THE ROLE OF INSULIN IN BODY COMPOSITION: EVIDENCE BASED RECOMMENDATIONS FOR RESISTANCE TRAINING APPLICATIONS

BY

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Abstract

Insulin's effects and practical uses are well documented for diabetes patients, but implications of endogenous insulin levels are seldom used functionally in other settings. This literature review examines existing literature describing the ramifications of insulin activity on body composition, and seeks to propose protocols – through nutrition and training – for improving body composition (lowering body fat, increasing lean body mass) based on these ramifications. It appears that a diet that elicits low insulin responses will promote insulin sensitivity, thereby attenuating insulin-dependent adipose tissue anabolism. When combined with a resistance training regimen, insulin sensitivity improves further; resistance training also elicits higher levels of glucose transporter 4 (GLUT-4) expression and translocation across muscle cell membranes. This phenomenon favorably affects nutrient partitioning toward lean body mass, preferentially allocating post-exercise nutrients to skeletal muscle tissue as opposed to adipose tissue. Once more researched and refined, applications include: clinicians wishing to lower BMI and improve body composition of patients; recreational athletes wishing to improve body composition for personal/aesthetic reasons; athletes of all levels for whom body composition is tantamount to performance and/or weight class – e.g. divers, swimmers, fighters, gymnasts, etc.

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I. Introduction

The actions of insulin are well documented in the context of Diabetes Mellitus. Namely, these actions concern glucose production, utilization, and storage. Due to the prevalence of Diabetes (especially Type II in developed countries), most laypersons are at least somewhat aware of these functions; however, a mainstream understanding of insulin only extends thus far. Insulin is used as an exogenous aid for both Type I and Type II diabetics for the purposes of glucose regulation, but insulin has many more documented functions than these. Bodybuilders have been taking advantage of insulin's anabolic properties, using insulin in recent years to gain weight, mostly in the form of skeletal muscle mass. They do this largely by administering insulin during feeding times. When used in this particular way, insulin is capable of acting beneficially on muscle tissue. Type II diabetics gain weight as well, but interestingly enough, their insulin-associated weight gain comes mainly in the form of fat mass. Even without a review of insulin's functions, simply by observing these two insulin-using populations it becomes clear that, when used exogenously, insulin can have appreciable effects on body composition. This observation, combined with the known functions of insulin on skeletal muscle (henceforth "muscle") and adipose tissue, leads to the hypothesis that endogenously produced insulin should also provide some salient effect on body composition. It follows that for individuals with either no personal or medical reasons for using insulin exogenously, it would be desirable to manipulate endogenous insulin levels to bring about beneficial changes in body composition – i.e. greater muscle:fat ratio.

Objective

For the purpose of improving body composition, it may be possible to use nutrition and exercise training to manipulate insulin in order to allocate more resources to skeletal muscle tissue and less resources to adipose tissue. Applications for combined nutrition and exercise protocols span a wide range, from laypersons wishing to improve body composition for personal reasons to clinicians wishing to lower the BMIs of their overweight and/or obese patients. This review seeks to briefly elucidate existing literature on insulin's effects on tissues body composition, and also aims to propose a framework for which to plan nutrition and exercise training protocols for applications including – but not limited to – those previously mentioned. Further human trials would need to occur in order to verify the effectiveness of these protocols, but any recommendations found in this review will be based on current evidence from the literature.

II. Actions of Insulin on Relevant Tissues

In non-diabetic individuals, insulin is normally secreted in response to ingestion of either carbohydrate or leucine (Fig. 1). As a regulator of metabolism, one of insulin's most important (and well known) functions is to stimulate uptake of glucose from the bloodstream.

In terms of body composition, there are a few effects of insulin on the following processes that are of particular importance:

1. Fat Metabolism, due to the fact that lipolysis and lipogenesis affect fat mass. A decrease in fat mass is the objective; however, insulin generally has undesirable

effects on fat metabolism, instead promoting postprandial storage of triglycerides in adipose tissue (i.e. *increase* in fat mass) by way of the following mechanisms:

a. Activation of lipoprotein lipase in adipose tissue: lipoprotein lipase generates fatty acids by hydrolysis of triglycerides in circulating lipoproteins. The fatty acids are subsequently taken up by adipose tissue (12).
b. Inhibition of lipoprotein lipase in skeletal muscle: inhibition of lipoprotein lipase diverts triglycerides from muscle tissue – where they would undergo oxidation – to be stored in adipose tissue (13).
c. Increase in intracellular glycerol-3-phosphate: insulin-dependent glucose transport into adipose cells increases glycolytic activity, resulting in elevated levels of glycerol-3-phosphate. This metabolite is involved in free fatty acid esterification into triglycerides (38).
d. Inhibition of hormone-sensitive lipase: hormone-sensitive lipase (HSL) is a rate-limiting factor in lipolysis, and may be dephosphorylated and inactivated by an insulin-dependent protein phosphatase (33), (25). Inhibition of ASL can also occur with an insulin-dependent lowering of intracellular cAMP levels, the downstream effect of which is downregulating phosphorylation (and therefore activation) of HSL (34), (11).

2. Protein Metabolism, due to the fact that muscle protein synthesis contributes favorably to muscle mass. An increase in muscle mass is the objective. Insulin has desirable effect on muscle mass in the following ways:

a. Permissive effect on muscle protein synthesis: although studies conflict on insulin dose for eliciting muscle protein synthesis (ranging from low to

supraphysiological), a common thread seems to be that at any dose, insulin initiates muscle protein synthesis provided that the intramuscular levels of amino acids are sufficient to do so. The inverse is also supported – without sufficient intramuscular amino acid levels, muscle protein synthesis is improbable regardless of insulin dose (39), (21).

b. Anti-catabolic effect: albeit dose-dependent, insulin has the ability to mitigate whole body proteolysis – again, provided that amino acids are present in basal levels. Hypoaminoacidemic conditions lessen insulin's ability to blunt protein breakdown (14).

Insulin is largely an anabolic hormone, and this characteristic is observed in both fat and protein metabolism. Based on its effects on adipose and muscle tissue, it appears that insulin tends to increase body fat storage. It also tends to increase net muscle protein synthesis, but with the added condition that amino acid levels must be sufficient. Insulin's dually anabolic nature presents a problem for body composition, as muscle protein is desirable and adipose tissue is not. Ideally, one would be able to elicit insulin's anabolic effect on muscle protein without the corresponding uptick in adipose tissue anabolism. It would be difficult to accomplish this type of nutrient partitioning through diet alone, since ingestion of both carbohydrate and leucine stimulate insulin secretion.

III. Insulin and Nutrition

Since insulin release is triggered chiefly by ingestion of carbohydrate and leucine, it would be prudent to examine nutrition as a method of insulin regulation. Research suggests insulin can have an anabolic effect on fat mass, so it stands to reason that constant

elevation would prove to be detrimental to body composition. Reducing and/or blunting insulin response could possibly reduce postprandial glucose storage as adipose tissue.

Method 1: Reduce consumption of insulinogenic foods

The simplest way to achieve a reduction in insulin response would be to adhere to a diet that reduces overall insulin response. This would involve consuming meals that are lower in two of insulin's main triggers: carbohydrate and leucine (which is found in many protein rich foods). Such meals would elicit less of an insulin response according to the insulin index (17). In order to translate this into an isocaloric diet, this would involve increasing overall proportion of dietary fat consumed per meal – relative to carbohydrate and protein – since ingestion of dietary fat itself is not a main trigger of insulin release (Fig. 1). Protein ingestion tends to more greatly attenuate a rise in glucose level through greater stimulation of insulin secretion, most likely due to an abundance of leucine; on the other hand, dietary fat tends to slow gastric emptying which also has a blunting effect on a rise in blood glucose when consumed with carbohydrate (27).

Lowering overall carbohydrate and leucine (i.e. protein) consumption with a corresponding increase in dietary fat may therefore help to keep overall insulin levels – especially postprandial levels – lower. This would be similar in concept to a ketogenic diet, which is a high fat, medium protein, and very low carbohydrate diet. The benefits of such a diet are disputed, with existing evidence to suggest that it may be more effective than a low-fat diet for weight loss (4), but also that in doing so it may induce insulin resistance (23), despite being neuroprotective (15), (31). Based on the lack of consensus regarding its benefits, a ketogenic-type diet may therefore be more suitable for some individuals than others, and should be applied judiciously on an individual basis.

Method 2: Increase fiber consumption

The exact mechanism is unknown, but research suggests that fiber consumption markedly decreases postprandial insulin release (37), up to 50% in some cases (1), (2). Albrink et al used 18 grams of crude fiber for their high-fiber group which saw reductions in insulin response vs. a low fiber group with 1 gram of crude fiber, so at least 18 grams would be a possible starting point for individuals wishing to attenuate insulin release with this method. Recommended fiber intake can be as high as 38 grams for men and 25 grams for women, so "high fiber" does not seem to have a universal definition. Regardless, an intake in this range (with the lower limit being 18 grams) should suffice for the purposes of reducing insulin release.

Method 3: Combine Methods 1 and 2

Of course, one could combine both methods to create a third method of both decreasing insulinogenic food intake and increasing fiber consumption. However, little to no formal research exists on such a diet, so combining the two methods may or may not yield cumulative benefits. So, there are at least two methods to minimize overall insulin release and its subsequent anabolic effects on adipose tissue; however, following such methods would also minimize its anabolic and anti-catabolic effects on muscle tissue. To further improve body composition one must also take advantage of insulin's positive effects on muscle mass. In order to more selectively partition nutrients to muscle tissue benefit from insulin's permissive effects on muscle protein synthesis, exercise training must be utilized as well.

IV. Insulin and Exercise Training

In the two populations given as examples in the introduction, a major difference in their lifestyles is exercise; specifically, a method of training favored by bodybuilders: resistance training (in the form of lifting weights). For the purposes of this review, a working definition of resistance training is any form of exercise that uses resistance to elicit muscular contractions. Exercise involving muscle contraction offers myriad valuable adaptations, including sensitization of muscle tissue to nutrient uptake – especially glucose (30), (22). Resistance training also has beneficial effects on glucose tolerance, insulin sensitivity, power output, performance, and of course body composition (32).
(Note: since resistance training employs muscular contraction as its foremost mechanism, the terms "resistance training" and "muscular contraction" will be used interchangeably.)

Importance of Glucose Transporter 4

Glucose transporter 4 (henceforth GLUT4) is a cellular vesicle that is primarily responsible for transporting glucose across cell membranes in adipose and skeletal/cardiac muscle tissues (36). In order for these vesicles to do so, they must be translocated from the intracellular space to the cell membrane. This can occur through two pathways: one, the presence of insulin can induce the translocation; two, muscular contraction can elicit the same translocation (29), (28). These two pathways may be regulated by two different cellular pools of GLUT4, one pool for each pathway (6). GLUT4 intracellular expression and translocation is increased by way of resistance training (8), (9), (19), both in acute training bouts and long term training contexts; this is perhaps one of the most significant

adaptations to this type of training due to the benefits of increased glucose uptake by muscle tissue (36).

Another glucose transporter, GLUT1, also plays a role in basal glucose transport; however, in the context of exercise and muscle contraction, GLUT4 is the glucose transporter of interest due to its unique ability to clear blood glucose after translocation through resistance training alone (16). There is also evidence that GLUT12 functions in a similar manner to GLUT4, but GLUT4 is more prevalent in the relevant tissues of adipose and muscle (35).

Heightened post-exercise GLUT4 translocation subsequently increases glucose uptake even in the absence of insulin sensitivity – this phenomenon is especially useful for Type II diabetic patients, allowing them to clear blood glucose without exogenous insulin administration (18), (5). In healthy individuals, these two pathways can be stimulated not only concurrently, but also additively – combining exercise with insulin release can further increase glucose uptake beyond solely one or the other (7), (28). This additive nature is very valuable, as it increases the likelihood that nutrients will be partitioned to muscle instead of adipose tissue.

So, in healthy individuals, post-exercise consumption of insulinogenic foods may in fact be beneficial, as the combination of insulin-independent GLUT4 and insulin-stimulated GLUT4 create an opportunity for muscle-specific glucose uptake. Insulinogenic substances like carbohydrate and leucine can in fact increase muscle protein synthesis when ingested after resistance training (10). A healthy individual could therefore benefit from post-exercise ingestion of insulinogenic foods, maximizing nutrient uptake by muscle tissue through translocation of both pools of GLUT4. However, nutrient timing remains a

controversial topic, with the classic model of immediate post-exercise ingestion being called into question (3), with another model being pre-exercise ingestion to take advantage of insulin's anti-catabolic effects (although a pre-exercise insulin spike would not take advantage of exercise-induced GLUT4 translocation, and could also possibly incite exercise-induced hypoglycemia). It seems that benefits from a training bout (improved insulin sensitivity and GLUT4 translocation) last for at least several hours (26), so spiking insulin either with leucine or a carbohydrate/leucine combination within this time frame would likely still be beneficial.

It has been shown that in order to avoid being overly anabolic (both adipose and muscle), one should seek to limit insulin release. However, it is also evident that resistance training and post-exercise nutrient ingestion perhaps offer a way to reap the anabolic effects of insulin on muscle tissue. Reconciling the two is difficult, and current research does not describe such a combination; therefore, protocols included in this review are based on hypotheses drawn from existing literature.

V. Proposing an Evidence-Based Protocol

Disclaimer: the nutrition and resistance training protocol in this review provides an overview of implementation of suggested methodologies. They are not meant to be a substitute for medical advice, nor are they meant to treat, cure, or prevent any disease. Possible protocols to improve body composition are simple in very general terms. More research is needed to confirm the validity and efficacy of such protocols, as they are based on insulin's known actions on the relevant tissues of adipose and skeletal muscle.

A protocol aimed at improving body composition through the manipulation of endogenous insulin is as follows (in bullet format for brevity):

- Nutrition with the objective of reducing the anabolic effects of insulin, particularly on adipose tissue.
    - With the exception of the post-exercise timeframe, either:
        a. Consume a diet lower in insulinogenic foods (e.g. carbohydrates and protein), approximating a ketogenic-style diet.
        b. Consume a high fiber diet including at least 18 daily grams of fiber.
        c. Combine a. and b.
    - During the post-exercise timeframe, either:
        d. Consume a protein and carbohydrate rich meal.
        e. Consume a protein and carbohydrate rich supplement.
        f. Consume a meal or supplement that is high in leucine specifically (carbohydrates optional).
- Resistance Training with the objective of increasing the anabolic effects of insulin specifically on muscle tissue.
    - Perform resistance training that elicits muscular contractions in order to stimulate additive insulin and exercise-induced GLUT4 translocation, such as:
        a. Weight training (e.g. free weights, weight machines).
        b. Body weight exercises (e.g. calisthenics).
        c. Banded exercises (with resistance bands).
        d. Other implements (medicine balls, etc.).

- At a minimum, perform resistance training exercises in multiple sets of 8 to 12 repetitions to elicit training adaptations (32).
- In order retain the GLUT4 adaptation to muscle contraction, training should be performed at least every 48 hours, as this training benefit can be diminished within 48 hours after training cessation (26).
- To further maximize muscle anabolism, emphasis should be placed on training large muscle groups with multi-joint movements to stimulate a greater amount of GLUT4 expression and translocation.

VI. Discussion

Insulin can have notable effects on tissues contributing to body composition, namely adipose tissue and skeletal muscle tissue. Its anabolic effects on adipose tissue make chronic elevation of this hormone undesirable, but its anabolic effects on skeletal muscle hint at a possible model in which targeted elevation would allocate more nutrients to muscle tissue. The model proposed in this review is one in which an individual consumes a low-insulinogenic diet for most of the day (achievable through at least two distinct methods), but consumes insulinogenic nutrients following resistance training. In theory, such a protocol would reduce insulin's anabolic effects on fat while maximizing its anabolic effects on muscle tissue by taking advantage of the additive insulin and exercise-induced GLUT4 translocation, ultimately resulting in a higher muscle:fat ratio.

Caveats and Limitations

The protocols proposed in this review are based in evidence, but operate hypothetically. They would need to be performed in human trials to determine their practical veracity and efficacy. There are other factors that play substantial roles in body composition as well, such as insulin sensitivity – although, a discussion of insulin sensitivity seemed unwarranted, as these protocols involved stimulating an insulin-independent pathway, and were also proposed for healthy, nondiabetic individuals whose insulin sensitivity would likely be improved by resistance training regardless. It's also important to note that insulin is but one hormone in the human body, and that it does not operate in a vacuum; other hormones and intrinsic factors could alter or attenuate insulin's effects in different ways.

Unfortunately, no exercise threshold was found in the research for GLUT4 translocation, as different studies employed different exercise types and schemes to elicit the response, so no strict guideline was imposed on the volume of resistance training. Instead, the recommended scheme for resistance training is simply drawn from Stone's review of resistance training adaptations and the volume needed to elicit them. GLUT4 activation (24) and insulin sensitivity (20) can also be obtained through moderate to high intensity aerobic exercise but muscle contraction is the key, which is why resistance training applications were favored.

Future research

There is a great need for more research in testing protocols (i.e. specific nutrition and specific training) involving manipulation of endocrinology for the purpose of

improving body composition on a whole-body scale, as these sorts of protocols could have widespread application. More research is also needed to determine specificity of such protocols, including algorithms for more individual customization.

Once more researched and refined, applications include: clinicians wishing to lower BMI and improve body composition of patients; recreational athletes wishing to improve body composition for personal/aesthetic reasons; athletes of all levels for whom body composition is tantamount to performance and/or weight class – e.g. divers, swimmers, fighters, gymnasts, etc.

Figure 1: Regulation of Insulin Release

Regulation of insulin release

Factors that stimulate insulin release
Glucose, mannose
Leucine
Vagal stimulation
Sulfonylurea drugs
Factors that amplify glucose-induced insulin release
Enteric hormones
Glucagon-like peptide 1
Gastric inhibitory peptide
Cholecystokinin
Secretin
Gastrin
Neural amplifiers
Beta-adrenergic stimulation
Amino acids
Arginine
Prostaglandin E2
Inhibitors of insulin release
Neural
Alpha-adrenergic effect
Humoral
Somatostatin
Drugs
Diazoxide
Phenytoin
Vinblastine
Colchicine

References:

1. **Albrink MJ.** Dietary fiber, plasma insulin, and obesity. *Am. J. Clin. Nutr.* 31: 10 Suppl: S279, 1978.

2. **Albrink MJ, Newman T and Davidson PC.** Effect of high- and low-fiber diets on plasma lipids and insulin. *Am. J. Clin. Nutr.* 32: 7: 1486-1491, 1979.

3. **Aragon AA and Schoenfeld BJ.** Nutrient timing revisited: is there a post-exercise anabolic window? *J Int Soc Sports Nutr* 10: 1: 5, 2013.

4. **Bueno NB, de Melo, Ingrid Sofia Vieira, de Oliveira SL and da Rocha Ataide T.** Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. *Br. J. Nutr.* 110: 7: 1178-1187, 2013.

5. **Christ-Roberts CY, Pratipanawatr T, Pratipanawatr W, Berria R, Belfort R, Kashyap S and Mandarino LJ.** Exercise training increases glycogen synthase activity and GLUT4 expression but not insulin signaling in overweight nondiabetic and type 2 diabetic subjects. *Metab. Clin. Exp.* 53: 9: 1233-1242, 2004.

6. **Coderre L, Kandror KV, Vallega G and Pilch PF.** Identification and Characterization of an Exercise-sensitive Pool of Glucose Transporters in Skeletal Muscle. *J. Biol. Chem.* 270: 46: 27584-27588, 1995.

7. **Constable SH, Favier RJ, Cartee GD, Young DA and Holloszy JO.** Muscle glucose transport: interactions of in vitro contractions, insulin, and exercise. *J. Appl. Physiol.* 64: 6: 2329-2332, 1988.

8. **Daugaard JR, Nielsen JN, Kristiansen S, Andersen JL, Hargreaves M and Richter EA.** Fiber type-specific expression of GLUT4 in human skeletal muscle: influence of exercise training. *Diabetes* 49: 7: 1092-1095, 2000.

9. **Dela F, Handberg A, Mikines KJ, Vinten J and Galbo H.** GLUT 4 and insulin receptor binding and kinase activity in trained human muscle. *J Physiol* 469: 615-624, 1993.

10. **Dreyer HC, Drummond MJ, Pennings B, Fujita S, Glynn EL, Chinkes DL, Dhanani S, Volpi E and Rasmussen BB.** Leucine-enriched essential amino acid and carbohydrate ingestion following

resistance exercise enhances mTOR signaling and protein synthesis in human muscle. *Am J Physiol Endocrinol Metab* 294: 2: E400, 2008.

11. **Duncan RE, Ahmadian M, Jaworski K, Sarkadi-Nagy E and Sul HS.** Regulation of lipolysis in adipocytes. *Annu. Rev. Nutr.* 27: 79-101, 2007.

12. **Farese RV, Yost TJ and Eckel RH.** Tissue-specific regulation of lipoprotein lipase activity by insulin/glucose in normal-weight humans. *Metab. Clin. Exp.* 40: 2: 214-216, 1991.

13. **Fielding BA and Frayn KN.** Lipoprotein lipase and the disposition of dietary fatty acids. *Br. J. Nutr.* 80: 6: 495-502, 1998.

14. **Flakoll PJ, Kulaylat M, Frexes-Steed M, Hourani H, Brown LL, Hill JO and Abumrad NN.** Amino acids augment insulin's suppression of whole body proteolysis. *Am. J. Physiol.* 257: 6 Pt 1: 839, 1989.

15. **Gasior M, Rogawski MA and Hartman AL.** Neuroprotective and disease-modifying effects of the ketogenic diet. *Behav Pharmacol* 17: 5-6: 431-439, 2006.

16. **Gaster M, Staehr P, Beck-Nielsen H, Schrøder HD and Handberg A.** GLUT4 is reduced in slow muscle fibers of type 2 diabetic patients: is insulin resistance in type 2 diabetes a slow, type 1 fiber disease? *Diabetes* 50: 6: 1324-1329, 2001.

17. **Holt SH, Miller JC and Petocz P.** An insulin index of foods: the insulin demand generated by 1000-kJ portions of common foods. *Am. J. Clin. Nutr.* 66: 5: 1264-1276, 1997.

18. **Holten MK, Zacho M, Gaster M, Juel C, Wojtaszewski JFP and Dela F.** Strength Training Increases Insulin-Mediated Glucose Uptake, GLUT4 Content, and Insulin Signaling in Skeletal Muscle in Patients With Type 2 Diabetes. 3: 2004/02/01.

19. **Houmard JA, Shinebarger MH, Dolan PL, Leggett-Frazier N, Bruner RK, McCammon MR, Israel RG and Dohm GL.** Exercise training increases GLUT-4 protein concentration in previously sedentary middle-aged men. *Am. J. Physiol.* 264: 6 Pt 1: 896, 1993.

20. **Houmard JA, Tanner CJ, Slentz CA, Duscha BD, McCartney JS and Kraus WE.** Effect of the

volume and intensity of exercise training on insulin sensitivity. *J. Appl. Physiol.* 96: 1: 101-106, 2004.

21. **Jefferson LS.** Lilly Lecture 1979: role of insulin in the regulation of protein synthesis. *Diabetes* 29: 6: 487-496, 1980.

22. **Jessen N and Goodyear LJ.** Contraction signaling to glucose transport in skeletal muscle. *J. Appl. Physiol.* 99: 1: 330-337, 2005.

23. **Jornayvaz FR, Jurczak MJ, Lee H, Birkenfeld AL, Frederick DW, Zhang D, Zhang X, Samuel VT and Shulman GI.** A high-fat, ketogenic diet causes hepatic insulin resistance in mice, despite increasing energy expenditure and preventing weight gain. *Am. J. Physiol. Endocrinol. Metab.* 299: 5: 808, 2010.

24. **Kraniou GN, Cameron-Smith D and Hargreaves M.** Acute exercise and GLUT4 expression in human skeletal muscle: influence of exercise intensity. *J. Appl. Physiol.* 101: 3: 934-937, 2006.

25. **Lass A, Zimmermann R, Oberer M and Zechner R.** Lipolysis - a highly regulated multi-enzyme complex mediates the catabolism of cellular fat stores. *Prog. Lipid Res.* 50: 1: 14-27, 2011.

26. **Lehnen AM, Angelis KD, Markoski MM and Schaan B.** Changes in the GLUT4 Expression by acute exercise, Exercise training and detraining in experimental models. 10: 2, 2012.

27. **Moghaddam E, Vogt JA and Wolever TMS.** The Effects of Fat and Protein on Glycemic Responses in Nondiabetic Humans Vary with Waist Circumference, Fasting Plasma Insulin, and Dietary Fiber Intake. *J. Nutr.* 136: 10: 2506-2511, 2006.

28. **Nesher R, Karl IE and Kipnis DM.** Dissociation of effects of insulin and contraction on glucose transport in rat epitrochlearis muscle. *Am. J. Physiol.* 249: 3 Pt 1: 226, 1985.

29. **Ploug T, Galbo H, Vinten J, Jørgensen M and Richter EA.** Kinetics of glucose transport in rat muscle: effects of insulin and contractions. *Am. J. Physiol.* 253: 1 Pt 1: 12, 1987.

30. **Richter EA and Hargreaves M.** Exercise, GLUT4, and skeletal muscle glucose uptake. *Physiol. Rev.* 93: 3: 993-1017, 2013.

31. **Stafstrom CE and Rho JM.** The Ketogenic Diet as a Treatment Paradigm for Diverse

Neurological Disorders. *Front Pharmacol* 3: 2012.

32. **Stone MH, Fleck SJ, Triplett NT and Kraemer WJ.** Health- and performance-related potential of resistance training. *Sports Med* 11: 4: 210-231, 1991.

33. **Strålfors P, Björgell P and Belfrage P.** Hormonal regulation of hormone-sensitive lipase in intact adipocytes: identification of phosphorylated sites and effects on the phosphorylation by lipolytic hormones and insulin. *Proc. Natl. Acad. Sci. U.S.A.* 81: 11: 3317-3321, 1984.

34. **Strålfors P and Honnor RC.** Insulin-induced dephosphorylation of hormone-sensitive lipase. Correlation with lipolysis and cAMP-dependent protein kinase activity. *Eur. J. Biochem.* 182: 2: 379-385, 1989.

35. **Stuart CA, Howell MEA, Zhang Y and Yin D.** Insulin-stimulated translocation of glucose transporter (GLUT) 12 parallels that of GLUT4 in normal muscle. *J. Clin. Endocrinol. Metab.* 94: 9: 3535-3542, 2009.

36. **Tremblay F, Dubois M and Marette A.** Regulation of GLUT4 traffic and function by insulin and contraction in skeletal muscle. *Front. Biosci.* 8: 1072, 2003.

37. **Ullrich IH and Albrink MJ.** The effect of dietary fiber and other factors on insulin response: role in obesity. *J. Environ. Pathol. Toxicol. Oncol.* 5: 6: 137-155, 1985.

38. **Vila MC and Farese RV.** Insulin rapidly increases glycerol-3-phosphate-acyltransferase activity in rat adipocytes. *Arch. Biochem. Biophys.* 284: 2: 366-368, 1991.

39. **Wolfe RR.** Effects of insulin on muscle tissue. *Curr Opin Clin Nutr Metab Care* 3: 1: 67-71, 2000.