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Review

Factors affecting obesity and its treatment

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ABSTRACT

Adipose tissue plays an important role in energy homeostasis by secreting different hormones and peptides which regulate whole body metabolism. Lower or higher level secretion of adipokines leads to obesity and many other diseases. Moreover, inflammation in adipose tissue of obese people leads to insulin resistance, therefore causing obesity. Inflammatory cytokines emerge as a key player in the progression of obesity. In addition to obesity, many other factors are also responsible for insulin resistance. Investigations conducted over the past decade have revealed a great deal about how inflammation in adipose tissue responsible for the development of insulin resistance. Many drugs have a dramatic effect on insulin resistance like Thiazolidinediones (TZDs) which shows anti-inflammatory effect as it activates Peroxisome proliferator-activated receptor gamma (PPARγ). PPARγ have a significant impact on insulin sensitivity. Along with obesity many other factors also involve in insulin resistance like mitochondrial dysfunction, endoplasmic stress, oxidative stress, etc. Insulin resistance is considered to be the main cause of Diabetes-2. Treatment for obesity is limited because of the side effects of conventional drugs. Inflammatory cytokines like TNF-α, IL-6 also have a significant impact on gut microbiota and IL-15 participates in insulin resistance and in their beneficial activities. Enhanced level of inflammatory cytokine due to obesity also responsible for the polycystic ovary syndrome (PCOS), therefore PCOS also associates to the obesity. It was also found that in visceral adipose tissue of the PCOS patient, reduced form of β subunit of insulin receptor was found. Therefore, in this review we will also discuss how insulin and inflammatory cytokines involve in PCOS. There is a growing interest to enhance remodeling of white fats into brown as a strategy to fight obesity and diabetes; it may be beneficial to overcome obesity as well as insulin resistance. Consequently, in this review, we have explored the different pathways which linked to insulin resistance and try to catch a glimpse how a drug acts to control insulin resistance and its mechanism of action.

1. Introduction

Obesity is the outcome of energy imbalance between food intake and energy expenditure. World Health Organization (WHO) reported that about 41 million children under the age of 5 were found overweight in the year 2016 (WHO, 2016). From last few decades, researchers have shown that obesity also linked to other diseases like cardiovascular, insulin resistance, dyslipedimia, hypertension and Type-2 Diabetes (Halpern et al., 2010; De Rosa et al., 2018). Adipose tissue is known to be one of the key players that regulate the obesity; it is composed of adipocytes and stromovascular cells. Adipocytes developed from fusiform cell and belong to mesenchymal origin; its size is the key determinant for the secretion of adipokines (Coelho et al., 2013). In obesity, the size of adipocytes becomes increases (Hypertrophy) that correlates with increased secretion of macrophage inflammatory protein (MCP) which consequently enhance macrophage infiltration and ultimately enhanced the secretion of different inflammatory cytokines like Tumor necrosis factor alpha (TNF-α), IL-6, IL-1, and IL-18 (Jianping, 2013). TNF-α decreases the insulin sensitivity by enhancing IKK-NF-κB signaling and downregulates 5′ AMP-activated protein kinase (AMPK) pathway. TNF-α enhance lipolysis and inhibit lipogenesis by reducing the level of PPARγ expression (Cawthorn and Sethi, 2008). TNF-α decrease PPARγ expression by JNK signaling pathway, however TNF-α also inhibit the uptake of glucose by inhibiting the GLUT-4 transporter (Cawthorn and Sethi, 2008). Along with these cytokines, leptin, adiponectin, resistin also involve in obesity and insulin resistance. Leptin regulates appetite and its receptor present in hypothalamus (Sáinz et al., 2015). Adiponectin to be used as anti obesity adipokines because it is negatively regulated in obesity. Therefore, adiponectin replacement therapy in humans might be probable efficient targets for the treatment of obesity (Achari and Jain, 2017). TNF-α work through the p55 receptor to reduce IRS-1 in the

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insulin signaling pathway (Jianping, 2013). Endoplasmic reticulum stress also responsible for insulin resistance as it activates both JNK and IKK pathways (Hong et al., 2017). Adipose tissue dysfunction leads to the elevation in the free fatty acid level (FFAs) (Heilbronn et al., 2004). FFAs metabolites like ceramide, long chain fatty acyl Co enzyme A and di-acyl glycerol (DAG) also play significant role in insulin resistance by inhibiting PKB (AKT) pathway (Greenfield and Campbell, 2004). Insulin resistance might lead to type 2 diabetes and polycystic ovary syndrome (PCOS). Physical activity and weight loss shows positive impact for the treatment of obesity linked insulin resistance. Some insulin sensitizing drugs like Metformin and thiazolidinediones (TZD) might also useful in the therapy of insulin resistance (Greenfield and Campbell, 2004). Hyperinsulineimia is also is one of the main cause of insulin resistance which increases the ATP level and downregulate the AMPK pathway (Czech, 2017).

2. Adipose tissue

Major function of adipose tissue is to stores fats along with the regulation of metabolism of fatty acid and glucose. Though, adipose tissue not only restricted to store fats, it also acts as an endocrine organ (Zhang et al., 1994). Adipose tissue secretes different kind of adipokines (cytokines) and peptides. Adipose tissue regulates food intake and energy expenditure. It has been shown that lack of adipose tissue leads to the elevation in free fatty acid that successively damage the insulin sensitivity in both animal and human (Khan and Joseph, 2014).

It is well known fact that adipose tissue is the site for both the synthesis and degradation of lipid. In lipoyzes the tri-acyl glycerol (TAG) into free fatty acid and glycerol which gives energy at the time of fasting or prolonged exercise when the body's energy needs exceed. Hormone sensitive lipase breaks the TAG into free fatty acid and glycerol, whereas it is inhibited by insulin and activated by glucagon and epinephrine. However, during the processes of lipogenesis, synthesis of TAG occurs which is utilized as energy reserves (Coelho et al., 2012). The vital processes of lipogenesis are inhibited by polyunsaturated fatty acids and also in fasting too. Catecholamine, natriuretic peptides and insulin are chief regulator of lipolysis and lipogenesis. The β2-adrenergic receptors induce a lipolytic phenomenon, while, α2-adrenergic receptor transmits an anti-lipolytic signal. The atrial Natriuretic peptide (ANP) and the brain Natriuretic peptide (BNP) are also very significant factor responsible for the lipolysis. Natriuretic peptides (NP) binds to NP-A receptor and activates its guanine cyclise activity, therefore cyclic GMP level also becomes elevated which activates protein kinase G (PKG) which consequently activates protein kinase A (PKA). PKA then phosphorylates hormone sensitive lipase (HSL) and induces the translocation of HSL to the lipid droplet (LD). PKA phosphorylate perilipin 1 (PLIN1) and promotes fragmentation of LD. NP-C also expressed in adipose tissue and it works opposite to NP-A. NP-C is mainly responsible for NP internalization and degradation (Morigny et al., 2016). Fig. 1 explains how change in the structure or number of adipose tissue results in differential outcome.

3. Types of adipose tissue

3.1. White adipose tissue (WAT)

WAT generally divides into two main types that are subcutaneous WAT and visceral adipose tissue. The main function of WAT is energy storage and to provide insulation (Choe et al., 2016). Recent studies have shown that WAT can be induced into 'brown-like' heat-producing adipocytes (Hu and Christian, 2017). Cold stimulation, Norepinephrine, gastrointestinal hormone, insulin, glucagon, thyroid hormone and many other factors which regulate the browning of WAT (Hu and Christian, 2017). Fibroblast growth factor 21 (FGF21), a cytokine that have the capacity for WAT browning was also significantly augmented after cold stimulation. Main site of secretion of FGF21 is liver but it can also be secreted by adipose tissue, it has potential to boost the process of thermogenesis in adipose tissue. Norepinephrine is a key player in WAT browning; it is released from the endings of sympathetic nerve system and acts on β-adrenergic receptors at the surface of brown adipocytes. It enhances the expression of uncoupling protein (UCP) that increases mitochondrial oxidation and intracellular lipolysis and also responsible for the TAG stimulation and its uptake. The β3-adrenergic receptor participates in the browning of WAT. In β3-adrenergic knockout mouse, activation of both β1 and β2 are able to activate brown adipose tissue (BAT) formation (Hu and Christian, 2017). Recent studies have suggested that the β3-adrenergic receptor is not required for browning of WAT since cold exposure can also promotes browning of WAT. Therefore, cold exposure is a powerful stimulus for activation of BAT in humans as well as in small rodents. Some other vital factors like insulin also involve in browning of WAT that helps in glucose uptake and its metabolism. Previous studies have shown that insulin regulates browning of WAT. According to Mossenbock et al., insulin does not impair browning capacity of the primary pre-adipocytes. They have isolated primary adipocytes precursor cells from inguinal fat depots of C57BL6 mice and stimulate the browning of adipocytes in the presence of prostacyclin inside culture cells in the presence or absence of insulin. They found that there was very modest impact on differentiation of adipocytes in presence or absence of insulin. Adipocytes derived peptide BMP4 also promotes browning of WAT. BMP-4 belongs to the BMP family which influences the differentiation of mesenchymal stem cells (Marlatt and Ravussin, 2018).

PPARγ1 and PPARγ2 isoforms are the central regulator of adipogenesis that also regulates the expression of different white and brown adipose tissue genes. Under the influence of TZD, PPARγ1 induced a similar level of UCP1expression as PPARγ2. PPARγ1 was less effective than PPARγ2 to induce representative brown gene Elovl3. Mitochondrial respiratory enzymes encoding genes Cox7a1 and Cox8b and some other brown gene Dio2, Cidea and Pgc-1a expression were found reduced in induction with PPARγ2. White adipose tissue gene like Leptin, Wdnm1L and Angiotensinogen (Agt) were considerably upregulated by PPARγ1 (Thomas and Apovain, 2017).

3.2. Brown adipose tissue (BAT)

Conventionally BAT was considered as a thermogenic organ that maintains core body temperature during cold exposure in newborn and animals (van Marken Lichtenbelt et al., 2009). Thermogenic potential of BAT might be targeted to increase energy expenditure and thus might provide an anti-obesity effect. There are several factors that regulate the differentiation of BAT like bone morphogenic protein 7, PRDM16, Mir193b-365, orexin, forkhead Box C2, Plac8, and RIP140, but in human many regulators of brown adipocytes are yet still unknown. Colour of BAT are browns because of high content of mitochondria, it contains many UCP on the inner mitochondrial membrane which major function is to maintain thermogenesis (Tam et al., 2012). Table 1 discuss about the protein molecules secreted by adipose tissue and its function.

3.3. Obesity and insulin resistance

In glucose metabolism, insulin secreted from β-islets of the pancreas play major role. In insulin resistance, insulin signaling pathway is altered. Hyperinsulineimia and Hyperglycaemia responsible for the impaired glucose tolerance, impaired insulin tolerance, decreased glucose infusion rate, increased hepatic glucose production (Jianping, 2013). In obesity, inflammation play key role in insulin resistance along with other factors like hyperinsulineimia, mitochondrial dysfunction, oxidative stress, aging, endoplasmic stress, lipodystrophy and pregnancy. In both feeding and fasting condition, adipocytes break stored fats (TAG) under the influence of glucagon/epinephrine. In obesity, the structure and function of adipocytes become severely altered

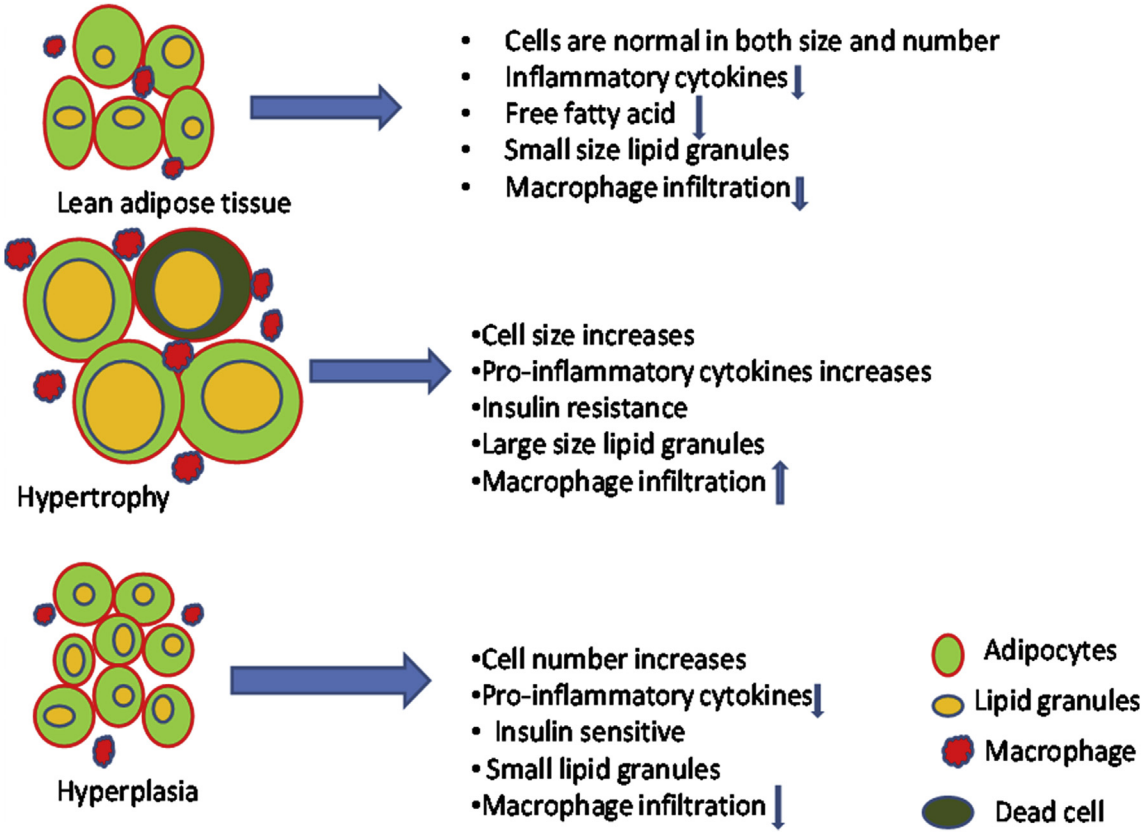

Fig. 1. This figure explains how change in the structure or number of adipose tissue results in differential outcome.

(Guilherme et al., 2008).

It has been suggested that obesity enhances the intestinal permeability which is responsible for the increased level of lipopolysaccharide (LPS) in the body which cause potential inflammation through TOLL like receptor4 (TLR4) or via pattern recognition receptors (PRRs). However, by gut derived LPS due to inflammation occur in visceral adipose tissue which covers the gut mainly in mesenteric adipose tissue. Therefore, the expansion of mesenteric adipose tissue is very effective in preventing the spreading of inflammation to other tissue. Anti-inflammatory drugs that effectively prevents the expansion of mesenteric adipose tissue (Reilly and Saltiel, 2017). Some evidences exhibits that gut microbiota suppress the AMPK activation which leads to down-regulation of mitochondrial fatty acid oxidation, ketogenesis, glucose uptake, and insulin secretion; on the other hand it causes up-regulation of lipogenesis, cholesterol synthesis and triglyceride synthesis. Gut microbiota also produces some signaling molecules like SCFA (short chain fatty acid) which produces by fermentation of dietary fibers. These SCFA binds to GPCR (G protein-coupled receptors) such as GPCR41, GPCR43, and GPCR109A which are expressed in gut endocrine cells that influence the insulin sensitivity in adipocytes and peripheral organs. Upon binding of SCFA, GPCR leads to the activation of peptide YY (PYY) which is responsible for the changes in gut motility and structure ultimately nutrient absorption. Some results showed that GPCR41-deficient mice have more lean body mass and less body fat than their wild-type mice. However, a more recent study shows contrasting results, with GPCR41 knockout mice showing increased amounts of body fat and decreased energy expenditure in comparison with wild-type mice (Boulangé et al., 2016). The use of antibiotics and probiotics for modification of gut microbiota might be a therapeutic target in the gut associated inflammation. According to the P.D. Cani and associates, high-fat feeding changes gut microflora which then increase intestinal LPS permeability which leads to the development of metabolic endotoxemia (Cani et al., 2008). Furthermore, it has been suggested that antibiotic treatment dramatically changed the obese mice gut microbiota; reduced Lactobacillus spp., Bifidobacterium spp., and Bacteroides-Prevotella spp. and lowered the metabolic endotoxin

Table 1
This table discuss about the protein molecules secreted by adipose tissue and its function.

Protein molecules secreted by adipose tissue	Functions
LEPTIN	Leptin primary role is to regulate food intake and energy expenditure.
ADIPONECTIN	Induce glucose uptake and fatty acid oxidation.
RESISTIN	Resistin had major effects on insulin action, potentially linking obesity with insulin resistance.
ANGIOTENSINOGEN	Regulate the blood pressure and electrolyte homeostasis.
VESICLE ECTODERM GROWTH FACTOR (VEGF)	New blood vessel formation.
TNF-α	Major cause for obesity linked Insulin resistance.
IL-6	Regulation of body weight and glucose and lipid metabolism.
Plasminogen activator inhibitor −1 (PAI-1)	Inhibit the clot degradation by inhibiting plasminogen activator.
Acylation promoting enzyme	Promotes synthesis of TAG.
IGF-1	Regulate cell growth and development.
VISFATIN	Induce activation of leucocytes and stimulates production of TNF-α and IL-6.

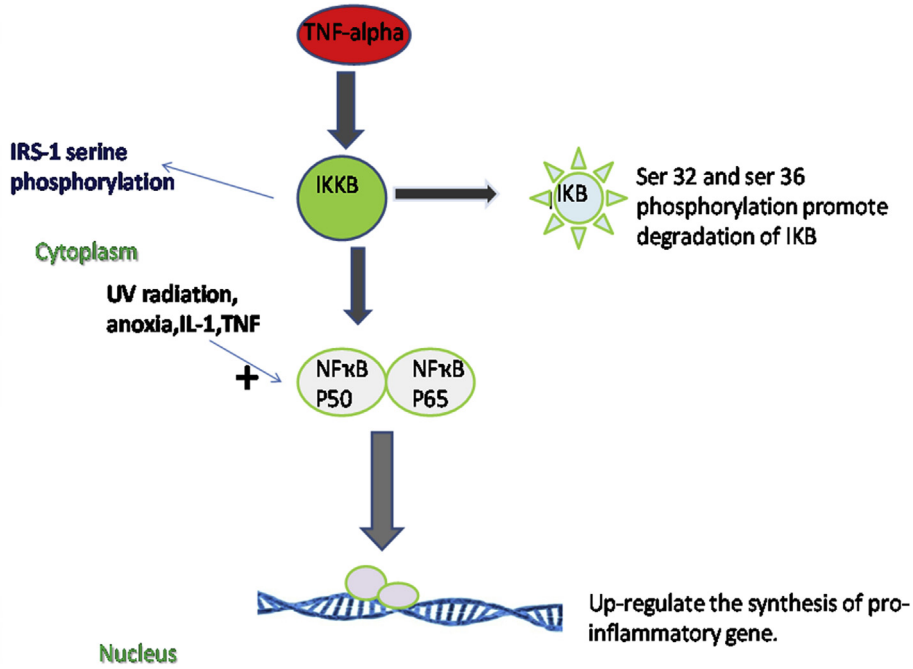

Fig. 2. This figure explains how TNF- alpha activates IKKB which promote IKB degradation and finally activates NF-κB.

and thus ultimately reduces the intestinal LPS levels in mice (Gomes et al., 2014).

The relationship between obesity and insulin has been recognised from decades, insulin maintains the blood sugar level by different signaling pathways. It induces the glucose uptake in skeleton muscle, liver and heart. If there is any defect in this process of glucose uptake, it will exhibits hyperglycemia and hyperinsulineimia. This defect is due to the impairment in tissue response for insulin which is generally called insulin resistance (Kahn and Flier, 2000). Normally insulin reduces the synthesis of glucose in liver, small intestine and kidney, promotes synthesis of fatty acid and glycogen, and also stimulates cell proliferation. In obesity, inflammation inhibited the insulin signaling pathway by targeting the insulin receptor substrate 1 (IRS1) and insulin receptor (Jianping, 2014). In insulin signaling two pathways plays major role, first one is Phosphatidylinositol 3-kinase (PI3K)-AKT pathway and second is Ras-mitogen activated protein kinase (MAPK) pathway. First pathway that is PI3K-AKT pathway involves in regulation of glucose metabolism, on the other hand second pathway MAPK interact with PI3K-AKT pathways to regulates cell growth and differentiation. Recent studies have shown that MAPK pathways also take part in glucose uptake as like PI3K kinase pathway (Harmon et al., 2004). IRS1 is common between these two pathways. Upon insulin receptor activation tyrosine phosphorylation of IRS1 takes place so that signal transduction initiated. Serine kinases like I kappa B kinase beta (Ikkb) and C-Jun N-terminal kinase 1 (Jnk1) phosphorylates IRS1 on serine 307, thus its downstream signaling ability is diminished. In the case of inflammation, IRS1 is negatively regulated by differential suppression of cytokine signaling (de Luca and Olefsky, 2008). TNF also downregulates the IRS1 by phosphorylating its serine. According to previous studies, it has been found that TNF expression was elevated in adipose tissue of rodent mice. A study by Hotamisligil et al., 1993 showed that TNF-α expression in adipose tissue of obese mice was tenfold higher than lean mice. In the same study, they also found that neutralization of TNF-α by using TNFR-IgG (TNF-α receptor immunoglobulin G) chimeric protein affects the sensitivity to insulin in obese-diabetic animals and increase the peripheral uptake of glucose in response to insulin. Under the normal physiological condition muscle cell are main organ that take glucose by GLUT4 in response of insulin, whereas adipose tissue are not actively participates in glucose uptake. It has been reported that in obesity and Type II diabetes, GLUT4 expression in adipocytes becomes decreased. According to Yang et al. (2005), transgenic mice with adipose-specific overexpression of human GLUT4 (adipose-GLUT4-Tg mice) have enhanced glucose tolerance and insulin sensitivity which persists even in the diabetic state induced by pancreatic β-cell destruction. Adipose tissue is main organ which is responsible to accommodate excess fat; due to this it required some biological changes in its structure. Therefore, enlarge adipocytes shows insulin resistance due to accumulation of several toxic products like ceramide, Diacylglycerol (DAG) and insufficient oxygen supply (hypoxia) (Hardy et al., 2012). On the other hand, the link between obesity and insulin resistance has focused on fat distribution. It was reported that insulin sensitivity was reduced in visceral adipose tissue but not in subcutaneous tissue. This might be due to the excess lipid accumulation in liver (Lebovitz and Benerji, 2005). Thus, obesity is potentially linked to the insulin resistance and mostly obsessed people are insulin resistance but not all obese are insulin resistance, therefore, targeting on adipose tissue dysfunction and calories uptake might leads to the potential therapeutic option to prevent obesity linked diseases.

3.4. Hypertrophy and hyperplasia

In obesity, the number of free fatty acid become increases to manage the structure of adipocytes mainly its size and also number by hypertrophy (enlarged adipocytes), hyperplasia (increased numbers of adipocytes). Hypertrophic adipocytes show necrotic like behaviour and promote cell death. However, due to the increased in size these adipocytes secrete larger amount of pro-inflammatory cytokines like MCP-, TNF-α, IL-6 (Sun et al., 2011).

In hyperplasia pre-adipocytes converted into adipocytes under the influence of many transcription factors and cytokines like Peroxisome proliferator-activated receptor γ (PPARγ), and CCAAT/enhancer binding protein families which regulate this adipogenesis process (Choe et al., 2016). Fig-3 explains how TNF-α downregulate the PPARγ, however PPARγ upregulate the TAG synthesis and lipid droplet protein, ultimately increases the insulin sensitivity.

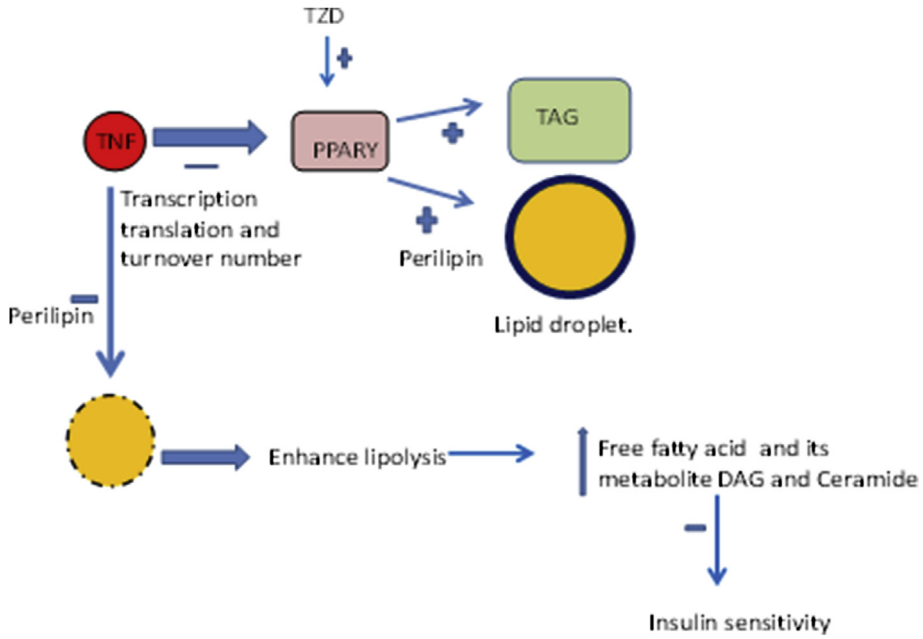

Fig. 3. This figure explains how TNF-alpha downregulate the PPARγ, however PPARγ upregulate the TAG synthesis and Lipid droplet protein, ultimately increases the insulin sensitivity.

3.5. TNF-α

TNF- α is a cytokine secreted by macrophages, it enhances NF-κB activity and inhibit IRS-1 by using IKK and JNK-AP pathway. NF-κB contain Rel homology domain which helps in its localisation in nucleus and generally this site has been used by inhibitor for binding and prevents its nuclear translocation (Karin, 1999). The activity of NF-κB is regulated by IKB-α. NF-κB activated by serine-specific IkB kinase (IKK). IKK is an unusual kinase in that in most cells it contains at least three distinct subunits: IKK alpha, IKK beta and IKK gamma. IKK-α and IKK-β are related catalytic kinase subunits, and IKK-λ (NEMO) is a regulatory subunit that serves as a sensing scaffold and integrator of upstream signals for activation of the catalytic subunits (Yamamoto and Gaynor, 2003). IKK promote IKB degradation by phosphorylating a specific serine residue. TNF-α signaling pathway use JNK c-Jun NH2-terminal kinase to phosphorylate numerous cellular proteins, including IRS-1(phosphorylate S307) IRS-2, Grb2 and Shc (White, 2002). Fig-2 explains how TNF-α activates IKKB which promote IKB degradation and finally activates NF-κB.

3.6. AMPK pathway

Adenosine Monophosphate-Activated Protein kinase (AMPK) signaling Pathway regulates glucose metabolism and weight gain. AMPK made up of a heterotrimeric complex with a subunit α and two regulatory units' β and γ. AMPK have two isoforms which is expressed differently in mammalian tissues. AMPK inhibit the inflammation induced by LPS by using a 5-aminoimidazole-4-carboxamide riboside (AICAR) (Long and Zierath, 2006). Phosphorylation of Thr172 in the catalytic domain activates the AMPK pathway and it enhances GLUT 4 translocation to the cell membrane for the uptake of glucose and also enhances fatty acid oxidation by inhibiting acetyl-CoA carboxylase (ACC) activity (Steinberg et al., 2010). AMPK phosphorylates serine residue in the ACC which results in reduced conversion of acetyl-CoA to malonyl-CoA. Reduced malonyl CoA leads to decreases in lipogenesis and promotes lipolysis. It has been reported that TNF-α suppress AMPK signaling pathway by activating the expression of an inhibitor protein phosphatase 2C, an inhibitor of AMPK activity. AMPK downregulates the synthesis of inflammatory cytokines and inhibiting the phosphorylation of NF-κB p65 and it also upregulate PPARγ expression which is very beneficial in reducing inflammation. PPARγ (Proxisome proliferator-activated receptor γ) and SIRT1 (silent information regulator1) are downstream mediator used by AMPK to inhibit NF-κB signaling (Long and Zierath, 2006). AMPK is a fuel sensing enzyme; it activates the enzymes which produces ATP. Adiponectin indirectly activates AMPK by activating protein phosphatase 2A which dephosphorylate and deactivates the PKC and dephosphorylate the ser301 residue of liver kinase B1 and allow PKB1 translocation from nucleus to cytoplasm and then activates the AMPK. APPL1 is a downstream signaling molecule of adiponectin, which is mainly involved in activation of AMPK (Hinchy et al., 2018).

3.7. Proxisomal proliferator activator receptor γ (PPARγ)

PPARγ related to the family of PPAR, it contains two more isoforms PPARα and PPARβ. PPAR form heterodimer with retinoid X receptor and binds to the DNA response element which in turn regulate the transcription. PPARγ regulates adipogenesis and it also stimulates insulin sensitivity (Kintscher and Law, 2005). It has been reported that TZD increases insulin-stimulated PI3K pathway and translocation of GLUT4 along with glucose uptake (Semple et al., 2017). PPARγ is highly expressed in adipose tissues but its expression is lesser in other tissues such as skeletal muscle and liver, as a result it shows that adipose is the main target for insulin sensitizing drugs. The insulin sensitizing drugs like troglitazone (Rezulin), rosiglitazone (Avandia), and pioglitazone (Actos), stroglitazone (Rezulin) acts on PPARγ. According to Zhang et al., PPARγ are also of two types, PPARγ1 and PPARγ2. They also suggested that mice lacking PPARγ2 survived according to Mendelian inheritance. There was no evidence of gross abnormality in $PPAR\gamma 2^{-/-}$ mice up to age of 24 weeks. $PPAR\gamma 2^{-/-}$ mice may offer a tool to study the role of PPARγ2 in obesity and diabetes. In $PPAR\gamma 2^{-/-}$ mice, there is reduction in white adipose tissue but it has no any effect on brown adipose tissue (Zhang et al., 2004).

TNF-α downregulates PPARγ at different level for example at the transcriptional, translational and also at the level of turnover of protein. PPARγ regulate the gene which encodes degradation and synthesis of fatty acid TAG. TNF-α enhances lipolysis whereas PPARγ inhibit lipolysis. TNF-α attenuates the expression of lipid droplet protein like

perilipin (Guilherme et al., 2008). Free fatty acid concentration becomes increases in obesity which convert into its metabolite like DAG (Diacglycerol) and ceramide which stimulates the protein kinase C activity which in turn phosphorylates the serine of IRS-1 and finally inhibits the insulin cascading (Greenfield and Campbell, 2004). PKC belongs to the serine threonine kinase family; it is subdivided into three subfamily (α, β1and β2) which requires both calcium and diacylglycerol for activation. A Study revealed that activation of PKC by phorbal acetate cause insulin resistance (Schmitz-Peiffer and Biden, 2008). Ceramide also play significant role in insulin resistance by activating Akt. Ceramide promote dephosphorylation of Akt which leads to the activation of Akt. Ceramide activates protein phosphatase 2A which dephosphorylate the act which leads to the activation of Akt (Samuel and Shulman, 2012).

3.8. Adiponectin therapy in obesity linked insulin resistance

Adiponectin hormone secreted by adipose tissue is negatively correlated with obesity. Adiponectin secreted in three forms that is high molecular weight (HMW), Low molecular weight (LMW) and Medium molecular weight (MMW). Adiponectin is very similar to the Complement 1q and its C-terminal have globular domain and N-terminal have collagen domain (Kadowaki et al., 2006). Adiponectin works with AMPK pathway, it enhance insulin sensitivity. TZDs elevate the adiponectin level whereas TNF-α downregulates the adiponectin level (Achari and Jain, 2017). Adiponectin signaling mediate by AdipoR1, AdipoR2 receptor and T cadherin also act as a receptor for hexameric and HMW adiponectin formation. Adiponectin synthesized by the APM1 gene which contains different SNPs which might regulate the adiponectin level. It was found that mutations in adiponectin lead to hypoadiponectinemia and type-2 diabetes. Recombinant adiponectin therapy is beneficial because it increased the insulin sensitivity. Adiponectin secretion and biosynthesis is regulated by different chaperones in endoplasmic reticulum Endoplasmic Reticulum resident protein 44 (ERp44), ER oxidoreductase 1-La (Ero1-La), and disulfide-bond A oxido reductase-like protein (DsbA-L). ERp44 forms disulfide bonds with a cysteine residue in adiponectin and retain it in endoplasmic reticulum whereas the Ero1-La released the retain adiponectin from ERp44 and enhance its secretion. DsbA-L regulates the adiponectin disulfide bond formation; it acts as a protein disulfide isomerase. O-linked glycosylation determined the half life that significantly regulates its clearance from the blood stream (Achari and Jain, 2017).

3.9. Macrophages (M1 and M2)

As like T cell (Th1 and Th2), macrophages also divides into two classes on the basis of secretion of cytokines and different receptors. M1 macrophages which activated by interferon (IFN), TNF or LPS. M2 macrophages further divides into M2a, M2b and M2c. M2 macrophages activated by IL-4, IL-13, IL-1R, and IL-10. M2a is involved in parasite killing, M2b involves in immune regulation and M2c involves in matrix deposition and wound healing. M1 express F4/80, CD11b, CD11c, CD86, CD32 and CCR7 markers while M2 express F4/80, CD11b, CD301, Arg1 and CD206 markers (Thomas and Apovain, 2017). M1 macrophages are the main contributor of inflammation and its level increases in obese adipose tissue whereas in the case of lean adipose tissue M2 level is high. M1 macrophages promote insulin resistance and M2 macrophages promote insulin sensitivity (Martinez and Gordon, 2014).

3.10. IL-15 as an attractive target in obesity

Now days IL-15 emerge as an attractive player to cure obesity. IL-15 secreted from adipose tissue and skeletal muscle and regulates many pathways like lipid deposition and its mobilization, brown adipose tissue (BAT) function, mitochondrial activity along with insulin sensitivity. IL-15 belongs to IL-12 super family (Duan et al., 2017). Under the influence of IL-15, mitochondrial membrane potential was significantly increased compared to control adipocytes. This finding suggests that IL-15 has direct effects on the mitochondria in adipose tissue. Interestingly, IL-15 has major effects on adiponectin secretion as it enhances the secretion of adiponectin from 3T3L1 adipocytes (Duan et al., 2017). However IL-15 also reduces fatty liver by decreasing the TAG storage in liver. In obese subcutaneous adipose tissue, IL-15 level is high in contrast to lean subcutaneous adipose tissue and there was no differences found in the level of IL-15 in the skeleton muscle of lean and obese mice (Pierce et al., 2015).

4. Factors responsible for insulin resistance

4.1. Endoplasmic stress

ER is the site for protein folding and its transport, it has suggested that unfolded protein level when increases in ER which generates stress. This stress created by unfolding protein is called unfolded protein response (UPR). This process is mediated by proteins activating transcription factor 6 (ATF6), PERK (PKR-like endoplasmic – reticulum kinase: PERK). This UPR ultimately causes the insulin resistance (Ron and Walter, 2007).

UPR sensed by integral protein of the ER and transmit signal to the cytoplasm. IRE-1 is of two types, IRE1α expressed in the pancreas and IRE1β, mainly express in the epithelium of the gastrointestinal tract. IRE-1 contains kinase and ribonuclease activity (Back and Kaufman, 2012).

ATF6 is a Bip chaperone (immunoglobulin binding protein) proteins binds to ATF6 in unstressed condition and keep it inactive but in stress condition ATF6 becomes free and responsible for the protease activity in the Golgi body, finally it transported to the nucleus and upregulate the UPR gene. Cyclic AMP-responsive element binding protein3 (CREBH), another protein which has been recently discovered in ER stress which play a very important role in inflammation (Ron and Walter, 2007).

4.2. PERK

PERK is cytosolic kinase which mediates autophosphorylation and dimerization in ER stress. PERK phosphorylate the α subunit of eIF2α at ser 51 residue, as a result of which phosphorylation guanine nucleotide exchange factor activity becomes inhibited that causes low level of new protein synthesis which helps in resolving of ER stress (Back and Kaufman, 2012). ER stress leads to the activation of JNK and IKK which play major role in insulin resistance. CREBH also play role in insulin resistance by causing inflammation (Back and Kaufman, 2012).

4.3. Oxidative stress

Oxidative stress also plays very considerable role in insulin resistance. ROS (Reactive oxygen species) generated in mitochondria during the oxidation of glucose and fatty acid. Equivalent level of ROS is required for normal cell signaling but when its level becomes increases it cause insulin resistance by activating PKC, JNK, and NF-κB (Jianping, 2013). It was also reported that oxidative stress is elevated in obese WAT of mice due to higher expression of NADPH oxidase enzyme (Furukawa et al., 2004). Macrophage infiltration is higher in obese adipose tissue which is responsible for the generation of ROS (Furukawa et al., 2004). This might be responsible for higher expression of NADPH oxidase in obese mice. It is speculated that H_2O_2 exposure may also stimulate insulin resistance as it promoted Ser307 phosphorylation of IRS1 and this led to the enhancement of IRS proteolysis (Furukawa et al., 2004).

4.4. Drugs and their site of action

Currently Metformin and thiazolidinediones are used to treat insulin resistance. Metformin activates AMPK signaling which deactivates the tyrosine phosphatase and enhance insulin signaling. Metformin also inhibit the gluconeogenesis in hepatic cells and enhance glucose uptake via glucose transporter. Metformin increases the activity of tyrosine kinase in the β subunit of the insulin receptor. It is well established fact that Metformin activates AMPK which in turn causes fatty acid oxidation (Greenfield and Campbell, 2004). Metformin also reduces the complication which was created by PCOS. Thiazolidinediones (rosiglitazone and pioglitazone) are agonists of the nuclear Peroxisome proliferator-activated receptor gamma (PPARγ). It enhances insulin sensitivity by reducing the adipocytes cytokines like TNF-α and increases the adiponectin secretion. It enhances adipogenesis, lipogenesis and glucose uptake. Rimonabant drug used for suppressing CB1 (endocannabinoid receptor-1) to reduce adiposity, it also enhances adiponectin synthesis. Sibutramine increases glucose uptake in the muscle cell, it acts through primary amine metabolite M2. Bromocriptine-improves insulin sensitivity and glycaemic control in type 2 diabetes. PPAR-gamma agonists bind to the PPAR gamma receptor and transmit signals (eg. halofenate, metaglidasen and FK614) (Bailey, 2007). Many Thiazolidinediones act as an agonist of both PPARα and PPARγ. Isoferulic acid inhibits phosphoenol pyruvate carboxykinase (PEPCK) which is involved in gluconeogenesis, so isoferulic acid decreases gluconeogenesis (Bailey, 2007). It increases the expression of GLUT-4 and muscle glucose transport. Bromocriptine acts as an agonist for the dopamine D2 receptor and helpful in increasing insulin sensitivity and the α-lipoic acid act as cofactor for dehydrogenases which involve in glycolysis and the Krebs cycle. It is very helpful in insulin sensitivity by enhancing muscle glucose transport and tyrosine phosphorylation of IRS-1 (Bailey, 2007).

4.5. PCOS and insulin resistance

PCOS characterized by hyperandrogenism, ovulation abnormalities and the presence of enlarged and/or polycystic ovaries in ultrasound images. Hyperinsulineimia also involved significantly in PCOS formation as it increases the chances for different diseases like cardiovascular diseases, insulin resistance, and atherosclerosis. Insulin stimulates the secretion of testosterone from theca cell of the ovary which in turn causes hyperandrogenism (Bednarska and Siejka, 2017). It has been reported that the B subunit of insulin receptor becomes decreases which create insulin resistance in visceral adipose tissue in women with the PCOS. Insulin-sensitizing drugs such as Metformin, pioglitazone and inositol isoforms have been widely used as therapeutic options in PCOS, targeting metabolic and reproductive abnormalities. Lifestyle changes including diet and exercise is the effective metabolic strategy for PCOS women with abdominal obesity. Dyslipedimia is the major widespread metabolic aberration in PCOS which is most frequently represented by atherogenic dyslipedimia characteristic of the states of IR. It characterized hypertriglyceridaemia, decreased HDL cholesterol levels, and increased small dense LDL cholesterol (Macut et al., 2017). Hyperinsulineimia regulates different pathway in PCOS, it activates CYP17 which enhance the generation and release of androgens and also promotes arrests of pre-antral follicle development within the ovary. In addition, hyperinsulineimia stimulates adrenal p450c17a activity and suppression of hepatic sex hormone binding globulin production (Macut et al., 2017).

4.6. Leptin resistance

Leptin is encoded by db gene. It plays a role in energy regulation and food intake. Its receptor present in the central nervous system (CNS). Insulin resistance (IR) activates pro-opiomelanocortin (POMC) neurons and enhances the levels of the anorectic peptide α-melanocyte stimulating hormone and inhibits neuropeptide-Y (NPY) neurons rodents (Sáinz et al., 2015). It has been reported that diet induce obesity has been combated by hyperleptinemia. However, type of foods and duration of the diet also mediates its impact on leptin resistance in the body, according to Haring et al., fat and sugars have different effects on leptin response. It has also been shown that high fructose diet for 6 months developed leptin resistance and removal of fructose from diet prevents leptin resistance. Obesity disturbs the leptin synthesis in adipose tissues. Leptin resistance is the state of obesity in which hyperleptinemia or decreased leptin response was found. In obesity, the inflammation causes an increment in the cytokines like CRP, TNF-α and IL-6 which increases the leptin secretion which may be responsible for hyperleptinemia and leptin resistance (Sáinz et al., 2015).

4.7. Catecholamine resistance

Catecholamine resistance also leads to obesity which was observed in women, man and children suffering from obesity. In catecholamine resistance, signaling of β-adrenergic pathway becomes reduced as a result the process of lipolysis thermogenesis and mitochondrial biogenesis also becomes decreases (Shin et al., 2016). Moreover, there is increased in expression of the TGF-β receptor ALK7 found in catecholamine resistance (Guo et al., 2014). An inhibitor of IKK and TBK1, amlexanox restored catecholamine sensitivity. It has been reported that long-time activation of TNF results in catecholamine resistance by reducing lipolysis (Guo et al., 2014).

4.8. Mitochondrial dysfunction

Mitochondrial dysfunction is beneficial in insulin resistance because it increases the β-oxidation, as a result of which number of free fatty acids increases and finally causes insulin resistance (Jianping, 2013). Drugs like (etomoxir or oxfenicine) are used to inhibit the β-oxidation of mitochondria to improve insulin sensitivity. It has been also reported that mice with a hepatic-specific deficiency in mitochondrial fatty acid oxidation ($Cpt2^{L-/-}$ mice) are resistant to the major physiological features elicited by a high fat diet (HFD), including obesity and glucose intolerance (Lee et al., 2017).

4.9. Hypoxia

As the adipose tissue starts expanding for accommodating the increased fats the hypoxia created in adipose tissue due to low oxygen supply, this hypoxia might be an initiator of inflammation. It has been reported hypoxia is connected with upregulation of hypoxia-inducible factor 1α (encoded by *Hif1a*) which have been found in adipose tissue from obese rodents (Jiang et al., 2011).

4.10. Adipose tissue remodeling

Excessive nutrients responsible for remodeling of adipose tissue in shape, size and structure which start changing for accommodating the excess nutrients. So the extracellular matrix and others protein which are responsible for the shape and structure of adipocytes coordinate for remodeling of adipose tissue. Extracellular matrix (ECM) composed of collagens, laminins, fibronectin, and proteoglycans. As we discuss previously, those adipocytes increases their size by hypertrophy during the ECM accumulation and turn over number both becomes increases (Martinez-Santibañez and Lumeng, 2014). Collagen plays significant role in adipose tissue remodeling. Collagen VI is more frequently found in adipose tissue. According to khan et al., gene expression profiling of epididymal fat from ob/ob and db/db mice shows significantly increased levels of col6a3 (collagen VI, alpha 3) during states of metabolic stress with upregulation of 1.3-fold and 1.4-fold respectively. However, treatment with PPARγ agonist reduced levels of all of collagen VI by1.4–1.5 fold in epididymal fat (Khan et al., 2009).

Angiogenesis also involved in adipose tissue remodeling. Vascular endothelial growth factor (VEGF) is a chief angiogenic factor which helps in recovering obesity along with other angiogenic factors like Fibroblast growth factor, Osteonectin, Placental growth factor, angiopoietins, Thrombospondins also involved in angiogenesis (Lijnen, 2008). Recent findings have suggested that the expression pattern of angiogenic components in adipose tissue is might open a new window for the treatment of obesity. A better understanding of the regulation of their expression will be very helpful in the progress of specific approaches linked to obesity.

5. Summary

Insulin stimulates glucose uptake, glycogenesis, fatty acid synthesis along with it play significant role in diabetes. In insulin resistance, the function of β cells of pancreas becomes altered or insulin receptor not responds properly. Therefore, our body starts to adapt this situation by choosing another pathway but this may create much complication as discuss above. If we are discussing about obesity then first things come to our mind is inflammation. Inflammation plays very important role in insulin resistance; as a result use of anti-inflammatory drugs might be a potential therapy in obesity linked insulin resistance. Another factor for insulin resistance is hyperinsulineimia condition, in this case insulin itself responsible for insulin resistance. Insulin increases the production of ATP which decreases the AMPK pathway and ultimately affects insulin sensitivity. Therefore, if ATP production becomes inhibited it might helpful in insulin resistance. Adipose tissue is the main player in obesity linked insulin resistance; if white adipose tissue turns to big adipose tissue then it might beneficial for insulin sensitivity. Oxidative stress also involved in insulin resistance and antioxidants is useful in this particular process. TNF-α plays major role in insulin resistance, so anti-TNF may be helpful to resolve this problem. But it was found that anti TNF treatment is successful in mice and rodents but in human it was not very beneficial. Treatment with engineered humane anti TNF CDP571 had no effect on insulin sensitivity in obese NIDDM subjects (Ofei et al., 1996). Up regulation of lipid droplet proteins like perilipin may be helpful in prevention of lipolysis to minimize the concentration of free fatty acids and its metabolite DAG and ceramide. Various insulin signaling pathways might also be a very promising target for the obesity related diseases. The upstream and downstream regulator of this signaling pathways show better treatment option for obesity. Obesity is a major cause of insulin resistance so weight loss is beneficial in insulin resistance. Further research is needed to identify other factor responsible for obesity and its treatment.

Conflicts of interest

None.

References

Achari, A.E., Jain, S.K., 2017. Adiponectin, a therapeutic target for Obesity,Diabetes, and endothelial dysfunction. Int. J. Mol. Sci. 18 (6), e1321. https://doi.org/10.3390/ijms18061321.

Back, S.H., Kaufman, R.J., 2012. Endoplasmic reticulum stressand type 2 diabetes. Annu. Rev. Biochem. 81, 767–793. https://doi.org/10.1146/annurev-biochem-072909-095555.

Bailey, C.J., 2007. Treating insulin resistance: future prospects. Diabetes Vasc. Dis. Res. 4 (1), 20–31. https://doi.org/10.3132/dvdr.2007.002.

Bednarska, S., Siejka, A., 2017. The pathogenesis and treatment of polycystic ovary syndrome: what's new? Adv. Clin. Exp. Med. 26 (2), 359–367. https://doi.org/10.17219/acem/59380.

Boulangé, C.L., Neves, A.L., Chilloux, J., etal, 2016. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. Genome Med. 8 (1), 42. https://doi.org/10.1186/s13073-016-0303-2.

Cani, P.D., et al., 2008. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet–induced obesity and diabetes in mice. Diabetes 57 (6), 1470–1481. https://doi.org/10.2337/db07-140.

Cawthorn, W.P., Sethi, J.K., 2008. TNF-α and adipocyte biology. FEBS Lett. 582 (1), 117–131. https://doi.org/10.1016/j.febslet.2007.11.051.

Choe, S.S., Huh, J.Y., Hwang, I.J., Kim, J.I., Kim, J.B., 2016. Review adipose tissue remodeling: its role in energy metabolism and metabolic disorders. Front. Endocrinol. (Lausanne) 7, 30. https://doi.org/10.3389/fendo.2016.00030.

Coelho, M., Oliveira, T., Fernandes, R., 2013. Biochemistry of adipose tissue: an endocrine organ. Arch. Med. Sci. 9 (2), 191–200. https://doi.org/10.5114/aoms.2013.33181.

Czech, M.P., 2017. Insulin action and resistance in obesity and type 2 diabetes. Nat. Med. 23, 804–814. https://doi.org/10.1038/nm.4350.

de Luca, C., Olefsky, J.M., 2008. Inflammation and insulin resistance. FEBS Lett. 582 (1), 97–105 9.

De Rosa, S., Arcidiacono, B., Chiefari, E., Brunetti, A., Indolfi, C., Foti, D.P., 2018. Type 2 diabetes mellitus and cardiovascular disease: genetic and epigenetic links. Front. Endocrinol. 9, 2. https://doi.org/10.3389/fendo.2018.000002.

Duan, Y., Li, F., et al., 2017. Interleukin-15 in obesity and metabolic dysfunction: current understanding and future perspectives. Obes. Rev. 18 (10), 1147–1158. https://doi.org/10.1111/obr.12567.

Furukawa, S., Fujita, T., et al., 2004. Increased oxidative stress in obesity and its impact on metabolic syndrome. J. Clin. Investig. 114, 1752–1761. https://doi.org/10.1172/JCI21625.

Gomes, A.C., Bueno, A.A., Graziany, R., de Souza, M., Mota, J.F., 2014. Gut microbiota, probiotics and diabetes. Nutr. J. 13, 60. https://doi.org/10.1186/1475-2891-13-60.

Greenfield, J.R., Campbell, L.V., 2004. Insulin resistance and obesity. Clin. Dermatol. 22 (4), 289–295. https://doi.org/10.1016/j.clindermatol.2004.01.011.

Guilherme, A., Virbasius, J.V., Puri, V., Czech, M.P., 2008. Adipocyte dysfunctions linking obesity to insulin resistance and type 2 diabetes. Nat. Rev. Mol. Cell Biol. 9 (5), 367–377. https://doi.org/10.1038/nrm2391.

Guo, T., et al., 2014. Adipocyte ALK7 links nutrient overload to catecholamine resistance in obesity. Elife 3, e03245. https://doi.org/10.7554/eLife.03245.

Halpern, A., Mancini, M.C., Magalhães, M.E.C., Fisberg, M., Radominski, R., Bertolami, M.C., Bertolami, A., de Melo, M.Ed, Zanella, M.T., Queiroz, M.S., Nery, M., 2010. Metabolic syndrome, dyslipidemia, hypertension and type 2 diabetes in youth: from diagnosis to treatment. Diabetol. Metab. Syndrome 2, 55. https://doi.org/10.1186/1758-5996-2-55.

Hardy, O.T., Czech, M.P., Corvera, S., 2012. What causes the insulin resistance underlying obesity? Curr. Opin. Endocrinol. Diabetes Obes. 19 (2), 81–87. https://doi.org/10.1097/MED.0b013e3283514e13.

Harmon, A.W., Paul, D.S., Patel, Y.M., 2004. MEK inhibitors impair insulin-stimulated glucose uptake in 3T3-L1 adipocytes. Am. J. Physiol. Endocrinol. Metab. 287, E758–E766. https://doi.org/10.1152/ajpendo.00581.2003.

Heilbronn, L.K., Rood, J., Janderova, L., Albu, J.B., Kelley, D.E., Ravussin, E., Smith, S.R., 2004. Relationship between serum resistin concentrations and insulin resistance in nonobese, obese, and obese diabetic subjects. J. Clin. Endocrinol. Metab. 89 (4), 1844–1848. https://doi.org/10.1210/jc.2003-031410.

Hinchy, et al., 2018. Mitochondria-derived ROS activate AMP-activated protein kinase (AMPK) indirectly. J. Biol. Chem. 293 (44), 17208–17217. https://doi.org/10.1074/jbc.RA118.002579.

Hong, J., Kim, K., Kim, J.-H., Park, Y., 2017. The role of endoplasmic reticulum stress in cardiovascular disease and exercise. Int. J. Vasc. Med. 2049217. https://doi.org/10.1155/2017/2049217.

Hotamisligil, G.S., Shargill, N.S., Spiegelman, B.M., 1993. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science 259 (5091), 87–91.

Hu, J., Christian, M., 2017. Hormonal factors in the control of the browning of white adipose tissue. Horm. Mol. Biol. Clin. Investig. 31 (1), 07–21. https://doi.org/10.1515/hmbci-2017-0017.

Jiang, C., et al., 2011. Disruption of hypoxia-inducible factor 1 in adipocytes improves insulin sensitivity and decreases adiposity in high-fat diet-fed mice. Diabetes 60 (10), 2484–2495. https://doi.org/10.2337/db11-0174.

Jianping, Ye, 2013. Mechanisms of insulin resistance in obesity. Front. Med. 7 (1), 14–24. https://doi.org/10.1007/s11684-013-0262-6.

Kadowaki, T., et al., 2006. Adiponectin and adiponectin receptors in insulinresistance, diabetes, and the metabolic syndrome. J. Clin. Investig. 1784–1792. https://doi.org/10.1172/JCI29126.

Kahn, B.B., Flier, J.S., 2000. Obesity and insulin resistance. J. Clin. Investig. 106, 473–481.

Karin, M., 1999. Beginning of the end: IKB kinase (IKK)) and NF-KB activation. J. Biol. Chem. 274, 27339–27342. https://doi.org/10.1074/jbc.274.39.27339.

Khan, et al., 2009. Metabolic dysregulation and adipose tissue fibrosis: role of collagen VI$^{\nabla\,\dagger}$. Mol. Cell. Biol. 29 (6), 1575–1591. https://doi.org/10.1128/MCB.01300-08.

Khan, M., Joseph, F., 2014. Adipose tissue and adipokines: the association with and application of adipokines in obesity. Scientifica (Cairo) 328592. https://doi.org/10.1155/2014/328592.

Kintscher, U., Law, R.E., 2005. PPARγ-mediated insulin sensitization: the importance of fat versus muscle. Am. J. Physiol. Endocrinol. Metab. 288, E287–E291. https://doi.org/10.1152/ajpendo.00440.2004.

Lebovitz, H.E., Banerji, M.A., 2005. Point: visceral adiposity is causally related to insulin resistance. Diabetes Care 28 (9), 2322–2325.

Lee, J., Choi, J., et al., 2017. Loss of hepatic mitochondrial long chain fatty acid oxidation confers resistance to diet-induced obesity and glucose intolerance. Cell Rep. 20 (3), 655–667. https://doi.org/10.1016/j.celrep.2017.06.080.

Lijnen, H.R., 2008. Angiogenesis and obesity. Cardiovasc. Res. 78, 286–293. https://doi.org/10.1093/cvr/cvm007. 2008.

Long, Y.C., Zierath, J.R., 2006. AMP-activated protein kinase signaling in metabolic regulation. J. Clin. Investig. 116 (7), 1776–1783. https://doi.org/10.1172/JCI29044.

Macut, D., et al., 2017. Insulin and polycystic ovary syndrome. Diabetes Res. Clin. Pract. 130, 163–170. https://doi.org/10.1016/j.diabres.2017.06.011.

Marlatt, K.L., Ravussin, E., 2018. Brown adipose tissue: an update on recent findings. Curr. Obes. Rep. 6 (4), 389–396. https://doi.org/10.1007/s13679-017-0283-6.
Martinez, F.O., Gordon, S., 2014. The M1 and M2 paradigm of macrophage activation: time for reassessment. F1000Prime Rep. 6, 13. https://doi.org/10.12703/P6-13.
Martinez-Santibañez, G., Lumeng, C.N., 2014. Macrophages and the regulation of adipose tissue remodeling. Annu. Rev. Nutr. 34, 57–76. https://doi.org/10.1146/annurev-nutr-071812-161113.
Morigny, P., Houssier, M., Mouisel, E., Langin, D., 2016. Adipocyte lipolysis and insulin resistance. Biochimie 125, 259–266. https://doi.org/10.1016/j.biochi.2015.10.024.
Pierce, J.R., Maples, J.M., Hickner, R.C., 2015. IL-15 concentration in skeletal muscle and subcutaneous adipose tissue in lean and obese humans: local effects of IL-15 on adipose tissue lipolysis. Am. J. Physiol. Endocrinol. Metab. 308 (12), E1131–E1139. https://doi.org/10.1152/ajpendo.00575.2014.
Reilly, S.M., Saltiel, A.R., 2017. Adapting to obesity with adipose tissue inflammation. Nat. Rev. Endocrinol. 13 (11), 633–643. https://doi.org/10.1038/nrendo.2017.90.
Ron, D., Walter, P., 2007. Signal integration in the endoplasmic reticulum unfolded protein response. Nat. Rev. Mol. Cell Biol. 8 (7), 519–529. https://doi.org/10.1038/nrm2199.
Sáinz, N., Barrenetxe, J., Moreno-Aliaga, M.J., Martínez, J.A., 2015. Leptin resistance and diet-induced obesity: central and peripheral actions of leptin. Metab. Clin. Exp. 64, 35–46. https://doi.org/10.1016/j.metabol.2014.10.015.
Samuel, V.T., Shulman, G.I., 2012. Integrating mechanisms for insulin resistance: common threads and missing links. Cell 148 (5), 852–871. https://doi.org/10.1016/j.cell.2012.02.017.
Schmitz-Peiffer, C., Biden, T.J., 2008. Protein kinase C function in muscle, liver, and β-cells and its therapeutic implications for type 2 diabetes. Diabetes 57 (7), 1774–1783. https://doi.org/10.2337/db07-1769.
Semple, R.K., Krishna, V., Chatterjee, K., Rahilly, S.O., 2017. PPARγ and human metabolic disease. J. Clin. Investig. 116 (3), 581–589. https://doi.org/10.1172/JCI28003.
Shin, J.H., et al., 2016. AHNAK deficiency promotes browning and lipolysis in mice via increased responsiveness to β-adrenergic signalling. Sci. Rep. 6, 23426. https://doi.org/10.1038/srep23426.
Steinberg, G.R., O'Neill, H.M., Dzamko, N.L., Galic, S., et al., 2010. Whole body deletion of AMP-activated protein kinase β2 reduces muscle AMPK activity and exercise capacity. J. Biol. Chem. 285 (48), 37198–37209. https://doi.org/10.1074/jbc.M110.102434.
Sun, K., Kusminski, C.M., Scherer, P.E., 2011. Adipose tissue remodeling and obesity. J. Clin. Investig. 121 (6), 2094–2101. https://doi.org/10.1172/JCI45887.
Tam, C.S., Lecoultre, V., Ravussin, E., 2012. Brown adipose tissue mechanisms and potential therapeutic targets. Circulation 125 (22), 2782–2791. https://doi.org/10.1161/CIRCULATIONAHA.111.042929.
Thomas, D., Apovain, C.M., 2017. Macrophage function in lean and obese adipose tissue. Metabolism 72, 120–143. https://doi.org/10.1016/j.metabol.2017.04.005.
van Marken Lichtenbelt, W.D., Vanhommerig, J.W., et al., 2009. Cold-activated Brown adipose tissue in healthy men: N. Engl. J. Med. 360 (15), 1500–1508.
White, M.F., 2002. IRS proteins and the common path to diabetes. Am. J. Physiol. Endocrinol. Metab. 283, E413–E422. https://doi.org/10.1152/ajpendo.00514.2001.
World Health Organization, 2016.
Yamamoto, Y., Gaynor, R.B., 2003. IκB kinases key regulators of the NF-κB pathway. Trends Biochem. Sci. 29 (2), 72–79. https://doi.org/10.1016/j.tibs.2003.12.003.
Yang, Q., Graham, T.E., Mody, N., Preitner, F., Peroni, O.D., Zabo-lotny, J.M., Kotani, K., Quadro, L., Kahn, B.B., 2005. Serum retinolbinding protein 4 contributes to insulin resistance in obesity and type 2diabetes. Nature 436, 356–362.
Zhang, J., Fu, M., Cui, T., et al., 2004. Selective disruption of PPARγ2 impairs the development of adipose tissue and insulin sensitivity. Proc. Natl. Acad. Sci. 101 (29), 10703–10708. https://doi.org/10.1073/pnas.0403652101.
Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., Friedman, J.M., 1994. Positional cloning of the mouse obese gene and its human homologue. Nature 372 (6505), 425–432. https://doi.org/10.1038/372425a0.