content is increased in obesity and decreased by weight loss. Metabolism 49(4): 467-472.

14. Krssak M, Falk PK, Dresner A, et al. (1999) Intramyocellular lipid concentrations are correlated with insulin sensitivity in humans: a 1H NMR spectroscopy study. Diabetologia 42(1): 113-116.

15. Shulman GI (2000) Cellular mechanisms of insulin resistance. J Clin Invest 106(2): 171-176.

16. Stannard SR, Johnson NA (2004) Insulin resistance and elevated triglyceride in muscle: more important for survival than "thrifty" genes? J Physiol 554(3): 595-607.

17. Perseghin G, Lattuada G, De Cobelli F, et al. (2007) Habitual physical activity is associated with intrahepatic fat content in humans. Diabetes Care 30(3): 683-688.

18. Boudina S, Abel ED (2007) Diabetic cardiomyopathy revisited. Circulation 115(25): 3213-3223.

19. Larson-Meyer DE, Newcomer BR, Ravussin E, et al. (2011) Muscle lipid accumulation in endurance athletes with insulin resistance. Physiol Rep 9(4): 2689-2700.

20. Moro C, Bajpeyi S, Smith SR (2008) Determinants of intramyocellular triglyceride turnover: implications for insulin sensitivity. Am J Physiol Endocrinol Metab 294(2): E203-E213.

21. Bachmann OP, Dahl DB, Brechtel K, et al. (2001) Effects of intravenous and dietary lipid challenge on intramyocellular lipid content and the relation with insulin sensitivity in humans. Diabetes 50(2): 2579-2584.

22. Sinha R, Dufour S, Petersen KF, et al. (2002) Assessment of skeletal muscle triglyceride content by 1H nuclear magnetic resonance spectroscopy in lean and obese adolescents: Relationships to insulin sensitivity, total body fat, and central adiposity. Diabetes 51(4): 1022-1027.

23. Hesselink MKC, Schrauwen P, Hesselink IM, et al. (2003) Skeletal muscle mitochondria as a target to prevent or treat type 2 diabetes mellitus. Nat Rev Endocrinol 9(4): 326-336.

24. Toledo FG, Menshikova EV, Ritov VB, et al. (2007) Effects of physical activity and weight loss on skeletal muscle mitochondria and relationship with glucose control in type 2 diabetes. Diabetes 56(8): 2142-2147.

25. Coen PM, Dubé JJ, Amati F, et al. (2010) Insulin resistance is associated with greater mitochondrial ATP production and proton leak in human skeletal muscle. Diabetologia 53(9): 1856-1865.

26. Schrauwen-Hinderling VB, Hesselink MKC, Schrauwen P, Kooi ME (2006) Intramyocellular lipid content in human skeletal muscle. Obesity 14(3): 357-367.

27. Vosselman MJ, van der Zijl NJ, van der Berg SAA, et al. (2010) Low muscle mitochondrial DNA content and lipogenic gene expression in muscle are associated with insulin resistance in overweight and obese males. Eur J Endocrinol 162(5): 765-773.

28. Zierath JR, Krook A, Wallberg-Henriksson H (2000) Insulin action and insulin resistance in human skeletal muscle. Diabetologia 43(6): 821-835.

29. Højlund K, Staehr P, Hansen BF, et al. (2003) Increased phosphorylation of skeletal muscle insulin receptor substrate-1 serine 312 correlates with reduced insulin action in non-diabetic subjects. Diabetes 52(6): 1389-1394.