Adipose Tissue Remodeling and its Effect on Insulin Sensitivity in Obese Individuals: A Critical Review

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ABSTRACT

The objective of this literature review was to investigate adipose tissue remodeling that takes place in obesity and its effect on insulin sensitivity. The majority of relevant articles published and reviewed references. Lists in these articles were searched using Medline, Ovid, and Pro Quest bibliographic database. Adipose tissue (AT) acts as an endocrine organ by expressing and secreting a variety of bioactive adipokines. Defect in the secretory function of most obese AT has been implicated in several metabolic consequences such as insulin resistance (IR). For example, the released pro-inflammatory cytokines and fatty acids have been showed to activate N-terminal kinase, and inhibitor of nuclear factor kappa B kinase enzymes, which once activated, both enzymes can lead to IR either directly or indirectly. Adipose tissue remodeling that takes place in obesity leads to imbalance between pro-inflammatory and anti-inflammatory cytokines, which has been implicated in IR seen in obese individuals.

Keywords: Adipose Tissue, Remodeling, Inflammation, Insulin Resistance.

INTRODUCTION

Obesity is a serious global health issue that has reached an epidemic proportions in both developed and developing countries regardless of age, gender, socioeconomic groups or geographic location. obesity is a chronic lifestyle disease, which leads to serious conditions such as insulin resistance (IR), type 2 diabetes mellitus (T2DM), cardiovascular diseases, and certain types cancers (Berenson, 2012; Hossain et al., 2007; Suleiman et al., 2009).

Overweight and obesity combined are linked to more deaths worldwide than underweight (WHO, 2012). In 2008, the World Health Organization has reported that more than 1.4 billion adults (20 years and older) worldwide were overweight, of them over 200 million men and nearly 300 million women were diagnosed with obesity (WHO, 2012). In Jordan, the prevalence of overweight and obesity ranged between 57 to 73% (Suleiman et al., 2009).

Obesity is a complex multifactorial chronic disease, characterized by imbalance between energy intake and energy expenditure (Bray and Macdiarmid, 2000). Accumulating evidence demonstrated that obesity is associated with a state of chronic low-grade inflammation, which has been implicated in obesity-induced IR (Suganami et al., 2012).

Adipose tissue (AT) plays a major role in energy storage due to its ability to expand through hypertrophy and hyperplasia (Kershaw and Flier, 2004). It also acts as an endocrine organ by expressing and secreting a variety of bioactive adipokines including leptin, adiponectin, resistin, visfatin, tumor necrosis factor...
alpha (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1) and several others (Ahima, 2006; Kershaw and Flier, 2004).

Defect in the secretory function of AT has been implicated in several metabolic consequences such as IR and dyslipidemia. This defect is caused by the imbalance between anti-inflammatory and pro-inflammatory cytokines caused by either excess of AT in individuals with obesity or AT deficiency in individuals with lipodystrophy (Esteve et al., 2009; Herrero et al., 2009; Shoelson et al., 2006). Hence, this critical review aimed to discussing the process of AT remodeling that takes place during the course of transition from lean to obese state, and its effect on insulin sensitivity.

**Implications of the Inflammation Markers: A Historical Background**

The first clues of the role of inflammation in IR dated back to more than a century ago when a number of studies showed the ability of salicylate and aspirin, anti-inflammatory drugs, to lowering glucose excretion and blood glucose (Esteve et al., 2009; Herrero et al., 2009; Shoelson et al., 2006; Shoelson and Shulman, 2001). There was a significant correlation between increased levels of inflammation markers and the rising incidence of T2DM (Duncan et al., 2003; Festa et al., 2002; Spranger et al., 2003). Pradhan and colleagues (2001) found that the levels of IL-6 and C-reactive protein (CRP) were significantly higher among diabetic women than that among non-diabetics. Moreover, Festa and colleagues (2002) demonstrated that participants who developed T2DM had higher baseline levels of plasminogen activator inhibitor-1 (PAI-1), CRP, and fibrinogen as compared to participants who did not develop the disease.

Findings regarding the effect of salicylate on insulin secretion away from its effect on IR and that is because the role of insulin resistance in the pathogenesis of T2DM were inconclusive (Shoelson and Shulman, 2001; Shoelson et al., 2006). As such, mechanistic studies were undertaken in an effort to explain these findings. These studies showed that salicylate and aspirin improve insulin sensitivity through the inhibition of IKKβ/NF-κB pathway, thus implicating inflammation in the pathogenesis of IR (Kim et al., 2001; Kope and Ghosh, 1994; Shoelson et al., 2007).

**Adipose Tissue As An Endocrine Gland**

Adipose tissue has been identified as an endocrine organ due to its secretory role (Kershaw and Flier, 2004). Adipose tissue is the major site of sex steroids metabolism (Siiteri, 1987). It is also the main site for adipsin synthesis and secretion into the circulation, which can be a fat-derived hormone (Flier et al., 1987), moreover AT has the ability to secret leptin, a potent anorexigenic adipocyte-derived peptide hormone (Benoit et al., 2004) as well as TNF-α, a pleiotropic inflammatory cytokine, which is implicated in the pathogenesis of IR (Hotamisligil et al., 1993).

Adipose tissue expresses and releases a variety of bioactive adipokines that have pro-inflammatory or anti-inflammatory activities, including TNF-α, IL-6, MCP-1, adiponectin, visfatin, plasminogen activator inhibitor-1 (PAI-1), and others (Ahima and Flier, 2000; Cefalu, 2009; Scarpeelli and Tack, 2012).

In addition to adipocytes, AT consists of various stromal cells including preadipocytes, endothelial cells, fibroblasts, macrophages, and other immune cells (Ahima, 2006; Itoh et al., 2011; Olefsky and Glass, 2010). Both adipocytes and macrophages in AT are involved in the expression and secretion of these adipokines (Antuna-Puente et al., 2008). In AT, both leptin and adiponectin are produced exclusively in adipocytes; and therefore both were considered true
adipokines (Shoelson et al., 2006), whereas TNF-α, IL-6, and MCP-1 are produced in both adipocytes and macrophages (Cinti et al., 2005; Kolattukudy et al., 2012; Shoelson et al., 2006).

**Adipose Tissue Remodeling**

Adipose tissue of obese individuals undergoes functional and morphological changes; including adipocyte hypertrophy, increased angiogenesis, extracellular matrix overproduction, macrophages and other immune cells infiltration, and Phenotypic switching of adipose tissue macrophages (Suganami et al., 2012). These dynamic functional and morphological changes referred to as adipose tissue remodeling eventually lead to imbalance in the production of anti-inflammatory and pro-inflammatory adipokines (Itoh et al., 2011; Suganami et al., 2012; Sun et al., 2011).

Adipose tissue of obese individuals expresses increased amounts of pro-inflammatory adipokines such as TNF-α, IL-6, iNOS, CRP, PAI-1, and MCP-1 and lower amounts of adiponectin anti-inflammatory adipokines as compared with AT of lean individuals. Since pro-inflammatory adipokines have direct effects on cellular metabolism, the upregulation of pro-inflammatory and downregulation of anti-inflammatory adipokines by adipose tissue is implicated in the metabolic consequences of excess body weight (Weisberg et al., 2003). For instance, while TNF-α directly decreases insulin sensitivity (Hotamisligil et al., 1994), it increases lipolysis in adipocytes through the both activation of mitogen-activated protein kinase kinase (MEKK) and extracellular signal-related kinase (ERK), and the elevation of intracellular cAMP (Zhang et al., 2002). Moreover, IL-6 leads to hypertriglyceridemia by inducing lipolysis and hepatic triglyceride secretion (Weisberg et al., 2003).

The infiltration of macrophages into AT is concomitant with the development of IR and ectopic lipid deposition in obese humans and obese animals suggesting the role of infiltrated macrophages in the metabolic consequences of obesity which is regarded as the most critical event in AT remodeling (Suganami et al., 2012).

Adipose tissue has the ability to expand by hypertrophy and hyperplasia to fulfill its function as energy-storage organ during which AT undergoes undesirable changes that trigger the initiation of macrophages infiltration into AT. These undesirable changes include: hypoxia, death of adipocyte cells, increased hypertrophied adipocyte-derived chemokines, and increased FFA release from AT (Suganami and Ogawa, 2010; Sun et al., 2011).

Although the expansion of adipose tissue depends on the angiogenesis process, excessive AT expansion during the course of obesity development makes the rate of angiogenesis inadequate to support this excessive expansion leading to local hypoxia in the AT. Given that macrophages express and secret factors that increase angiogenesis like MCP-1, hypoxia can play a key role in the recruitment of macrophages into AT. Thus, the inhibition of macrophage infiltration may adversely affect adipose tissue expansion by interfering with angiogenesis (Neels and Olefsky, 2006; Ye, 2009).

**Adipocyte Death**

The frequency of adipocytes death is positively correlated to adipocyte size and therefore is increased in obese individulas (Cinti et al., 2005; Strissel et al., 2007). Adipocyte leaves a lipid droplet behind as it dies, which unless removed will be a source for cholesterol and cytotoxic fatty acids that can damage AT cells. Removing this lipid droplet is necessary to provide a room for the recruitment of preadipocytes and adipocyte precursors, which will differentiate and replace dead...
adipocytes to maintain the lipid-storage capacity of the AT (Cinti et al., 2005).

The vast majority of macrophages found in AT of obese mice and obese humans are localized to dead adipocytes (Cinti et al., 2005; Murano et al., 2008); macrophages aggregate to forming crown-like structures around the dead adipocytes. Macrophages within these crown-like structures fuse to phagocytose the inert lipid droplet forming large lipid-laden multinucleate giant cells, which is considered as a hallmark of chronic inflammation (Sun et al., 2011). Furthermore, it has been showed that one dead adipocyte recruits dozens of macrophages, which means that low frequency of adipocyte death recruits high number of macrophages that express and secrete high amount of pro-inflammatory cytokines and chemokines (Strissel et al., 2007; Cinti et al., 2005).

**Crosstalk between Adipocytes and Infiltrated Macrophages**

Typically, macrophages activation at sites of inflammation is transient and is needed for repairing process to restoring local tissue function. However, a persistent stimulus is developed in obesity which recruits macrophages to AT where they perform a paracrine loop with adipocytes (Suganami et al., 2007). This paracrine loop maintains macrophages in obese AT activated leading to a chronic state of inflammation (Strissel et al., 2007; Cinti et al., 2005).

Newly infiltrated macrophages start to secrete pro-inflammatory cytokines, such as TNF-α with receptors (TNFRs) on the surface of hypertrophied adipocytes inducing them to secrete free fatty acids by lipolysis. As such, free fatty acids bind toll like receptor-4 (TLR-4) on the surface of macrophages inducing macrophages to secrete its pro-inflammatory mediators.

This crosstalk between adipocytes and macrophages, referred to as a paracrine loop, leads to upregulation of pro-inflammatory adipokines and downregulation of anti-inflammatory adipokines (Figure 1). This leads to the development of the metabolic consequences like that are seen in most obese individuals (Wellen and Hotamisligil, 2003; Suganami et al., 2007; Coenen et al., 2007).

![Figure 1: Illustration of the crosstalk between adipocytes and infiltrated macrophages (Itoh et al., 2011).](image-url)
Obese Versus Lean Adipose Tissue Macrophages

There are quantitative and qualitative differences of macrophages in the AT of obese individuals as compared to that in lean AT. Adipose tissue of obese individuals contains higher amounts of macrophages; more than 90% of these macrophages form a crown-like structures around dead adipocytes to phagocytose residual lipid droplet (Altintas et al., 2010). Once phagocytosed, the residual lipid droplet, adipose tissue macrophages become lipid-laden foam cells. Furthermore, within these crown-like structures, macrophages fuse forming multinucleated giant cells (MGCs), which have higher capacity for lipid absorption. The presence of MGCs in AT considered as an indicator for chronic inflammation (Cinti et al., 2005; Strissel et al., 2007).

Qualitatively, one of the most critical events in AT remodeling during the progression from lean to obese state is the phenotypic switch of adipose tissue macrophages. Adipose tissue macrophages are of two types: M1 or classically activated macrophages which upon activation by pro-inflammatory mediators like lipopolysaccharide, produce pro-inflammatory cytokines, like TNF-α and IL-6, and reactive oxygen species like nitric oxide (NO), and M2 or alternatively activated macrophages which is activated by IL-4 and IL-13 to produce a high levels of anti-inflammatory cytokines like IL-10 (Nguyen et al., 2007), moreover M2 increases the capacity for tissue repair and angiogenesis (Galic et al., 2010).

While the macrophages of lean AT are of M2 phenotype, the newly infiltrated macrophages into AT during the course of AT expansion are of M1 phenotype. Thus, at the early stages of AT expansion, M2 may be able to partially prevent the activation and recruitment of M1 macrophages. However, with increasing AT expansion and increasing M1 macrophages recruitment, the pro-inflammatory effect of the M1 macrophages overwhelm the anti-inflammatory effect of M2 macrophages (Lumeng et al., 2007).

Molecular Mechanisms of Adipose Tissue Inflammation

Several stimuli have been showed to activate JNK and IKKβ enzymes through receptor (TLR-4, TNFR, RAGE, and IL-1R) dependent in obese individuals, which binds several ligands including; FA, TNF-α, AGEs, and IL-1β, and receptor independent (ROS, ER stress, and ceramides) mechanisms (Shoelson et al., 2006).

Once activated, both JNK and IKKβ can lead to IR through different mechanisms. JNK and IKKβ phosphorylate the serine residues of IRS leading to the disruption of insulin signaling cascade. In addition, IKKβ phosphorylates IκB, which then is degraded by proteasome, permitting the translocation of the transcription factor NF-κβ to the nucleus where it promotes the expression of several inflammatory-related genes whose products can lead to IR (Olefsky and Glass, 2010).

Adipose Tissue Remodeling and Ectopic Fat Deposition

Adipose tissue stores excessive fatty acids in the form of triglyceride (Kershaw and Flier, 2004; Suganami et al., 2012); free fatty acids released from AT act as ligands for toll like receptor-4 (TLR4) of macrophages inducing them to release their pro-inflammatory cytokines and chemokines, which lead to the recruitment of macrophages to the AT (Sun et al., 2011). Several chemokines are secreted by hypertrophied adipocytes, including MCP-1, osteopontin, angiopoietin-like protein 2 (Angptl2), and CXC motif chemokine ligand-14 (CXCL14). Upregulation of these chemokines in obesity enhances macrophages infiltration into obese AT (Nara et al., 2007).
In advanced stages of obesity, the release of fatty acids from AT increases leading to ectopic fat deposition (Goossens, 2001). This increase in the release of fatty acids from obese AT has been attributed to the high rate of lipolysis, decreased AT expandability, and decreased fat-storing capacity of AT. The reduction in expandability and fat-storing capacity of obese AT is due to the extracellular matrix overproduction, which is considered a critical event in AT remodeling during the course of obesity (Goossens, 2001).

Extracellular matrix of AT is composed of structural proteins, which including multiple types of collagen including I, IV, V, VI, VII, VIII and IX, and adhesion proteins such as fibronectin, laminin, elastins and proteoglycans (Divoux and Clément, 2011). The expression of some extracellular matrix proteins increases in obese individuals. Collagens, specifically collagen VI are highly upregulated in the adipose tissue of obese individuals (Pasari et al., 2009; Spencer et al., 2010). Extracellular matrix overproduction leads to fibrosis. This renders the extracellular environment around the adipocytes rigid, which leads to reduce adipocytes expandability, thus leading to ectopic fat deposition (Medina-Gomez et al., 2007).

Ectopic fat deposition impairs the metabolic function of non-adipose tissues like liver, muscles and pancreas; for instance lipotoxicity in liver and muscles leads to IR, whereas it leads to insufficient insulin secretion in pancreas (Goossens, 2001; Heilbronn and Campbell, 2008).

**Conclusion**

Adipose tissue acts as an endocrine organ by expressing and secreting a variety of bioactive adipokines. During the course of expansion, AT undergoes significant functional and morphological changes remodeling. This leads to hypoxia, fibrosis and adipocyte death, which recruits a high number of macrophages into AT. Newly infiltrated macrophages perform a paracrine loop with the adipocytes leading to a chronic state of inflammation in the AT. This local chronic inflammation of AT leads to systemic inflammation, which has been implicated in several metabolic consequences of obesity such as IR.

**REFERENCES**


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التغيرات في النسيج الدهني وتأثيرها على حساسية الأنسولين في الأشخاص البدينين: مراجعة نقدية

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ملخص

تهدف هذه المراجعة النقدية إلى البحث في التغيرات التي قد تطرأ على النسيج الدهني في مرحلة السمنة وتآثرها على حساسية الأنسولين. يعد النسيج الدهني عدة سماء، وذلك لإفراز مجموعات من الأيديوكاينز النشطة بيولوجيا. وقد تؤدي الاختلازات الأيضية المصاحبة للسمنة كمقاومة الأنسولين عند معظم الأشخاص المصابين بالسمنة إلى خلل في الوظيفة الأنزيلزية للنسيج الدهني، مما يؤدي إلى تормوز الإدراك الفائت، وتشويه الأنسولين، الأمر الذي قد يؤدي إلى مقاومة الأنسولين بشكل مباشر أو غير مباشر. تؤدي التغيرات التي تحدث في النسيج الدهني خلال السمنة إلى عدم التوازن في إفراز البروتينات المضادة للالتهاب والمحفزات للالتهاب، الأمر الذي قد يؤدي إلى ظهور مقاومة الأنسولين عند الأفراد المصابين بالسمنة.

الكلمات الدالة: السمنة، النسيج الدهني، الالتهاب، مقاومة الأنسولين.

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