Published in final edited form as:

Horm Mol Biol Clin Investig. 2013 September ; 15(1): 19–24. doi:10.1515/hmbci-2013-0032.

Adipose tissue inflammation and metabolic dysfunction: a clinical perspective

Charmaine S. Tam,

The Charles Perkins Centre, School of Biological Sciences, Sydney Medical School and The Boden Institute of Obesity, Exercise, Nutrition and Eating Disorders, The University of Sydney, NSW, Australia

Leanne M. Redman*

Pennington, Biomedical Research Center, Louisiana State University System, 6400 Perkins Rd, Baton Rouge, LA 70808, USA

Abstract

Obesity is characterized by a state of chronic low-grade inflammation due to increased immune cells, specifically infiltrated macrophages into adipose tissue, which in turn secrete a range of proinflammatory mediators. This nonselective low-grade inflammation of adipose tissue is systemic in nature and can impair insulin signaling pathways, thus, increasing the risk of developing insulin resistance and type 2 diabetes. The aim of this review is to provide an update on clinical studies examining the role of adipose tissue in the development of obesity-associated complications in humans. We will discuss adipose tissue inflammation during different scenarios of energy imbalance and metabolic dysfunction including obesity and overfeeding, weight loss by calorie restriction or bariatric surgery, and conditions of insulin resistance (diabetes, polycystic ovarian syndrome).

Keywords

adipose tissue; inflammation; obesity

Introduction

Obesity affects 1.7 billion individuals worldwide, with prevalence rates continuing to escalate in children and adults from developed and developing countries. Excess adiposity, particularly when located in the visceral compartment, increases morbidity and mortality through elevated risk of chronic conditions including type 2 diabetes, cardiovascular disease, osteoarthritis, and certain cancers [1]. A common mechanism linking obesity and the progression of associated pathologies such as insulin resistance and type 2 diabetes is chronic low-grade inflammation. Research in this area has flourished over the past 20 years

Copyright of Hormone Molecular Biology & Clinical Investigation is the property of De Gruyter and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.

*Corresponding author: Phone: 225-763-0947, Fax: 225-763-3030, leanne.redman@pbrc.edu.

and has been the focus of many excellent reviews [2, 3]. The vast majority of evidence supporting obesity-associated chronic inflammation has emerged using rodent models, where high-fat diet (60% calories as lard) provokes a nearly complete remodeling of the epididymal depot resulting in rapid and sustained leukocyte infiltration and subsequent secretion of proinflammatory adipokines into the circulation [4]. Interestingly, some discrepancies emerge when translating such findings to the clinical arena, perhaps due to difficulties in obtaining visceral adipose tissue in humans, the metabolically active adipose tissue depot. As such, the focus of work in humans has centered on subcutaneous adipose tissue depots. The use of anti-inflammatory therapies for treating obesity-associated insulin resistance remains an area of active investigation.

The aim of this review is to provide an update on clinical studies examining the role of adipose tissue in the development of obesity-associated complications in humans. We will discuss adipose tissue inflammation during different scenarios of energy imbalance and metabolic dysfunction including obesity and overfeeding, weight loss by calorie restriction or bariatric surgery, and in conditions of insulin resistance (diabetes, polycystic ovarian syndrome).

Obesity-induced chronic low-grade inflammation

Given that adipose tissue mass can account for over half the body weight in morbidly obese individuals, the role of adipose tissue as an inflammatory organ is vitally important. Increased local production of monocyte chemoattractant protein-1 (MCP-1) acts to recruit circulating monocytes/macrophages through interaction with the MCP-1 receptor chemokine receptor 2. Obese adipose tissue, particularly visceral adipose tissue, is characterized by increased accumulation of macrophages and changes in the activation status of these cells, a response which correlates with the degree of obesity. Over 20 adipokines are upregulated in the circulation of obese humans including proinflammatory cytokines (IL1 β , TNF, IL6, IL-8), chemokines (MCP1, CCL5), and acute phase reactants (hsCRP, serum amyloid A, haptoglobin) [5]. We now appreciate that a significant proportion of these adipokines are produced by macrophages in adipose tissue. It is important to recognize that circulating levels of inflammatory factors do not necessarily reflect the severity of inflammation within a specific tissue.

At the local level, obese adipose tissue, specifically visceral adipose tissue, has higher gene expression of a range of inflammation genes [5] and is characterized by macrophages aggregated in crown-like structures, which may act to mop up lipid from dying adipocytes [6–8]. In adipose tissue samples from 46 obese women having gastric surgery, HAM56+ macrophages were twofold higher in visceral (omental) compared to subcutaneous adipose tissue. Moreover, omental macrophage infiltration was associated with increased glucose, insulin, quantitative insulin sensitivity index, triglyceride, and aspartate amino transferase levels and the degree of hepatic fibro-inflammatory lesions [9]. Obese individuals with crown-like structures in their adipose tissue, albeit in subcutaneous adipose tissue, had higher insulin resistance (HOMA-IR) and impaired endothelium-dependent flow-mediated vasodilation as well as upregulated CD68 and TNF α mRNA levels and higher plasma CRP levels [10]. Macrophages in crown-like structures are CD11c+CD206+ and have a M1

proinflammatory phenotype [11]. Rodent studies have implicated a role for other immune cells including neutrophils, B cells, and T regulatory cells [12–14], although this has yet to be completely verified in human studies.

Does weight gain induce changes in inflammation in adipose tissue?

Given the clear evidence that obesity is associated with a state of chronic low-grade inflammation in circulation and locally in adipose tissue, an obvious question is whether positive energy excess directly causes these changes in humans. In order to address this question, well-controlled studies of overfeeding in humans need to be performed. In the first study of its kind, Tam and colleagues examined subcutaneous adipose tissue inflammation in 36 healthy participants before and after 28 days of +1250 kcal/day (45% fat) overfeeding [15]. Overfeeding resulted in an average of 2.7 kg weight gain, decreased in peripheral insulin sensitivity, and raised circulating levels of hsCRP and MCP1, but did not alter the number of adipose tissue macrophages or T-cells. Inflammatory gene expression and circulating immune cell number or expression of their surface activation markers was also unchanged [15]. Similar findings of unchanged numbers of macrophages and inflammatory cells were also seen in another overfeeding study with similar weight gain (+2.5 kg), albeit of longer duration (56 days) [16]. Given the inherent difficulty and impossibility of obtaining visceral adipose tissue samples in studies involving healthy humans, it is unknown how this metabolically active tissue responds to overfeeding in humans. It may be that repeated bouts of energy excess over an extended period of time reaches a critical threshold of adipose tissue accumulation (particularly in the visceral compartment) is required to instigate and propagate an obesity-associated inflammatory response [2]. Supporting this hypothesis, weight cycling in mice enhances the inflammatory response in adipose tissue and in the circulation, which may contribute to metabolic dysfunction [17, 18]; an area which has yet to be addressed in humans.

During pregnancy, fat mass stores expand considerably (up to 10 kg) depending on race, ethnicity, nutritional and environmental factors. In lean women, this fat mass gain accounts for ~30% of total weight gain. A study of gluteal adipose tissue biopsies collected from 11 lean women at preconception, early pregnancy (8–12 weeks), and late pregnancy (36–38 weeks) found a gene expression signature related to inflammation evident early in gestation through to delivery. Indeed, 30% of all genes modified during pregnancy, compared to the pregravid state, were related to immune-related processes including macrophage markers CD68, CD14, HLA-DR, HLA-DQ, and mannose receptor. The recruitment of inflammatory pathways appears to be a feature of healthy human pregnancy and precedes the appearance of maternal phenotypic changes in body composition and changes in insulin action, which peak later during pregnancy [19]. Similar to nonpregnant obese women, pregnant women with pregravid obesity exhibit a chronic low-grade inflammatory response early during pregnancy, which does not appear to have additive or synergistic effects on the inflammation associated with adiposity [20, 21]. Maternal blood and subcutaneous abdominal adipose tissue samples were collected from 24 women with pregravid obesity at the time of labor and delivery. Compared to lean women, women with pregravid obesity had higher systemic CRP and IL6 and threefold higher adipose mRNA levels of macrophage markers, CD68, EMR, and CD14. Gene expression for cytokines IL-6, TNF- α , IL-8, and MCP1 and for LPS-

sensing CD14, TLR4, TRAM2 was 2.5- to 5-fold higher in stromal cells of obese compared to lean. Strikingly, this low-grade inflammatory response was correlated with plasma endotoxin levels, suggesting that subclinical endotoxemia is associated with systemic and adipose tissue inflammation. In this model of pregnancy-induced weight gain, it may be that the recognition and sensing of bacterial-derived pathogens initiate or propagate the inflammatory response within adipose tissue [20].

Weight loss ameliorates adipose tissue inflammation

Regardless of the type (diet and/or physical activity, surgery) or length of intervention, weight loss of at least 5% results in significant improvements in circulating levels of inflammatory mediators in obese, but otherwise healthy, adults. A meta-analysis of weight loss intervention studies (lifestyle or surgery) performed between 1966 and 2006 found that for each kilogram of weight loss, CRP levels declined by 0.13 mg/L [22].

In one of the first studies of its kind, Clement and colleagues analyzed gene expression profiles of subcutaneous adipose tissue biopsies obtained from obese women before and after 28 days of very low-calorie diet (~6% weight loss) [23]. Cluster analysis revealed that 100 inflammation-related transcripts were changed after VLCD diet, consisting of a decrease in proinflammatory factors and an increase in anti-inflammatory molecules, an inflammatory gene signature, which was mostly attributed to the stroma-vascular component of adipose tissue [23]. Subsequent studies examined whether the macronutrient composition of energy-restricted diets (e.g., moderate fat, moderate carbohydrate vs. low-fat, high carbohydrate) have effects on inflammation gene expression and observed that it is weight loss/energy deficit per se rather than macronutrient composition that modifies the gene expression pattern in subcutaneous adipose tissue in humans [24, 25]. Of note, 10% weight loss in overweight (never obese) subjects has been reported to not invoke changes in systemic or subcutaneous inflammation gene expression, which strengthens the hypothesis that a critical threshold of adipose tissue mass needs to be reached before a low-grade inflammatory response occurs [2, 26]. Certainly in studies of obese or morbidly obese where the weight loss achieved is >10%, as is the case with longerterm dietary interventions or bariatric surgery, there are favorable improvements in systemic and adipose tissue inflammation, which often correlates with the degree of weight loss [6]. A 15-week lifestyle intervention resulting in 13%–14% weight loss was associated with significantly lower circulating CRP, IL6, IL8, and MCP1 and higher concentrations of adiponectin. Subcutaneous adipose tissue mRNA levels of IL-6, MCP1, and TNF- α were significantly reduced [27]. Even more dramatic decreases in subcutaneous adipose tissue mRNA levels of macrophage-related genes (MCP1, CSF3) were observed 3 months after gastric bypass resulting in 14% weight loss. Moreover, there were significant decreases in the number of HAM56+ macrophages in subcutaneous adipose tissue ($-11.6 \pm 2.3\%$), and macrophages were no longer clustered in crown-like structures, but were localized near blood vessels. Interestingly, 3 months after weight loss, macrophages stained positive for the anti-inflammatory marker IL-10 suggesting more of a remodeling type (M2) rather than pro-inflammatory type (M1) macrophage [6]. A subsequent study reported that substantial weight loss resulted towards more of an M2, rather than an M1, activation status in adipose tissue macrophages [28].

Impact of metabolic disease on adipose tissue dysfunction

Genetic mouse models (knockout mice, bone marrow transplantation of knockout mouse, and myeloid-specific knockout mice) clearly demonstrate that adipose tissue inflammation, particularly macrophage content is associated with insulin resistance [29]. However, this association has not been universally shown in human studies, and it is unknown whether such a response is independent of the effects of adiposity. A study of nondiabetic Pima Indians found that subcutaneous adipose tissue macrophage content did not correlate with insulin action independent of adiposity, although subjects had a fairly wide range of BMI [30]. Interestingly, whole-body glucose disposal rate was associated with macrophage activation markers, PAI1, and CD11c, independent of the effects of adiposity, suggesting that insulin action may be more related to macrophage activation status, rather than macrophage content [30]. In contrast, a recent study compared the associations between inflammation and insulin resistance in obese young adults with and without crown-like structures in subcutaneous adipose tissue [31]. Independent of total body fat, individuals with crown-like structures had higher visceral adipose tissue, hepatic fat, fasting glucose and insulin levels, and lower disposition index, a measure of β -cell function, compared to individuals without crown-like structures demonstrating a link between macrophage crown-like structures and impaired insulin signaling, independent of the effects of adiposity [31].

To date, the most compelling evidence for an association between adipose tissue inflammation and insulin resistance in humans have come from thiazolidinedione treatment studies in subjects with impaired glucose tolerance and type 2 diabetes [32, 33]. Thiazolidinediones, including rosiglitazones and pioglitazones, are a highly efficacious class of insulin-sensitizing drugs that mainly target adipose tissue by activating PPAR γ and are reported to have anti-inflammatory effects [34]. In subjects with impaired glucose tolerance, 10 weeks of pioglitazone treatment improved insulin sensitivity by 60% and reduced CD68 and MCP1 subcutaneous gene expression by >50%. Furthermore, CD68+ macrophages in adipose tissue were decreased and plasma TNF- α levels reduced [32]. Indeed, reduced adipose tissue macrophage content was associated with improved insulin sensitivity as early as 21 days after pioglitazone treatment in 26 subjects with type 2 diabetes [33]. Improved hepatic and peripheral insulin sensitivity (measured by hyperinsulinemic-euglycemic clamp) was seen after 21 days of pioglitazone, coinciding with a 69% reduction in macrophage content measured by the number of CD14+ cells in the stroma-vascular fraction of adipose tissue by FACs. This was confirmed by significant reductions in CD68 and CD14 gene expression. Interestingly, after 10 days of pioglitazone treatment, there were reductions in the gene expression of IL6, IL1 β , and a trend toward decreased TNF in whole adipose tissue with further reductions in arginase-1 and IL-10, M2 phenotype macrophage markers after 21 days of pioglitazone treatment [33]. Together, these two clinical studies suggest that the insulin-sensitizing effects of thiazolidinediones could be partially achieved through suppression of adipose tissue macrophage content and subsequent reduction of the production of inflammatory factors.

Polycystic ovarian syndrome (PCOS) is a complex endocrine disorder affecting 5%–10% of women of reproductive age. In addition to menstrual irregularity, hyperandrogenemia, and polycystic ovarian morphology, PCOS is highly associated with central adiposity and insulin

resistance. Emerging evidence suggests that PCOS is characterized by systemic and local tissue (ovarian) chronic low-grade inflammation, which may be exacerbated by androgen excess, thus, promoting adipocyte hypertrophy or vice versa [35, 36]. Compared to age and BMI-matched women controls, women with PCOS have significantly higher CRP [37–39], MCP1 [40], and IL-8 [41]. Conflicting evidence exists regarding IL-6 and TNF- α concentrations [37, 39] in women with PCOS. Histological analysis in ovaries from women with PCOS shows greater macrophage and lymphocyte accumulation compared to healthy women, although the PCOS group had a significantly higher BMI compared to the controls (23 vs. 21 kg/m²); unfortunately, the association of macrophage accumulation with BMI or insulin resistance was not evaluated in this study [42]. Further research controlling for the effects of obesity and insulin resistance is required in women in PCOS to clearly evaluate the independent role of low-grade inflammation on potentially regulating androgen excess.

Conclusions

There is little doubt that obesity is associated with a state of chronic low-grade inflammation as demonstrated by overwhelming literature in high fat-fed rodent models and visceral adipose tissue samples collected from obese subjects before and after weight loss interventions. However, it is not yet well-established whether similar persistent changes in adipose tissue and systemic inflammation occurs in less severe models of obesity (overfeeding, pregnancy, PCOS, etc). Further research in the clinical area needs to determine whether transitioning toward obesity is similarly associated with an inflammatory response and how this relates to the development of cardiometabolic disease.

Acknowledgments:

CST is supported by NHMRC Early Career Fellowship (#1037275), and LMR is supported by R00HD060762 and U01HD094418.

References

1. Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. *Physiol Rev* 2013;93:359–404. [PubMed: 23303913]
2. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. *Annu Rev Immunol* 2011;29:415–45. [PubMed: 21219177]
3. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol* 2011;11:98–107. [PubMed: 21233852]
4. Strissel KJ, Stancheva Z, Miyoshi H, Perfield JW, DeFuria J, Jick Z, Greenberg AS, Obin MS. Adipocyte death, adipose tissue remodeling, and obesity complications. *Diabetes* 2007;56:2910–8. [PubMed: 17848624]
5. Fain JN. Release of inflammatory mediators by human adipose tissue is enhanced in obesity and primarily by the nonfat cells: a review. *Mediators Inflamm* 2010;2010:513948. [PubMed: 20508843]
6. Canello R, Henegar C, Viguerie N, Taleb S, Poitou C, Rouault C, Coupaye M, Pelloux V, Hugol D, Bouillot JL, Bouloumie A, Barbatelli G, Cinti S, Svensson PA, Barsh GS, Zucker JD, Basdevant A, Langin D, Clement K. Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. *Diabetes* 2005;54:2277–86. [PubMed: 16046292]

7. Cinti S, Mitchell G, Barbatelli G, Murano I, Ceresi E, Faloia E, Wang S, Fortier M, Greenberg AS, Obin MS. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. *J Lipid Res* 2005;46:2347–55. [PubMed: 16150820]
8. Harman-Boehm I, Bluher M, Redel H, Sion-Vardy N, Ovadia S, Avinoach E, Shai I, Kloting N, Stumvoll M, Bashan N, Rudich A. Macrophage infiltration into omental versus subcutaneous fat across different populations: effect of regional adiposity and the co-morbidities of obesity. *J Clin Endocrinol Metab* 2007;92:2240–7. [PubMed: 17374712]
9. Canello R, Tordjman J, Poitou C, Guilhem G, Bouillot JL, Hugol D, Coussieu C, Basdevant A, Hen AB, Bedossa P, Guerre-Millo M, Clement K. Increased infiltration of macrophages in omental adipose tissue is associated with marked hepatic lesions in morbid human obesity. *Diabetes* 2006;55:1554–61. [PubMed: 16731817]
10. Apovian CM, Bigornia S, Mott M, Meyers MR, Ulloor J, Gagua M, McDonnell M, Hess D, Joseph L, Gokce N. Adipose macrophage infiltration is associated with insulin resistance and vascular endothelial dysfunction in obese subjects. *Arterioscler Thromb Vasc Biol* 2008;28:1654–9. [PubMed: 18566296]
11. Wentworth JM, Naselli G, Brown WA, Doyle L, Phipson B, Smyth GK, Wabitsch M, O'Brien PE, Harrison LC. Pro-inflammatory CD11c+CD206+ adipose tissue macrophages are associated with insulin resistance in human obesity. *Diabetes* 2010;59:1648–56. [PubMed: 20357360]
12. Talukdar S, Oh dY, Bandyopadhyay G, Li D, Xu J, McNelis J, Lu M, Li P, Yan Q, Zhu Y, Ofrecio J, Lin M, Brenner MB, Olefsky JM. Neutrophils mediate insulin resistance in mice fed a high-fat diet through secreted elastase. *Nat Med* 2012;18:1407–12. [PubMed: 22863787]
13. DeFuria J, Belkina AC, Jagannathan-Bogdan M, Snyder-Cappione J, Carr JD, Nersesova YR, Markham D, Strissel KJ, Watkins AA, Zhu M, Allen J, Bouchard J, Toraldo G, Jasuja R, Obin MS, McDonnell ME, Apovian C, Denis GV, Nikolajczyk BS. B cells promote inflammation in obesity and type 2 diabetes through regulation of T-cell function and an inflammatory cytokine profile. *Proc Natl Acad Sci USA* 2013;110:5133–8. [PubMed: 23479618]
14. Elgazar-Carmon V, Rudich A, Hadad N, Levy R. Neutrophils transiently infiltrate intra-abdominal fat early in the course of high-fat feeding. *J Lipid Res* 2008;49:1894–903. [PubMed: 18503031]
15. Tam CS, Viardot A, Clement K, Tordjman J, Tonks K, Greenfield JR, Campbell LV, Samocha-Bonet D, Heilbronn LK. Short-term overfeeding may induce peripheral insulin resistance without altering subcutaneous adipose tissue macrophages in humans. *Diabetes* 2010;59:2164–70. [PubMed: 20547978]
16. Alligier M, Meugnier E, Debard C, Lambert-Porcheron S, Chanseaux E, Sothier M, Loizon E, Ait HA, Brozek J, Scoazec JY, Morio B, Vidal H, Laville M. Subcutaneous adipose tissue remodeling during the initial phase of weight gain induced by overfeeding in humans. *J Clin Endocrinol Metab* 2012;97:E183–92. [PubMed: 22162470]
17. Barbosa-da-Silva S, Fraulob-Aquino JC, Lopes JR, Mandarim-de-Lacerda CA, Aguila MB. Weight cycling enhances adipose tissue inflammatory responses in male mice. *PLoS One* 2012;7:e39837. [PubMed: 22848362]
18. Anderson EK, Gutierrez DA, Kennedy A, Hasty AH. Weight cycling increases T cell accumulation in adipose tissue and impairs systemic glucose tolerance. *Diabetes* 2013, in press.
19. Resi V, Basu S, Haghiac M, Presley L, Minium J, Kaufman B, Bernard S, Catalano P, Hauguel-de MS. Molecular inflammation and adipose tissue matrix remodeling precede physiological adaptations to pregnancy. *Am J Physiol Endocrinol Metab* 2012;303:E832–40. [PubMed: 22811467]
20. Basu S, Haghiac M, Surace P, Challier JC, Guerre-Millo M, Singh K, Waters T, Minium J, Presley L, Catalano PM, Hauguel-de MS. Pregravid obesity associates with increased maternal endotoxemia and metabolic inflammation. *Obesity (Silver Spring)* 2011;19:476–82. [PubMed: 20930711]
21. Friis CM, Paasche Roland MC, Godang K, Ueland T, Tanbo T, Bollerslev J, Henriksen T. Adiposity-related inflammation: effects of pregnancy. *Obesity (Silver Spring)* 2013;21:E124–30. [PubMed: 23505192]
22. Selvin E, Paynter NP, Erlinger TP. The effect of weight loss on C-reactive protein: a systematic review. *Arch Intern Med* 2007;167:31–9. [PubMed: 17210875]

23. Clement K, Viguerie N, Poitou C, Carette C, Pelloux V, Curat CA, Sicard A, Rome S, Benis A, Zucker JD, Vidal H, Laville M, Barsh GS, Basdevant A, Stich V, Cancellato R, Langin D. Weight loss regulates inflammation-related genes in white adipose tissue of obese subjects. *FASEB J* 2004;18:1657–69. [PubMed: 15522911]
24. Dahlman I, Linder K, Arvidsson NE, Andersson I, Liden J, Verdich C, Sorensen TI, Arner P. Changes in adipose tissue gene expression with energy-restricted diets in obese women. *Am J Clin Nutr* 2005;81:1275–85. [PubMed: 15941876]
25. Viguerie N, Vidal H, Arner P, Holst C, Verdich C, Avizou S, Astrup A, Saris WH, Macdonald IA, Klimcakova E, Clement K, Martinez A, Hoffstedt J, Sorensen TI, Langin D. Adipose tissue gene expression in obese subjects during low-fat and high-fat hypocaloric diets. *Diabetologia* 2005;48:123–31. [PubMed: 15624093]
26. Tam CS, Covington JD, Ravussin E, Redman LM. Little evidence of systemic and adipose tissue inflammation in overweight individuals(dagger). *Front Genet* 2012;3:58. [PubMed: 22529850]
27. Bruun JM, Helge JW, Richelsen B, Stallknecht B. Diet and exercise reduce low-grade inflammation and macrophage infiltration in adipose tissue but not in skeletal muscle in severely obese subjects. *Am J Physiol Endocrinol Metab* 2006;290:E961–7. [PubMed: 16352667]
28. Aron-Wisnewsky J, Tordjman J, Poitou C, Darakhshan F, Hugol D, Basdevant A, Aissat A, Guerre-Millo M, Clement K. Human adipose tissue macrophages: M1 and M2 cell surface markers in subcutaneous and omental depots and after weight loss. *J Clin Endocrinol Metab* 2009;94:4619–23. [PubMed: 19837929]
29. Lee BC, Lee J. Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance. *Biochim Biophys Acta* 2013, in press.
30. Ortega Md, V, Xu X, Koska J, Francisco AM, Scalise M, Ferrante AW Jr., Krakoff J. Macrophage content in subcutaneous adipose tissue: associations with adiposity, age, inflammatory markers, and whole-body insulin action in healthy Pima Indians. *Diabetes* 2009;58:385–93. [PubMed: 19008342]
31. Le KA, Mahurkar S, Alderete TL, Hasson RE, Adam TC, Kim JS, Beale E, Xie C, Greenberg AS, Allayee H, Goran MI. Subcutaneous adipose tissue macrophage infiltration is associated with hepatic and visceral fat deposition, hyperinsulinemia, and stimulation of NF-kappaB stress pathway. *Diabetes* 2011;60:2802–9. [PubMed: 22025778]
32. Di Gregorio GB, Yao-Borengasser A, Rasouli N, Varma V, Lu T, Miles LM, Ranganathan G, Peterson CA, McGehee RE, Kern PA. Expression of CD68 and macrophage chemoattractant protein-1 genes in human adipose and muscle tissues: association with cytokine expression, insulin resistance, and reduction by pioglitazone. *Diabetes* 2005;54:2305–13. [PubMed: 16046295]
33. Koppaka S, Kehlenbrink S, Carey M, Li W, Sanchez E, Lee DE, Lee H, Chen J, Carrasco E, Kishore P, Zhang K, Hawkins M. Reduced adipose tissue macrophage content is associated with improved insulin sensitivity in thiazolidinedione-treated diabetic humans. *Diabetes* 2013;62:1843–54. [PubMed: 23349486]
34. Ghanim H, Dhindsa S, Aljada A, Chaudhuri A, Viswanathan P, Dandona P. Low-dose rosiglitazone exerts an antiinflammatory effect with an increase in adiponectin independently of free fatty acid fall and insulin sensitization in obese type 2 diabetics. *J Clin Endocrinol Metab* 2006;91:3553–8. [PubMed: 16804037]
35. Ebejer K, Calleja-Agius J. The role of cytokines in polycystic ovarian syndrome. *Gynecol Endocrinol* 2013;29:536–40. [PubMed: 23368758]
36. Ojeda-Ojeda M, Murri M, Insenser M, Escobar-Morreale HF. Mediators of low-grade chronic inflammation in polycystic ovary syndrome (PCOS). *Curr Pharm Des* 2013, in press.
37. Escobar-Morreale HF, Luque-Ramirez M, Gonzalez F. Circulating inflammatory markers in polycystic ovary syndrome: a systematic review and metaanalysis. *Fertil Steril* 2011;95: 1048–58. [PubMed: 21168133]
38. Kelly CC, Lyall H, Petrie JR, Gould GW, Connell JM, Sattar N. Low grade chronic inflammation in women with polycystic ovarian syndrome. *J Clin Endocrinol Metab* 2001;86:2453–5. [PubMed: 11397838]

39. Amato G, Conte M, Mazziotti G, Lalli E, Vitolo G, Tucker AT, Bellastella A, Carella C, Izzo A. Serum and follicular fluid cytokines in polycystic ovary syndrome during stimulated cycles. *Obstet Gynecol* 2003;101:1177–82. [PubMed: 12798522]
40. Hu W, Qiao J, Yang Y, Wang L, Li R. Elevated C-reactive protein and monocyte chemoattractant protein-1 in patients with polycystic ovary syndrome. *Eur J Obstet Gynecol Reprod Biol* 2011;157:53–6. [PubMed: 21530057]
41. Yang Y, Qiao J, Li R, Li MZ. Is interleukin-18 associated with polycystic ovary syndrome? *Reprod Biol Endocrinol* 2011;9:7. [PubMed: 21244650]
42. Xiong YL, Liang XY, Yang X, Li Y, Wei LN. Low-grade chronic inflammation in the peripheral blood and ovaries of women with polycystic ovarian syndrome. *Eur J Obstet Gynecol Reprod Biol* 2011;159:148–50. [PubMed: 21908093]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript