



Published in final edited form as:

*Nutrition*. 2010 ; 26(7-8): 686–693. doi:10.1016/j.nut.2009.10.013.

## Metabolic actions of insulin in men and women

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### Abstract

Insulin is an important regulator of glucose, lipid and protein metabolism. It suppresses hepatic glucose and triglyceride production, inhibits adipose tissue lipolysis and whole-body and muscle proteolysis and stimulates glucose uptake in muscle. In this review we discuss what is currently known about the control of substrate metabolism by insulin in men and women. The data available so far indicate that women are more sensitive to insulin with regards to glucose metabolism (both in the liver and in muscle) whereas there are no differences between men and women in insulin action on lipolysis. Potential differences exist in the regulation of plasma triglyceride concentration and protein metabolism by insulin and in changes in insulin-action in response to stimuli (e.g., weight loss and exercise) that are known to alter insulin sensitivity. However, these areas have not been studied comprehensively enough to draw firm conclusions.

### Keywords

glucose uptake; hepatic glucose production; lipolysis; triglyceride secretion; triglyceride clearance; proteolysis

### Introduction

Here we summarize recent findings on differences between men and women in insulin action on glucose, lipid and protein metabolism. Although quite often insulin's role is narrowly defined within the context of regulation of glucose metabolism (i.e., suppression of hepatic glucose production and stimulation of glucose uptake in muscle by insulin), its actions reach an array of metabolic pathways. Insulin is an important (if not the primary) inhibitor of adipose tissue lipolysis and fatty acid release into the blood stream [1,2]; it is involved in the regulation of hepatic lipoprotein metabolism (e.g., apolipoprotein and triglyceride secretion) [3,4] and blood lipid clearance (by stimulating lipoprotein lipase activity in adipose tissue [5]); and, it is a well-established and very potent inhibitor of protein breakdown [6–9] (Figure 1). It may also affect protein synthesis; however, the effect of insulin on protein synthesis cannot be

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BM is responsible for the conception of the project, and FM, XW, and BM are jointly responsible for the collection of information and the writing of the manuscript. The final manuscript has been seen and approved by all authors and that they have taken due care to ensure the integrity of their work and their personal scientific reputation.

generalized easily because it is largely dependent on the concomitant availability of amino acids [8–10], and potentially also the target protein of interest [11,12]. Accordingly, resistance to the actions of insulin will result in a multitude of metabolic abnormalities. Furthermore, resistance to the actions of insulin is not a global feature as there are cases of selective insulin resistance (e.g., in the vasculature, insulin resistance affects the PI3 kinase pathway but not other pathways of insulin signaling including the MAPK pathway [13,14]). In addition, there appears to be highly specific regulation of insulin action as evidenced by different sensitivities of different metabolic pathways to the action of insulin (e.g., glucose uptake vs. glucose production etc).

Between group differences in the metabolic actions of insulin can occur through alterations at multiple levels, including insulin secretion from  $\beta$ -cells, insulin delivery and trans endothelial transport, insulin receptor expression and signal transduction in the target tissue [15,16]. We have learned a lot about the mechanism(s) responsible for the regulation of insulin action, both at the whole-body and the cellular level. From a metabolic point of view, it is now well established that cross-talk between adipose tissue and the sites of insulin production and action plays a central role in regulating insulin action. Free fatty acids released during adipose tissue lipolysis inhibit glucose uptake in muscle, and increase glucose production from the liver [17,18]. On the other hand, free fatty acids stimulate insulin secretion from  $\beta$ -cells [19], which may help overcome the negative effects of FFA on insulin action (Figure 1). Interestingly, free fatty acids do not appear to inhibit proteolysis [20]. However, this conclusion was based on proteolytic enzyme expression only. The interaction between free fatty acids and insulin on proteolysis has not been evaluated to date. Adipokines can also affect insulin sensitivity [21]. In addition, insulin may indirectly affect substrate metabolism by acting as a vasodilator thereby regulating nutrient and insulin delivery to tissues [16].

Sex differences in the regulation of substrate metabolism by insulin have started to be recognized only fairly recently and the results from the relatively few studies in this area are not always conclusive. The best, although still understudied area, is the control of glucose metabolism by insulin in men and women. Interest in sexual dimorphism in lipoprotein metabolism was fueled by the well-established differences in the plasma lipid profile [39, 103–105], whereas interest in sex differences in lipid metabolism in adipose tissue and protein metabolism in skeletal muscle has arisen due to the obvious differences in body composition between the sexes. For the most part, the data available to date which cover these topics do not extend beyond the results from initial observational studies and there is a lot to discover with regards to the sexually dimorphic control mechanisms responsible for the observed differences. Here we discuss what is currently known about the control of substrate metabolism by insulin in men and women and potential differences between the sexes in changes in insulin-action in response to stimuli (e.g., weight loss and exercise) that are known to alter insulin sensitivity.

## Sex differences in the control of glucose metabolism by insulin

Insulin is a major regulator of plasma glucose concentration; it reduces endogenous glucose production (>90% from the liver) and stimulates peripheral glucose uptake. Suppression of endogenous glucose production occurs maximally at relatively low plasma insulin concentrations (<60 mU/l) [22,23], whereas stimulation of whole-body and skeletal muscle glucose uptake occurs maximally at much higher insulin concentrations (e.g., >120 mU/l in healthy, lean subjects) [24].

Fasting plasma glucose and insulin concentrations [25,26] and the basal rates of endogenous glucose production and whole-body glucose disposal, expressed per kg of body weight or lean mass, are typically not different between healthy adult men and women [27–31]; although there are some reports of slightly greater (10–20%) glucose turnover rates in women than in men

[32,33]. Total endogenous glucose production is greater in men than women [31,34] due to differences in body size between men and women. No sex differences in endogenous glucose production have been observed during exogenous insulin and dextrose infusion to achieve euglycemia and plasma insulin concentrations of ~50–120 mU/l [27–29]. However, during insulin infusion alone (to induce hypoglycemia) at rates that raise plasma insulin concentrations 20 to ~15–20 mU/l, women exhibited a greater and more prolonged suppression of endogenous glucose production rate than men [30]. And, the suppression of endogenous glucose production after a mixed meal (adjusted for body weight) which raised plasma insulin to peak concentrations of ~50 mU/l was also found to be greater in women than in men [33]. Considering that the insulin-mediated suppression of endogenous glucose production is a measure of hepatic insulin sensitivity [24], women therefore appear to be more sensitive to the effects of insulin in the liver and suppress their endogenous glucose production to a greater extent than men at low plasma insulin concentrations whereas maximal insulin-mediated suppression of endogenous glucose production appears to be the same in men and women.

The results from studies in which the hyperinsulinemic-euglycemic clamp procedure was combined with isotope labeled tracers to evaluate the effect of insulin on glucose rate of disappearance from plasma provide no evidence of sex differences in the insulin-mediated stimulation (percent increase from basal) of whole-body glucose uptake at plasma insulin concentrations between ~50 and 120 mU/l [27–29,35]. Although, there are some dissonant reports. Insulin infusion alone at a rate that raised plasma insulin concentrations to ~15–20 mU/l with a concomitant drop in plasma glucose concentration stimulated glucose uptake in men but failed to do so in women [30] suggesting that women are less insulin sensitive than men. On the other hand, Shadid et al. [34] found no differences in glucose disposal between men and women although plasma insulin concentrations were significantly greater in men than in women, suggesting that men are less insulin sensitive than women. In contrast, studies that measured glucose uptake by the leg/forearm (by using the arteriovenous balance technique or positron emission tomography) during systemic insulin infusion and euglycemia, or following glucose ingestion, have consistently demonstrated a significantly greater insulin-mediated glucose uptake rate per kg of skeletal muscle tissue in women than in men [36–38]. Glucose uptake in skeletal muscle therefore appears to be more sensitive to insulin in women than in men. This is interesting because free fatty acids and increased adipose tissue accumulation is associated with a decrease in insulin sensitivity [17,18] and women are fatter than men and relative to lean tissue mass have greater FFA release into the circulation [39–41]. The reasons for the apparent discrepancy between studies at the whole-body level and across a limb (mostly muscle) are unclear. It is unlikely that adipose tissue is responsible for this discrepancy. Although we are not aware of studies that evaluated insulin-mediated glucose uptake by adipose tissue in vivo in human subjects, the results from studies performed in vitro indicate that adipocytes from female rodents and humans are more insulin-sensitive than those from males with respect to glucose transport and utilization [42–44].

Recently, attempts have been made to unravel the mechanisms responsible for the greater skeletal muscle insulin sensitivity in women than in men; so far with little conclusive evidence other than the fact that differences in insulin receptor and glucose transporter expression, proximal insulin signaling intermediates, intramuscular triacylglycerol, ceramide and diacylglycerol concentrations are not likely the candidates mediating the differences in the response of skeletal muscle to insulin in men and women [37,45]. Furthermore there is no indication that differences in the sex hormone milieu are responsible for the differences between men and women in insulin-mediated glucose disposal. There is no evidence that menstrual cycle phase affects basal glucose metabolism [46–50] or insulin's action on endogenous glucose production or whole-body glucose disposal [49–52], although greater rates of glucose disposal during the follicular than the luteal phase of the menstrual cycle have been observed during a hyperglycemic (blood glucose > 200 mg/dl) hyperinsulinemic clamp [53].

Furthermore, there is no evidence that treatment with low-dose oral contraceptives [54] or estradiol or progesterone or a combination of both [55] affects basal glucose metabolism and insulin's action on endogenous glucose production and peripheral glucose uptake; although in cross-sectional studies decreased insulin sensitivity was reported in women who took oral contraceptive pills [27,46]. Moreover, pharmacological suppression of endogenous ovarian hormone secretion [52] and physiological loss of ovarian function during menopause [56,57] is not accompanied by differences in insulin-mediated whole-body glucose disposal. On the other hand, treatment with testosterone reduces insulin-mediated glucose disposal in women [58] and hyperandrogenemia might be the major culprit for the insulin resistance in women with polycystic ovary syndrome [59].

Results from studies that used the hyperinsulinemic (plasma insulin concentrations between 50 and 120 mU/l) euglycemic clamp technique without tracers to evaluate potential sex differences in the regulation of glucose metabolism in men and women provide contrasting results: in most studies no differences in glucose uptake per kg of body weight or lean mass were found between men and women [27–29,60–64], whereas some investigators report greater [36,45,65–67] and others found smaller [35,68,69] insulin-mediated glucose disposal rates in women than in men. However, interpretation of these results is somewhat difficult because this method does not account for potential differences in the contribution of endogenous glucose production to total glucose uptake. Similarly, the results from studies that relied on the oral glucose tolerance test (OGTT) to evaluate insulin sensitivity are equivocal [66,68,70–73] and difficult to interpret because the OGTT does not take into account differences in body size between men and women.

Initial investigations into the interaction of free fatty acids in plasma and the regulation of glucose metabolism by insulin indicated that women [28] do not exhibit free fatty acid-induced insulin resistance, which confirmed earlier works on rats [74]. This observation was later overturned by two independent groups of investigators who found that fatty acids do inhibit insulin-mediated glucose uptake and endogenous glucose production in women both during hyperglycemia-hyperinsulinemia and euglycemia-hyperinsulinemia [75,76]. It should be noted, however, that in the early work by Frias and coworkers [28] plasma insulin concentration was clamped at ~120 mU/l whereas plasma insulin concentration was clamped at 50 mU/l [75] and 85 mU/l [76] in subsequent studies. It is therefore possible that increased free fatty acid availability does not interfere with near-maximal or maximal insulin-stimulated glucose uptake but does reduce the responsiveness to insulin. Only recently Vistisen and colleagues [45] directly compared the lipid-induced inhibition of insulin-mediated glucose disposal in men and women and found it was the same. However, these findings are somewhat difficult to interpret because plasma free fatty acid concentrations were raised to ~2.4 mM in women and 3.7 mM in men; although this difference was not statistically significant, it is big enough to account for possible confounding of the results.

Three studies evaluated the effect of exercise on insulin-mediated glucose uptake in men and women; the results are equivocal. Perreault et al. [77] report that a single prolonged (90 min) bout of moderate intensity exercise augments insulin-mediated glucose disposal to a greater extent in lean women than in lean men. On the other hand, Vistisen and colleagues [45], who evaluated the effect of 30 min of low-intensity exercise on insulin-mediated glucose uptake during concomitant lipid infusion, found that the exercise-induced increase in glucose uptake was not different in obese men and women. And, O'Leary and colleagues [78] report no sex difference in the exercise training-induced improvement in whole-body glucose disposal in obese older adults but the number of subjects in the study was small (7 men), which may have limited statistical power. Clearly more rigorous evaluation of potential sex differences in the exercise-mediated changes in insulin action is needed. Only one study evaluated the effect of weight loss on insulin action in men and women separately and found that women appear to

experience lesser improvements (~20%) in insulin-mediated glucose uptake than men (~40% increase in glucose disposal rate during the clamp) [79,80]; however, the study was not specifically designed to evaluate differences in men and women and the difference did not reach statistical significance, most likely due to a type-II error. These are nonetheless important observations and warrant future research to determine whether exercise or weight loss should be emphasized differently in men and women to reverse the negative impact of obesity on glucose metabolism.

## Sex differences in the control of adipose tissue lipolysis by insulin

Insulin availability is one of the primary factors regulating adipose tissue lipolysis [1] and free fatty acid release into plasma [2]: an increase in insulin concentration (e.g., after meal ingestion) suppresses lipolytic rates and decreases plasma free fatty acid concentrations [81,82], whereas a decrease in insulin concentration (e.g., during fasting) leads to accelerated lipolysis and increased plasma free fatty acid concentrations [83,84]. Adipose tissue lipolysis and free fatty acid release into plasma are exquisitely sensitive to insulin and half-max suppression of lipolysis occurs within the range of normal fasting plasma insulin concentrations (<15 mU/l) [2,85,86] whereas suppression of basal insulin secretion approximately doubles the rate of lipolysis [2].

During the postabsorptive state, total free fatty acid rate of appearance (Ra) into plasma is generally not different between men and women [34,39,40]. However, because women have more body fat and less fat-free mass than men, basal free fatty acid Ra in relation to the amount of tissues that consume free fatty acids as a fuel and have high energy requirements is ~40–50% greater in women than in men [39–41] whereas free fatty acid Ra in relation to fat mass is the same in men and women [41].

An insulin dose-response study revealed that the plasma insulin concentration at which free fatty acid release into plasma is half-maximally suppressed is not different between men and women (both lean and obese) [85]. Furthermore, two studies evaluated plasma free fatty acid kinetics in men and women after consumption of an energy-adjusted mixed meal and found that the relative (to basal values) meal-induced decrease in free fatty acid Ra was the same in men and women [87,88]. Similarly, the suppression of plasma free fatty acid concentration following ingestion of a mixed meal adjusted for sex differences in energy requirements was found to be the same in men and women [89–91]. However, the suppression of plasma free fatty acid concentration after a standard OGTT is typically greater in women than in men [38,66,73,92,93], most likely because the greater glucose/insulin challenge in women. In addition, there is no evidence for differences between men and women in near-maximal or maximal suppression of plasma free fatty acid concentration and/or free fatty acid Ra during insulin or glucose infusion [27,28,34,45,93–95]. Thus, the response of adipose tissue lipolysis to insulin appears to be the same in the two sexes. Curiously however, the increase in glycerol Ra into plasma (index of adipose tissue lipolysis) during prolonged (~22 h) fasting has been reported to be smaller in women than in men despite a greater decrease in plasma insulin concentration [31], whereas the ability of insulin to suppress lipolysis and plasma free fatty acid concentrations after prolonged fasting (~38 h) is greater in women than in men [96]. It is therefore possible that stimuli that alter insulin sensitivity might affect the insulin response to a different degree in men and women.

Although data is limited, there is so far no evidence that menstrual cycle phase affects basal postabsorptive FFA kinetics [46–48,97,98] or meal fatty acid disposal [99]. The effect of sex hormones on insulin-mediated suppression of lipolysis has to our knowledge not been studied *in vivo* in human subjects.

## Sex differences in the control of plasma triglyceride metabolism by insulin

Insulin is an important regulator of plasma triglyceride homeostasis. Insulin reduces plasma triglyceride and VLDL-apoB-100 concentrations [100] by inhibiting hepatic VLDL-triglyceride and VLDL-apoB-100 production [3,4] and increasing LPL activity in adipose tissue [5]. Some but not all of the insulin-mediated suppression of hepatic VLDL-triglyceride and apoB-100 secretion is due to insulin mediated suppression of adipose tissue lipolysis and fatty acid release into the circulation. Plasma free fatty acid availability is a major regulator of VLDL-TG and VLDL-apoB-100 secretion, most likely by providing substrate for hepatic triglyceride formation [3,4,102]. Nonetheless, it has been demonstrated in mice that the secretion of VLDL-triglyceride by the liver is less sensitive to the inhibitory effect of insulin when compared to endogenous (hepatic) glucose production or insulin-mediated suppression of plasma free fatty acid concentration [101]. In fact, plasma insulin concentration at which VLDL-triglyceride secretion is half-maximally suppressed was similar to that at which whole-body glucose uptake was stimulated to half-maximal values and approximately twice as high as the plasma insulin concentration at which both endogenous glucose production and suppression of plasma free fatty acid concentration occurred [101].

Although there are well-established differences between men and women in basal VLDL-triglyceride kinetics [39,103–105] and in the plasma lipid profile both during fasted and fed conditions [39,89,106], few studies have examined potential sex differences in the metabolic control of VLDL kinetics, including potential sex differences in the sensitivity of VLDL-triglyceride metabolism to insulin. The results from these studies are inconclusive. It has been demonstrated that the relative decrease in total plasma triglyceride concentration after an oral glucose load is greater in women than in men at similar post-glucose challenge insulin concentrations (~20–30 mU/l) in men and women [92]. On the other hand, hyperinsulinemia (>50 mU/l) induced via glucose [107] or insulin and concomitant glucose infusion [28,45] suppressed total plasma triglyceride concentrations similarly in men and women. Furthermore, in two separate studies, one conducted in lean women, the other in lean men, it was found that infusion of insulin to achieve plasma insulin concentrations of ~65 mU/l during euglycemia (plasma glucose concentration at ~5.0 mM) reduces hepatic VLDL-triglyceride and VLDL-apoB-100 secretion rates both in lean men [108] and lean women [3] by ~65% (triglyceride) and ~50% (apoB-100); however, direct comparison of the response in men and women is lacking. We have recently found that moderate prolonged hyperinsulinemia (20–40 mU/l) in response to constant intravenous glucose infusion to achieve modest hyperglycemia (plasma glucose concentration ~7 mM) suppresses hepatic VLDL-triglyceride secretion to the same extent (~45%) in lean men, lean women and obese men [95]; obese women, on the other hand, were resistant to the inhibitory effect of hyperglycemia-hyperinsulinemia on VLDL-triglyceride secretion [95]. Similarly, it was reported that obese compared with lean women are resistant to the insulin-mediated suppression of VLDL-apoB-100 secretion [3]; although the insulin-mediated (at plasma insulin concentrations of ~65 mU/l.) suppression of VLDL-triglyceride secretion appeared to be the same as in lean women. Carefully planned studies are necessary to help put these findings into context and firmly establish or rule out differences between the sexes in the control of triglyceride homeostasis by insulin.

## Sex differences in the control of protein metabolism by insulin

Insulin is a potent inhibitor of whole-body and muscle protein breakdown. At the whole-body level, insulin suppresses whole-body protein breakdown (measured as leucine flux) in a dose-dependent manner to approximately 70% of basal values at supraphysiological plasma insulin concentrations. The plasma insulin concentration at which leucine flux was half-maximally suppressed was the same (~35  $\mu$ U/ml) as the insulin concentration at which whole-body glucose disposal is half-maximally stimulated; however, the corresponding insulin effect in

absolute terms corresponded to only ~15% suppression of leucine flux in contrast to a ~2.5 fold increase in glucose disposal [6]. Whole-body protein breakdown is therefore much less responsive to insulin than glucose disposal. On the other hand, muscle protein breakdown is maximally (~50%) suppressed at a plasma insulin concentration of 15–30  $\mu$ U/ml [7,9]. The effects of insulin on muscle protein synthesis are still not entirely clear but they seem to depend a lot on the availability of amino acids for protein synthesis (which themselves stimulate protein synthesis [8,109]) and may be indirect through insulin's effect on blood flow and consequently amino acid delivery [9,10,110,111].

Evidence for potential sex differences in protein metabolism is emerging [112–116] – the interest being stimulated in large part by the obvious differences in lean body and muscle mass between men and women [117–120]. Although to date there is too little data to draw firm conclusions and many investigators do not observe differences in the basal rate of muscle protein turnover between men and women [115,121–123]; interestingly, those that do find differences, report a greater rate of muscle protein synthesis in women than in men [112, 113]. This is against expectations because of the well-established anabolic effects of testosterone [124] which stimulates muscle protein synthesis and muscle hypertrophy [125–127] whereas female sex steroids inhibit muscle protein synthesis and muscle growth in rodents [128,129]. Data on potential differences between men and women in the control of protein metabolism by insulin is scarce. In a study of 30 y old men and women it was observed that the inhibitory effect of insulin on whole-body proteolysis (assessed during a hyperinsulinemic-euglycemic-isoaminoacidemic clamp) was not different between the sexes but women appeared to be resistant to the stimulatory effect of insulin on whole-body protein synthesis resulting in a smaller net anabolic response to hyperinsulinemia in women than in men [114]. This difference at the whole-body level was most likely not attributable to differences in muscle protein metabolism, which accounts for ~20–40% of a healthy person's whole-body protein turnover rate [130,131], because we have recently demonstrated that the stimulatory effect of insulin in the context of moderate hyperaminoacidemia (via intravenous amino acid infusion) on muscle protein synthesis is not different in 25–45 year old men and women [121]. On the other hand, we observed anabolic resistance with regards to the stimulatory effect of feeding which resulted in modest hyperinsulinemia, hyperaminoacidemia, and hyperglycemia in 65–80 year old women compared with age-matched men [113]. Future work in this area should be encouraged and will likely yield novel insights.

## Summary and Conclusion

In summary: i) women appear to be more sensitive to insulin with regards to glucose metabolism (both in the liver and in muscle); ii) there are no differences in insulin action on lipolysis in men and women; iii) the data available on the regulation of triglyceride and protein metabolism by insulin in men and women is too scarce to draw firm conclusions; and iv) there might be differences in the insulin-sensitizing effects of exercise and weight loss in men and women.

## Acknowledgments

During the preparation of this work, the authors have received support from National Institutes of Health (NIH) grants AR 49869, HD 057796, AG 031297, DK 56341 (Clinical Nutrition Research Unit) and grant number UL1 RR024992 from the National Center for Research Resources (NCRR), a component of the NIH and NIH Roadmap for Medical Research and the Longer Life Foundation.

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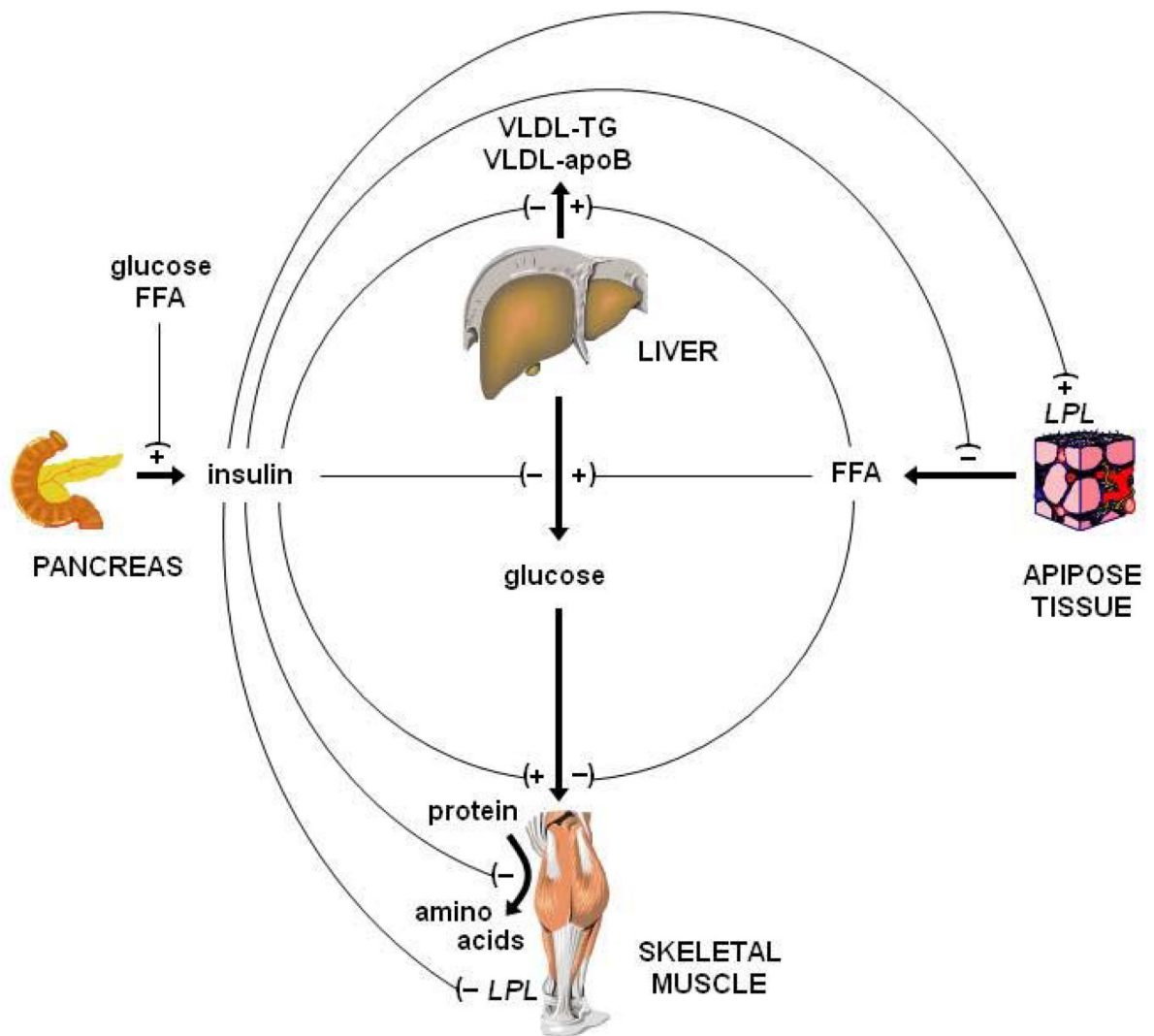
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**Figure 1.**

Summary of the major metabolic actions of insulin. Insulin suppresses hepatic glucose production, stimulates glucose uptake in muscle, suppresses adipose tissue lipolysis and fatty acid release into the blood stream; suppresses hepatic apolipoprotein B-100 and triglyceride secretion, stimulates lipoprotein lipase activity in adipose tissue, and inhibits protein breakdown. Adequate insulin action on adipose tissue lipolysis prevents fatty acid-induced insulin resistance in  $\beta$ -cells, muscle and the liver.