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Energy metabolism of white adipose tissue and insulin resistance in humans

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Abstract

Background. Insulin resistance occurs in obesity, but also in lipodystrophy. Although adipose tissue controls metabolic fluxes and participates in inter-organ crosstalk, the role of energy metabolism within white adipose tissue for insulin resistance is less clear.

Materials and methods. A Medline search identified in vivo studies in humans on energy and lipid metabolism in subcutaneous (SAT) and visceral adipose tissue (VAT). Studies in adipocyte cultures and transgenic animal models were included for the better understanding of the link between abnormal energy metabolism in adipose tissue and insulin resistance.

Results. The current literature indicates that higher lipolysis and lower lipogenesis in VAT compared to SAT enhance portal delivery of lipid metabolites (glycerol, fatty acids) to the liver. Thus, the lower lipolysis and higher lipogenesis in SAT favor storage of excess lipids and allow for protection of insulin-sensitive tissues from lipotoxic effects. In insulin-resistant humans, enhanced lipolysis and impaired lipogenesis in adipose tissue lead to release of cytokines and lipid metabolites, which consecutively promote insulin resistance. Adipose tissue of insulin-resistant humans also displays lower expression of proteins involved in mitochondrial function. In turn, this leads to lower availability of mitochondria-derived energy sources for lipogenesis in adipose tissue.

Conclusions. Abnormal mitochondrial function in human white adipose tissue likely contributes to the secretion of lipid metabolites and lactate, which are linked to insulin resistance in peripheral tissues. However, the relevance of adipose tissue energy metabolism for the regulation of human insulin sensitivity remains to be further elucidated.

Keywords: Adipose tissue, insulin resistance, type 2 diabetes, lipogenesis, lipolysis, mitochondrial function

Introduction

Interestingly, dysfunctional adipose tissue either due to adipose tissue expansion resulting from chronic overnutrition and inadequate physical activity [1] or due to decreased adipose tissue mass in lipodystrophy associates with marked insulin resistance [2]. Both conditions will lead to impaired lipid storage in adipose tissue, thereby giving rise to excessive systemic availability of lipids, which can cause insulin resistance in distant tissues [3].

White adipose tissue is not only responsible for sufficient lipid storage by lipogenesis, but also for fatty acid (FA) availability by lipolysis, thereby also generating substrates for energy metabolism via β-oxidation. Mitochondria in turn provide energy, in the form of adenosine triphosphate (ATP) for a wide range of cellular processes, like cell signaling, differentiation and growth [4].

The aim of this review was to summarize studies in humans, cell cultures and mouse models, both in vivo and in vitro, to investigate the role of mitochondrial function in white adipose tissue for systemic insulin sensitivity. Additionally, this review includes studies analyzing the relevance of lipogenesis and lipolysis in human adipose tissue for insulin resistance. Furthermore, this review examines the link of adipose tissue mitochondrial function with lipogenesis and lipolysis in insulin-sensitive and insulin-resistant humans.

We performed a Medline search for publications in English language from September 2017 until January 2018 with combination of the terms: ‘Adipose tissue AND insulin resistance OR type 2 diabetes AND lipogenesis OR lipolysis OR mitochondrial function’. We identified 24 original papers on humans, 14 publications in cell cultures, 36 publications on animal models and 16 reviews.

In the absence of prospective or outcome studies in humans, we reviewed only studies with cross-sectional cohort design as well as in vitro studies in cultured adipocytes and transgenic animal models with mechanistic approaches for the better understanding of the results

obtained from human studies. We further included only those studies, which reported data on lipogenesis, lipolysis or mitochondrial function in white adipose tissue of insulin-resistant human. We included only studies that assessed insulin sensitivity using gold standard methodology (hyperinsulinemic-euglycemic clamp) or accepted surrogate parameters (homeostasis model assessment or insulin sensitivity index). Finally, a total of 14 original papers on humans, 4 on cell cultures, 16 on animal models and 8 reviews met these criteria. Additionally, we identified publications from the reference lists of the described publications or from the authors' knowledge related to this topic. Of note, we excluded studies focusing on brown adipose tissue (BAT) or analyzing possible effects of BAT induction ("browning" or "beiging") in insulin-resistant humans. Even though the size of BAT can expand after exogenous stimulation such as cold exposure, it represents only a small fraction of human whole adipose tissue and its relevance for energy metabolism in adult humans is under debate [5]. In this review, therefore, the term "adipose tissue" refers only to any compartments of white adipose tissue.

Insulin resistance and compartmentation of white adipose tissue

Assessment of adipose tissue insulin resistance

In vivo, tracer-dilution techniques using stable isotope-labeled glycerol or FA tracers during intravenous insulin infusion represent the current gold standard to quantify insulin sensitivity of human adipose tissue [6]. Employing this method, higher systemic glycerol or free FA appearance reflects impaired insulin-mediated suppression of lipolysis and thereby determines insulin resistance of adipose tissue in vivo. Alternatively, lower reduction of the plasma concentrations of endogenous (unlabeled) free FA during the multi-step hyperinsulinemic-euglycemic clamp test also indicates adipose tissue insulin resistance. The

multi-step euglycemic clamp procedure further allows to assess insulin sensitivity and responsiveness in liver and skeletal muscle. Finally, the adipose tissue insulin resistance index (Adipo-IR), calculated from fasting plasma free FA and insulin levels, represents an accepted surrogate parameter for adipose tissue insulin resistance, but does not measure insulin action directly [7].

In vitro, reduced insulin-stimulated uptake of labeled deoxyglucose defines insulin resistance in cultured adipocytes [8]. It has been suggested that adipose tissue insulin resistance may even appear before the onset of whole-body insulin resistance from impairment of intracellular insulin signalling [9] and insulin-stimulated glucose uptake into adipocytes, [10]. However, most in vivo and in vitro studies did not completely evaluate the dose-response relationships for insulin action and mechanistic studies comparing insulin sensitivity of adipose tissue vs skeletal muscle and liver or their reciprocal interaction in human are still missing.

Adipose tissue compartments

Human adipose tissue consists of visceral (VAT) and subcutaneous adipose tissue (SAT), comprising a deep (DSAT) and superficial (SSAT) compartment. Depending on sex-specific differences, VAT accounts for 6-20%, SAT for 80-90% of whole-body adipose tissue [11] and DSAT accounts for 51% of SAT in females and for 66% in males [12]. Whole-body and hepatic insulin resistance correlates positively with volume of VAT [13], but not of SAT. Compared to women, men have higher VAT, whereas women have increased SAT volume [14], which is thought to have a protective function on insulin sensitivity [15]. Furthermore, White-Americans have higher VAT volume compared to Hispanics and African-Americans. In contrast, South-Asians have more VAT and a higher risk to develop type 2 diabetes than

Caucasians. Finally, abdominal VAT volume increases during aging independently of sex and body fat mass, which is in line with the higher risk for type 2 diabetes in the elderly [16].

Of note, lipolytic activity and insulin sensitivity are different in the different compartments of human adipose tissue. Insulin-resistant obese humans show a greater lipolytic response to catecholamines, but a decreased sensitivity to the antilipolytic effects of insulin in VAT compared to SAT in vivo [16, 17] (figure 1). The higher catecholamine response in VAT with consecutively enhanced portal plasma FA delivery to the liver may promote hepatic and whole-body insulin resistance [18]. On the other hand, reduced lipolytic activity and higher insulin sensitivity indicates a greater capacity of SAT to store excess FA in the form of triacylglycerols and protect other tissues from lipotoxic effects [15]. Accordingly, humans with reduced abdominal SAT, but higher VAT volume exhibit a phenotype similar to that of patients with lipodystrophy, whole-body insulin resistance and fatty liver [19].

Furthermore, abdominal SAT is divided by Scarpa's fascia into two putative metabolically distinct sub-depots, referred to as deep (DSAT) and superficial (SSAT) layers [20, 21]. Higher SSAT volume associates negatively with glycated hemoglobin A1c and positively with high-density lipoprotein cholesterol in patients with type 2 diabetes [22]. SSAT may therefore have a similar protective function as the metabolically inert femoral fat depot [23]. On the other hand, VAT and DSAT share inflammatory characteristics, which include higher macrophage infiltration compared to SSAT and associate with cardiovascular and liver diseases [12, 24]. DSAT, but not SSAT volume, showed a similar positive association with insulin resistance like VAT volume [25]. In contrast to VAT, DSAT associated with hepatic and whole-body insulin resistance only in males [26]. Furthermore, DSAT volume was suggested to be an even better predictor of fasting insulin levels than VAT volume [12]. Higher lipolysis in DSAT compared to SSAT was suggested to explain the association between DSAT and insulin resistance [27]. Although no functional data comparing insulin

action between SSAT and DSAT is available, higher GLUT4 protein expression in SSAT suggests differences in insulin signalling [28]. However, functional data analyzing FA metabolism in these depots to explore the relevance for insulin-resistant human are missing.

Fatty acid turnover of adipose tissue

Lipogenesis

Adipose tissue participates in homeostasis of circulating glucose and FA by regulating local glucose, but specifically lipid metabolism. Circulating FA result from dietary fat intake, but also from endogenous de novo lipogenesis (DNL), regulated mainly by acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) (figure 2). Also dietary intake of carbohydrate rich food, leads to activation of FAS in adipose tissue, which facilitates conversion of glucose to FA [29]. The relative role of adipose tissue DNL is quantitatively lower compared to liver in postprandial state. When glycogen stores are saturated, additional hepatic glucose uptake leads to DNL with consecutive triacylglycerol export to adipose tissue for storage in healthy humans [30]. Interestingly, adipose tissue and hepatic DNL correlate inversely suggesting a reciprocal interaction between both depots [31]. In line, adipose tissue DNL is compensatory increased, when hepatic DNL is reduced at least in mice with hepatocyte-specific deficiency of an escort protein transporting sterol regulatory element-binding protein (SREBP), named SREBP cleavage-activating protein (SCAP), to activate DNL [32].

In cultured human adipocytes, insulin increased FAS expression and activity via glucose 6-phosphate and carbohydrate responsive-element binding protein (ChREBP) [33-36]. GLUT4-mediated increase of intracellular glucose levels stimulates the ChREBPα isoform with consecutive ChREBPβ transcription for subsequent FAS-activated increase of DNL in adipose tissue [35, 36]. ACC seems to be activated independent of insulin by its substrate

citrate [37] to initiate DNL. Conversely, fasting with low circulating insulin levels resulted in lower adipose tissue glucose uptake and DNL [38]. Thus, the presence of insulin and intact insulin signalling is crucial for glucose uptake and subsequent adipocyte DNL. In line, insulin-resistant humans present with lower expression of the lipogenic genes, FAS and ACC [31, 39, 40] (table 1). This associates with reduced insulin stimulated incorporation of labeled glucose in triacylglycerols in both SAT and VAT [41]. There is increasing evidence from rodent models that impaired adipocyte DNL contributes to the pathogenesis of whole-body insulin resistance [42]. In a murine model, reduction of the FA binding protein adipocyte protein 2 (aP2) resulted in increased DNL in adipose tissue, enhanced insulin signalling in adipocytes and improved whole-body insulin sensitivity [43]. A product of DNL, palmitoleate may serve as a systemic signal [43]. Besides palmitoleate, DNL generates other metabolites such as FA esters of hydroxy FA, which also contribute to inter-organ crosstalk between adipose tissue and insulin-sensitive tissues to regulate insulin sensitivity and energy metabolism, as reviewed recently [44].

Previous studies in humans identified positive associations between DNL in VAT as well as SAT and whole-body insulin sensitivity [40, 41, 45-47] (table 1). Insulin-resistant obese humans with elevated fasting glucose and insulin levels present with lower ChREBPβ, FAS and GLUT4 expression in VAT than non-obese humans [31]. In contrast, ChREBPβ and FAS mRNA levels are increased in the liver of insulin-resistant obese compared to non-obese controls [31]. Of note, one study reported higher adipose tissue FAS gene expression in insulin-resistant compared to insulin-sensitive humans [48] (table 1). Nevertheless, these findings are in contrast to several previous reports [31, 39-41, 45, 49] (table 1) and may arise from differences in nutritional behavior [39] or mitochondrial function in adipose tissue.

Lipolysis

Adipose tissue lipolysis occurs by breakdown of triacylglycerols to diacylglycerols (DAG), monoacylglycerols (MAG), and finally glycerol and FA by the sequential action of adipose triacylglycerol lipase (ATGL), hormone-sensitive lipase (HSL) and monoacylglycerol lipase (MGL). Insulin secretion upon carbohydrate rich food intake promotes inhibition of lipolysis in adipose tissue and reduction of circulating plasma glycerol and FA (figure 1). During fasting, low insulin concentrations as well as activation of the β-adrenoreceptor signalling by catecholamines, which are released by stimulation of the sympathetic nervous system due to low blood glucose levels, favor triacylglycerol breakdown with augmented glycerol and FA release from adipose tissue. Activation of the β-adrenoreceptor signalling cascade leads to conversion of ATP to cyclic adenosine monophosphate (cAMP) by adenylate cyclase, which consecutively activates protein kinase A (PKA) with subsequent ATGL and HSL activation for breakdown of triacylglycerol in DAG (figure 1).

Adipose tissue of obese humans is characterized by low-grade inflammation with progressive immune cell infiltration. Infiltrated immune cells are stimulated by FA to release pro-inflammatory cytokines, such as tumor-necrosis factor α (TNFα) and interleukin-1β (IL-1β), which in turn activate lipolysis in adipocytes [50]. Increased lipolysis in adipose tissue raises the systemic availability of lipids, which cause insulin resistance in distant tissues [3]. In insulin-resistant humans, excessive lipolysis in adipose tissue not only stimulates the release of glycerol and FA, but also modifies cytokine secretion. These signals promote ectopic lipid accumulation and low-grade inflammation resulting in insulin resistance in liver and skeletal muscle (figure 3).

Although numerous animal models report improved insulin sensitivity in states of HSL and ATGL deficiency [51, 52], both decreasing lipolysis, recent evidence in humans question the associations between whole-body insulin resistance and increased lipolysis in adipose tissue

[41, 53] (table 1). Human carriers of HSL gene mutations present with dyslipidemia, hepatic steatosis, decreased glucose tolerance, partial lipodystrophy and increased risk for the development of type 2 diabetes [53]. Basal and isoproterenol-stimulated lipolysis decreased together with insulins' antilipolytic effect in SAT. Insulin receptor and insulin receptor substrate 1 protein expression were lower, while macrophage infiltration was higher in SAT. Additionally, ATGL protein expression and genes involved in DNL and triacylglycerol synthesis were reduced in SAT. Furthermore, all homozygous carriers of the HSL mutation displayed type 2 diabetes [53].

Accordingly, human patients with dominant-negative mutations in peroxisome proliferator-activated receptor (PPAR) γ showed lower lipolysis in both fasted and postprandial state in SAT together with muscle and hepatic insulin resistance and loss of protective gluteofemoral fat [54] (table 1). However, insulin-resistant patients with nonalcoholic steatohepatitis (NASH) showed higher lipolysis and insulin resistance in SAT [55] (table 1).

Interestingly, an 8-week treatment with nicotinic acid to inhibit lipolysis in human adipose tissue resulted in upregulation of lipogenic gene expression in SAT of obese men [52]. The authors conclude that decreased lipolysis in adipocytes reshapes energy fluxes into adipose tissue via induction of DNL, which consecutively improves whole-body insulin sensitivity.

Finally, lipolysis-dependent secretion of aP2 from adipocytes activates hepatic glucose production in lean mice and cultured hepatocytes [56]. Inhibition of ATGL and HSL activity could further prevent aP2 secretion from adipocytes [57]. Since neutralization of secreted aP2 prevented from diabetes in obese mice [56], these findings could explain the link between adipose tissue lipolysis and insulin resistance. Nevertheless, human studies for the effect of ATGL and HSL inhibition on whole-body insulin resistance are still missing.

Mitochondrial function of adipose tissue

Mitochondrial morphology and density of adipose tissue

The spherical human white adipocyte contains a single lipid droplet, which creates a small surrounding cytosol with few mitochondria. Human VAT features higher mitochondrial density with twice the amount of mitochondria per milligram of tissue than SAT [58]. Of note, possible differences in mitochondrial density between DSAT and SSAT compartments are unknown.

In insulin-resistant humans and type 2 diabetes patients, SAT has a lower mitochondrial density [59, 60]. The lower gene expression of PPARγ 1 coactivator α (PGC1α), suggests reduced mitochondrial biogenesis in insulin-resistant patients with type 2 diabetes [60]. Although mitochondrial density in SAT correlates positively with whole-body insulin sensitivity [59, 61], age and BMI may influence this association [61]. Nevertheless, the latter study also reported a strong correlation between mitochondrial density and ex vivo lipogenesis in adipose tissue.

Mitochondrial lipid handling

During prolonged fasting, adipose tissue derived FA serve as substrates for mitochondrial β-oxidation to provide or ATP generation and to maintain whole-body energy homeostasis [62]. In turn, ATP is required for insulin signalling in adipocytes [63], and thereby for insulin stimulated antilipolytic effects [59] and lipogenesis [64].

AMP-activated protein kinase (AMPK), activated by the turnover of intracellular ATP to cAMP, consecutively increases ATP-producing pathways [65] such as glycolysis, β-oxidation or glucose uptake, to sustain sufficient energy levels in adipose tissue [66]. On the other hand, inhibition of AMPK leads to activation of ATP-dependent pathways like protein,

cholesterol, glycogen or FA synthesis [66]. In particular, inactivation of PKA via cAMP induction was shown to increase AMPK activity, which consecutively reduced HSL activity in adipocytes [67]. Consistent with these findings, activation of AMPK by adrenoreceptor agonists lowered lipolysis in adipocytes [68]. Interestingly, inhibition or genetic deletion of ATGL, resulting in lower lipolysis, led to reduced catecholamine-induced AMPK activation [69].

These observations suggest that AMPK activation is reciprocally regulated by lipolytic activity and does not decrease lipolysis via downstream signalling from catecholamine-stimulated signalling. Nevertheless, studies elucidating mechanism of AMPK activation during chronic states of increased lipolysis are still missing and interpretation of these findings for whole-body insulin resistance remain difficult.

Mitochondrial function in insulin resistance

Mitochondrial respiration expressed per milligram of tissue is higher in human VAT than in SAT [58]. However, because of greater mitochondrial density in VAT, mitochondrial respiration is lower in VAT after normalization for mitochondrial content [58]. Of note, possible differences in mitochondrial function and density between DSAT and SSAT compartments are unknown.

Proteins relevant for mitochondrial function are lower in SAT of insulin-resistant compared to insulin-sensitive human [70]. Accordingly, abnormal mitochondrial function in adipose tissue leads to systemic insulin resistance in mice [71]. Development of insulin resistance was suggested to result from decreased production of energy sources in mitochondria for highly energy dependent pathways in adipose tissue [72]. Accurate lipogenesis, lipolysis, secretion of adipokines [73], insulin signalling [74], and glucose uptake [75] revealed to be dependent on sufficient energy sources.

Abnormal mitochondrial function in human adipose tissue impairs secretion of autocrine, paracrine and endocrine mediators affecting whole-body insulin sensitivity [76]. Impaired mitochondrial function increases anaerobic energy metabolism in adipose tissue to compensate for decreased pyruvate turnover in mitochondria. Hypertrophic adipocytes, as assessed in insulin-resistant humans, show elevated lactate production in both in vitro and in vivo studies [77, 78]. Accordingly, increased fasting lactate levels in plasma are observed in insulin-resistant obese humans and associate with whole-body insulin resistance [79]. Elevated plasma lactate levels were shown to induce hepatic gluconeogenesis and impair glucose uptake in muscle [80] (figure 3).

Abnormal mitochondrial function in adipose tissue of mice leads to inflammation and enhances whole-body insulin resistance. Inflammation and adipocytes hypertrophy can further lead to hypoxia in adipose tissue. Hypoxia in VAT induces hypoxia-inducible factor 1 α (HIF1α) with subsequent inhibition of sirtuin 2 (SIRT2), which lead to diminished deacetylation PGC1α with consecutive lower β-oxidation [81]. Insulin-resistant obese humans revealed higher HIF1α and lower SIRT2 protein levels as well as lower expression of genes involved in FA oxidation, mitochondrial biogenesis, respiratory chain and ATP synthase in mitochondria of human adipose tissue when compared to lean controls [81] (table 1, figure 3).

In agreement with results in humans, studies in mice analyzing the effects of thiazolidinediones on mitochondrial function suggested that increased mitochondrial oxidative capacity in adipocytes induce whole-body insulin sensitization [82]. Whereas more than the half of analyzed genes coding for mitochondrial function were downregulated in adipose tissue of obese mice previous to the treatment with rosiglitazone, after treatment about half of those genes were upregulated [82, 83]. Increased mitochondrial mass and enhanced oxygen consumption was suggested to increase lipid utilization in adipose tissue of

mice, which consecutively improves whole-body insulin sensitivity [83]. Furthermore, thiazolidinediones were shown to increase transcription of genes for glycerol synthesis with subsequent initiation of FA esterification on glycerol backbone in adipocytes for triacylglycerol synthesis [64, 82, 84], which consecutively improves whole-body insulin sensitivity. Since intact mitochondrial function is required for glycerol synthesis [84], dysfunctional mitochondria may affect production of glycerol and consecutive triacylglycerol synthesis in adipose tissue.

Conclusions

VAT displays higher lipolytic activity and lower insulin sensitivity than SAT. Thus, VAT contributes to the portal delivery of glycerol and FA to the liver for hepatic triacylglycerol storage and interaction with insulin signalling. On the other hand, SAT has a greater capacity for FA storage in the form of triacylglycerol and thereby helps to protect insulin-sensitive tissues from lipotoxic effects. DSAT exhibits higher lipolysis and lower GLUT4 protein expression compared to SSAT. However, functional data analyzing FA metabolism in these depots to explore the relevance for insulin resistance in humans need to be addressed in future studies.

In insulin-resistant humans, excessive lipolysis and impaired lipogenesis in adipose tissue not only stimulated the release of glycerol and FA, but also modify cytokine secretion. These mediators promote ectopic lipid accumulation and low grade inflammation resulting in insulin resistance in liver and skeletal muscle (figure 3). In addition, adipose tissue of insulin-resistant humans exhibits lower expression of proteins involved in mitochondrial function, which may alter adipocyte mitochondrial function and systemic insulin sensitivity due to enhanced release of lipid metabolites and lactate. However, the relevance of energy

metabolism in adipose tissue for the physiological regulation of whole-body insulin sensitivity in humans remains to be elucidated.

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Figure legends

Figure 1. Lipolytic and antilipolytic pathways in visceral and subcutaneous adipose tissue of insulin-resistant obese humans.

The activation of the β-adrenoreceptor signalling cascade via catecholamines leads to conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP) by adenylate cyclase [85]. This consecutively activates protein kinase A (PKA) and subsequently activates adipose triacylglycerol lipase (ATGL) and hormone-sensitive lipase (HSL) for breakdown of triacylglycerol (TAG) in diacylglycerols (DAG) and monoacylglycerols (MAG) [86]. Activation of the insulin receptor (IR) cascade via insulin receptor substrate (IRS) phosphorylation and subsequent phosphatidylinositol 3-kinase (PI3K) and protein kinase B (PKB, Akt) activation [87, 88] leads to glucose transporter 4 (GLUT4) translocation into adipocyte membrane and activation of mammalian target of rapamycin (mTORC1) [89, 90]. The antilipolytic effect of insulin is mediated via various negative feedback signals resulting from IR activation. Akt activated mTORC1 lowers lipolysis via inhibition of β-adrenoreceptor induced ATGL transcription, while PKA inhibits mTORC1 [89]. Of note, mTORC1 activates sterol regulatory element-binding protein (SREBP1c) for the induction of lipogenic pathways. The insulin signalling cascade inhibits lipolysis through activation of adipose-specific phospholipase A2 (AdPLA2), which consecutively inhibits adenylate cyclase [91, 92]. PKA activity is reduced by Akt via decreased cAMP levels resulting from phosphodiesterase activation [93]. Diacylglycerol acyltransferase (DGAT), fatty acids (FA), monoacylglycerol acyltransferase (MGAT). Dotted arrows implicate dependence of respective pathway on depicted substrate. Arrows in boxes implicate upregulation in respective tissues. Downward directed arrows implicate downregulation in insulin-resistant state.

Figure 2. Lipid and energy metabolism in insulin-resistant human white adipocytes.

FA can endogenously be synthesized de-novo from glucose via acetyl coenzyme A (CoA), in the presence of adenosine triphosphate (ATP) by acetyl-CoA carboxylase (ACC) and subsequently via malonyl-CoA in the presence of $NADH+H^+$ by fatty acid synthase (FAS), both key enzymes in lipogenic pathways. Furthermore, triacylglycerol (TAG) breakdown (lipolysis) is induced by activation of the β-adrenoreceptor signalling cascade via catecholamines and supplies FA for ß-oxidation to produce energy sources in mitochondria. Adenosine diphosphate (ADP), carbohydrate-responsive element-binding protein (ChREBP), carnitine palmitoyltransferase 1 (CPT1), diacylglycerols (DAG), glucose transporter 4 (GLUT4), insulin receptor (IR), monoacylglycerols (MAG). Dotted arrows implicate dependence of respective pathway on depicted substrate. Up- or downward directed arrows implicate up- or downregulation in insulin-resistant state.

Figure 3. Systemic consequences of impaired mitochondrial function and insulin resistance in human white adipose tissue.

Abnormal mitochondrial function in human white adipose tissue impairs secretion of autocrine, paracrine and endocrine mediators affecting insulin sensitivity in skeletal muscle and liver. Impaired mitochondrial function increases anaerobic energy metabolism in white adipose tissue to compensate for decreased pyruvate turnover in mitochondria. Increased fasting lactate level in plasma may induce hepatic gluconeogenesis and impair glucose uptake in skeletal muscle. Insulin resistant obese human show inflammation of white adipose tissue, which further leads to enhanced cytokine release with subsequent increased lipolysis in white adipose tissue. Inflammation and adipocytes hypertrophy can further lead to hypoxia in white adipose tissue, leading to activation of hypoxia-inducible factor 1 α (HIF1α) with subsequent inhibition of sirtuin 2 (SIRT2) followed by diminished deacetylation of peroxisome

proliferator-activated receptor γ 1 coactivator α (PGC1α) with consecutive impaired mitochondrial function. Abnormal mitochondrial function, decreased lipogenesis and increased lipolysis in white adipose tissue increase the release of lipid metabolites (glycerol and fatty acids) and cytokines (TNFα, IL-1β), which further promotes ectopic lipid accumulation and decrease glucose uptake in liver and skeletal muscle. Fatty acid (FA), reactive oxygen species (ROS). Dotted arrows implicate suspected effects of depicted substrate. Up- or downward directed arrows implicate increase or decrease in insulin resistant state.

Table 1.

In vivo and in vitro studies exploring the role of energy metabolism in human subcutaneous and visceral adipose tissue for insulin resistance

Cross-sectional design						
Reference	**Cohort**	**Whole-body insulin sensitivity**	**AT depot**	**AT insulin sensitivity**	**Lipogenesis**	**Comment**
Ranganathan, G., et al. J Lipid Res, 2006 [40]	NGT (n=13)		SAT			
	IGT (n=37)	↓ (S_I) [vs NGT]		n.a.	↓ DGAT and FAS mRNA [vs NGT]	
Berndt, J., et al. Diabetologia 2007 [48]	NGT (n=129)		SAT & VAT			↑ FAS mRNA [VAT vs SAT] FAS mRNA and protein correlated positively FAS mRNA and IS correlated negatively
	IGT & T2D (together n=67)	↓ (M-value)		n.a.	↑ FAS mRNA	
Kursawe, R., et al. Diabetes, 2010 [49]	low VAT/[VAT+SAT] (n=20)		SAT			
	high VAT/[VAT+SAT] (n=18)	↓ (M-value)		↑ insulin receptor gene expression	↓ ACC, FAS, PPARγ and SREBP1 mRNA	↑ liver fat content (MRI) Trend of p=0.08 for ↓ insulin stimulated DNL (^{14}C glucose incorporation in TAG)
Mayas, M.D., et al., Nutr Metab, 2010 [45]	CON (n=n.k.)	↓ (HOMA)	VAT			
	high glycemia (n=n.k.)			n.a.	↓ FAS mRNA	FAS mRNA correlated negatively with insulin resistance
Ortega, F.J., et al., Obesity, 2010 [39]	lean CON (n=27)		VAT			↓ FAS, ACC mRNA in SAT [non-OBE vs OBE+OBE-T2D]
	overweight CON (n=24)	↔(HOMA) [vs lean CON]		n.a.	↓ FAS mRNA [vs lean CON]	
	OBE (n=49)	↓ (HOMA) [vs lean CON]		n.a.	↓ FAS, ACC mRNA [vs lean CON]	
	OBE-T2D (n=19)	↓ (HOMA) [vs lean CON]		n.a.	↓ FAS, ACC mRNA [vs lean CON]	
Kursawe, R., et al. Diabetes, 2013 [41]	NGT (n=43*)		SAT			
	IGT (n=5) & T2D (n=5)**	↓ Liver (suppression of HGP during clamp) ↓ muscle (Rd)		↔ (suppression of glycerol during clamp)	↓ insulin stimulated DNL (^{14}C glucose incorporation in TAG) ↓ ChREBP, SREBP1c, FAS, GLUT4 mRNA	↑ ChREBP, SREBP1c mRNA in liver
Eissing, L., et al. Nat Commun, 2013 [31]	CON (n=19)		SAT & VAT			
	OBE (n=21)	↓ (HOMA) [vs CON]		↓ GLUT4 mRNA (only in VAT) [vs CON]	↓ ChREBP-β mRNA (only in VAT) [vs CON]	↑ ChREBP-β mRNA in liver [vs CON]
	OBE-T2D (n=21)	↓ (HOMA) [vs CON]		↓ GLUT4 mRNA & protein [vs CON] (protein only in VAT)	↓ FAS, GLUT4, (ACC only in VAT) mRNA [vs CON] ↓ FAS, GLUT4, ACC protein (all only in VAT) [vs CON]	↑ ChREBP-β, FAS, ELOVL6 mRNA in liver ↓ ChREBP-α in liver [vs CON]

Table 1. cont.

Reference	Cohort	Whole-body insulin sensitivity	AT depot	AT insulin sensitivity	Lipolysis	Comment
Savage, D.B., et al., Diabetes, 2003 [54]	CON (n=76)		SAT			
	PPARγ -/++ (n=3)	↓ Liver (suppression of HGP during clamp) ↓ muscle (Rd)		n.a.	↓ (glycerol release in fasted state) ↓ (glycerol/FA release during MMT#)	↓ limb and buttock SAT (MRI) ↔ abdominal VAT & SAT
Armstrong, M.J., et al., Diabetes Obes Metab, 2014 [55]	CON (n=15)		SAT			
	NASH (n=16)	↓ Liver (suppression of HGP during clamp) ↓ muscle (Rd)		↓ (glycerol/FA suppression during clamp)	↑ (glycerol release during MMT#)	
Albert, J.S., et al., The New England journal of medicine, 2014 [53]	CON (n=7)		SAT			
	HSL -/+ (n=10)	↓ (HOMA/OGTT) [vs CON]		↓ (glycerol/FA suppression after in vitro insulin stimulation)	↔ (Phenylisopropyl adenosine-suppressed (basal) & isoproterenol-stimulated glycerol release in vitro) [vs CON]	↓ HSL protein [vs CON]
	HSL -/- (n=2)	↓ (HOMA) [vs CON]		↓ (glycerol/FA suppression after in vitro insulin stimulation)	↓ (Phenylisopropyl adenosine-suppressed (basal) & isoproterenol-stimulated glycerol release in vitro) [vs CON] ↓ ATGL, HSL, PLIN1 mRNA [vs CON] ↓ ATGL, HSL protein [vs CON; vs HSL-/+]	↓ SREBP1a/c, FAS, DGAT, GPAT, GLUT4 mRNA [vs CON] ↑ liver fat (electron-beam CT) [vs CON; vs HSL-/+]

Reference	Cohort	Whole-body insulin sensitivity	AT depot	AT insulin sensitivity	Mitochondrial function	Comment
Krishnan, J., et al., Genes Dev, 2012 [81]	lean CON (n=9)		VAT			HIF1α & SIRT2 protein expression inversely correlates ↑ adipocyte size [vs lean CON]
	OBE (n=9)	↓ (M-value)		n.a.	↓ SIRT2, CPT1, ↑ HIF1α protein ↓ FATP1, FACS1, Thiolase, AK2, CPT1 mRNA (FA oxidation) ↓ NRF1, ERR1β, TFAM, TFB2M, SSBP1 mRNA (mitochondrial biogenesis) ↓ ATP5J mRNA (ATP synthase) ↓ COX3, CYB5A, MTND1, COX6C, CoVa mRNA (mitochondrial respiratory chain)	
Xie, X., et al., Obesity, 2016 [70]	Insulin-sensitive (n=13)	↓ (M-value)	SAT			
	Insulin-resistant (n=10)			n.a.	↓ proteins of complexes I, III and IV ↓ ANT and other mitochondrial proteins	
Xie, X., et al., Int J Obes, 2017 [59]	NGT (n=13)		SAT			
	IGT (n=7)	↓ (M-value)		↓ (FA suppression during clamp)	↓ mtDNA ↔NADH cytochrome C reductase activity	

Table 1. cont.

* normal glucose tolerant participants (NGT) divided in participants with 2-h glucose levels <120 mg/dl (n=27) and between 120 and 140 mg/dl (n=16), ** impaired glucose tolerant participant (IGT) and type 2 diabetes (T2D) pooled in one group, # using microdialysis in adipose tissue (AT). Acetyl-CoA carboxylase (ACC), adenine nucleotide translocators (ANT), adenylate kinase 2 (AK2), adipose triacylglycerol lipase (ATGL), ATP synthase-coupling factor 6 (ATP5J), body mass index (BMI), carbohydrate-responsive element-binding protein (ChREBP), carnitine palmitoyltransferase 1 (CPT1), computed tomography (CT), cytochrome b5 type A (CYB5A), cytochrome c oxidase polypeptide Va (CoVa), cytochrome c oxidase subunit 6C (COX6C), cytochrome c oxidase subunit III (COX3), de-novo-lipogenesis (DNL), diacylglycerol acyltransferase (DGAT), estrogen-related receptor (ERR) 1β, fatty acid (FA), fatty acid elongase 6 (ELOVL6), fatty acid synthase (FAS), fatty acid transporter 1 (FATP1), fatty acyl-CoA synthetase 1 (FACS1), glucose transporter 4 (GLUT4), glycerol-3-phosphate acyltransferase (GPAT), healthy controls (CON), hepatic glucose production (HGP), heterozygous dominant-negative mutations (-/++), heterozygous negative mutations (-/+), homeostasis model assessment (HOMA), homozygous negative mutations (-/-), hormone-sensitive lipase (HSL), hypoxia-inducible factor (HIF) 1α, insulin sensitivity (IS), insulin sensitivity index (S_I), magnetic resonance imaging (MRI), mitochondrial deoxyribonucleic acid (mtDNA), mitochondrial transcription factors A and B2 (TFAM and TFB2M respectively), mitochondrial NADH dehydrogenase 1 (MTND1), mixed meal test (MMT), nonalcoholic steatohepatitis (NASH), not assessed (n.a.), not known (n.k.), nuclear obese participants (OBE), perilipin 1 (PLIN1), peroxisome proliferator-activated receptor (PPAR) γ, rate of disappearance (Rd), respiratory factor (NRF) 1/2, single-stranded DNA-binding protein 1 (SSBP1), sirtuin 2 (SIRT2), sterol regulatory element-binding protein 1 (SREBP1) a/c, subcutaneous adipose tissue (SAT), triacylglycerol (TAG), visceral adipose tissue (VAT), whole-body insulin sensitivity (M-value). Unless not indicated all parameters were analyzed in fasted state.