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**RESEARCH ARTICLE**

**RELATIONSHIP BETWEEN OBESITY AND IMMUNE SYSTEM  
 A REVIEW ARTICLE**

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**Abstract**

It now appears that, in most obese patients, obesity is associated with a low-grade inflammation of white adipose tissue (WAT) resulting from chronic activation of the innate immune system. Excess fat is thought to stimulate white blood cells (WBC) that produce inflammatory molecules as a part of the normal immune response upon injury or infection. Obese adipose tissue mainly releases pro-inflammatory cytokines among which are TNF- $\alpha$ , IL-6, leptin, visfatin, resistin, angiotensin II, and plasminogen activator inhibitor 1. Regarding the complement system, in spite of the strong associations of C3 with obesity and metabolic syndrome, the underlying mechanisms remain unexplained. AT biology can be influenced by a variety of complement components. As the common factor linking adipose tissue to the metabolic context of obesity, insulin resistance and atherosclerosis are associated with a low-grade chronic inflammatory status, to which the complement system is an important contributor.

**Conclusion:-** There are inflammatory and immune system responses in overweight and obese individuals offer unique opportunities for intervention strategies to help ameliorate the risk of obesity-associated disease such as hypertension and Diabetes Mellitus.

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**Background:-**

Obesity is actually an epidemic problem in the world; it has become truly a global problem affecting countries rich and poor. An estimated 500 million adults worldwide are obese and 1.5 billion are overweight or obese [1].

Much of the information about obesity among adults rest in the use of body mass index (BMI) to define obesity, which will be defined as a BMI 30 kg/m<sup>2</sup> or greater unless otherwise stated [2].

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Obesity is a consequence of many risk factors, as increased energy consumption and reduced physical exercise. Many studies also implicate chronic low grade inflammation in the interplay between obesity and metabolic complications [3].

### **Obesity and inflammation:-**

The discovery that obesity itself results in an inflammatory state in metabolic tissues ushered in a research field that examines the inflammatory mechanisms in obesity [4].

In recent years, it has been demonstrated that obesity is associated with chronic systemic inflammation, this status is conditioned by the innate immune system activation in adipose tissue that promotes an increase in the production and release of pro-inflammatory cytokines that contribute to the triggering of the systemic acute-phase response [5].

The origin of inflammation during obesity and the underlying molecular mechanisms that explain its occurrence are not still fully understood, but pro-inflammatory cytokines play a central role. In obesity, there are higher circulating concentrations of inflammatory cytokines than in lean beings. The main source of pro-inflammatory cytokines in obesity is the adipose tissue; they are mainly produced by infiltrating macrophages, although adipocytes play a role [6].

There is a strong relationship between metabolism and immunity, which can become deleterious under conditions of metabolic stress. Obesity, considered a chronic inflammatory disease, is one example of this link[7]

Several key inflammatory markers have been consistently associated with both obesity and risk of adverse outcomes in obesity-associated diseases, such as hypertension and Diabetes Mellitus. There is evidence supporting perturbation of the intestinal microbiota and changes in intestinal permeability as potential triggers of inflammation in obesity. Characterization of the mechanisms underpinning the triggers of such inflammatory responses in overweight and obese individuals offer unique opportunities for intervention strategies to help ameliorate the risk of obesity-associated disease [8].

### **Obesity and white blood cells (wbcs):-**

Fat is an endocrine organ, secreting many factors that immune cells respond to – excess fat is thought to stimulate white blood cells (WBC) that produce inflammatory molecules as a part of the normal immune response upon injury or infection. Fat cells may also produce these inflammatory molecules [9].

Obesity is associated with elevated numbers of circulating immune cells and total WBC [10].

As shown in the Georgia study results, in the male participants, obesity was associated with significantly increase in the percentage of neutrophils. There was a significant increase in the total number of white blood cells in male obese subjects. There were also significant increases of lymphocytes counts in female obese subjects and significant increases of neutrophil counts in male obese subjects which were due to the increases of the total number of white blood cells in obese cases [11].

An imbalance between an enzyme called neutrophil elastase and its inhibitor causes inflammation, obesity, insulin resistance, and fatty liver disease. This enzyme is produced by white blood cells called neutrophils, which play an important role in the body's immune defense against bacteria. When the team reversed this imbalance in a mouse model and fed them a high-fat diet, the mice were resistant to body weight gain, insulin resistance (a precursor to type 2 diabetes), and fatty liver disease [12].

Inflammation underlies the pathophysiology of non-alcoholic steatohepatitis, which is associated with the metabolic syndrome of obesity, diabetes, hyperlipidemia, and cardiovascular disease [13].

The WBC count is elevated in obese patients and in patients with impaired glucose tolerance [14]. Feeding mice a high-fat diet induced obesity and caused a 20- fold increase in infiltrating neutrophils in adipose tissue that was associated with a marked increase in neutrophil elastase release. Notably, mice treated with a neutrophil elastase inhibitor showed improved glucose tolerance, while treatment with recombinant elastase led to markedly greater glucose intolerance [15].

**Obesity and chemokine in blood serum and plasma:-**

Adipose tissue disorders, such as those encountered in obesity and lipodystrophy, cause alterations to adipose tissue distribution and function with broad effects on cytokine, chemokine, and hormone expression, on lipid storage, and on the composition of adipose-resident immune cell populations [16].

Adipose tissue from lean individuals preferentially secretes anti-inflammatory adipokines such as adiponectin, transforming growth factor beta (TGF $\beta$ ), interleukin (IL)-10, IL-4, IL-13, IL-1 receptor antagonist (IL-1Ra), and apelin. In contrast, obese adipose tissue mainly releases proinflammatory cytokines among which are TNF- $\alpha$ , IL-6, leptin, visfatin, resistin, angiotensin II, and plasminogen activator inhibitor 1 [17].

Obese adipose tissue exhibits increases in CCL2 (chemokine ligand 2, or monocyte chemo attractant protein-1), an important macrophage-recruiting factor. CCL2 has effects on metabolism that are independent of its macrophage-recruiting capabilities. Importantly, we conclude that CCL2 is not critical for adipose tissue macrophage recruitment. The dominant factor for recruiting macrophages in adipose tissue during obesity therefore remains to be identified [18].

Kitade et al. recently identified and characterized a critical role for CCR5, another C-C motif chemokine receptor, in the regulation of obesity-induced WAT inflammatory response and insulin resistance [19].

In humans, recent studies have also shown up regulation of CCR5 in the visceral fat of morbidly obese individuals in whom macrophage infiltration has been confirmed [20].

The enhanced release of IL-8, a factor involved in neutrophil chemo-taxis, by hypertrophic adipocytes, may partly explain neutrophil recruitment. Adipose tissue neutrophils produce chemokine and cytokines, facilitating macrophage infiltration, which could contribute to development of insulin resistance [21].

In a study carried out to characterize the adipokine, cytokine and chemokine protein profile in serum from control, lean and obese mice. It was reported that, lean mice, relative to the control group, displayed increased concentrations of insulin-like growth factor (IGF) binding protein-3, -5 and -6 and adiponectin and decreased IGF-1. These mice also showed increased concentrations of interleukin (IL)-10, IL-12 p40/p70, eotaxin, monocyte chemo-attractant protein-5 and SDF-1. In contrast, diet-induced obese mice displayed increased leptin, IL-6 and LPS-induced chemokine and decreased concentrations of all chemokines/cytokines measured relative to control mice. As such, these data indicate that diet-induced obese may lead to an inflammatory state characterized as a shift towards a T helper lymphocyte type 1-skewed responsiveness. The demonstration of differential adipokine, cytokine and chemokine protein profile in control, lean and diet-induced obese mice may have implications for immune responsiveness and risk of disease [22].

**Obesity and cytokines:-**

Obesity is actually an epidemic problem in the world; it has become truly a global problem affecting countries rich and poor. An estimated 500 million adults worldwide are obese and 1.5 billion are overweight or obese [23].

Much of the information about obesity among adults rest in the use of body mass index (BMI) to define obesity, which will be defined as a BMI 30 kg/m<sup>2</sup> or greater unless otherwise stated [24].

Obesity is a consequence of many risk factors, as increased energy consumption and reduced physical exercise. [25]. Obesity is characterized by chronic low-grade inflammation and serves as a major risk factor for hypertension, coronary artery disease, dyslipidemias, and type-2 diabetes [26].

Obesity results from an imbalance between food intake and energy expenditure, which leads to an excessive accumulation of adipose tissue. Adipose tissue is now recognized not only as a main site of storage of excess energy derived from food intake but also as an endocrine organ. The expansion of adipose tissue produces a number of bioactive substances, known as adipocytokines or adipokines, which trigger chronic low-grade inflammation and interact with a range of processes in many different organs [27].

Although the precise mechanisms are still unclear, dysregulated production or secretion of these adipokines caused by excess adipose tissue and adipose tissue dysfunction can contribute to the development of obesity-related

metabolic diseases. Multiple lines evidence provides valuable insights into the roles of adipokines in the development of obesity and its metabolic complications [28].

Because it contains various immune cells, either adaptive (B and T lymphocytes; such as regulatory T cells) or innate (mostly macrophages and, more recently identified, myeloid-derived suppressor cells), the adipose tissue is now considered as a bona fide immune organ, at the cross-road between metabolism and immunity. Adipose tissue disorders, such as those encountered in obesity and lipodystrophy, cause alterations to adipose tissue distribution and function with broad effects on cytokine, chemokine, and hormone expression, on lipid storage, and on the composition of adipose-resident immune cell populations [29].

In a study carried out to examine changes in metabolic hormones, inflammatory cytokines, and immune function, in lean, overweight, and obese chimpanzees in a controlled environment. The examiners observed increased plasma circulating levels of proinflammatory TH-1 cytokines, Interferon gamma, interleukin-6, interleukin-12p40, tumor necrosis factor, soluble CD40 ligand, and Interleukin-1 $\beta$  and anti-inflammatory TH-2 cytokines, Interleukin-4, Interleukin-RA, Interleukin-10, and Interleukin-13 in overweight and obese chimpanzees. [30].

#### **Obesity and complement and complement peptide:-**

In recent years, there have been an increasing number of studies focusing on complement and innate immune system proteins in relation to obesity, inflammation, and dyslipidemias [31, 32]. However, in spite of the strong associations of C3 with obesity and metabolic syndrome, the underlying mechanisms remain unexplained. [33]

AT biology can be influenced by a variety of complement components. Adipocytes are a major source of adipsin, which is identical to the murine factor D [34] that participates in alternative complement activation. Interestingly, adipsin contributes to the maturation of pre-adipocytes into adipocytes, suggesting that this complement component has functions over and above its role in innate immunity [35].

Subsequent studies have demonstrated the presence of further components of the alternative pathway, including C3, fB, properdin, fH, and fI, in the AT [36,37], providing a basis for the hypothesis that local complement activation can influence AT biology.

Interestingly, C5L2-deficient mice fed a diabetogenic diet display delayed postprandial TG clearance and reduced adipocyte size, as well as higher glucose uptake and lipid deposition in the liver [38,39].

Recent experimental evidence suggests that antagonists of C3aR and C5aR administered to diet-induced obese rats prevent metabolic dysfunction and cause a decrease in body weight [40], which could be ascribed to the effects of C3a and C5a on adipocytes with regard to incorporation of glucose and inhibition of lipolysis, as well as on macrophages with regard to pro-inflammatory cytokine secretion [40].

Complement components C3 and C5 and their derivatives C3a, C3a<sup>desArg</sup> (ASP), and C5a are central players influencing the physiology and pathology of these metabolic organs. Basal levels of complement activation have rather beneficial metabolic effects, ranging from stimulation of insulin secretion in pancreatic  $\beta$ -cells (ASP, fH) [41,42] to insulin-like actions with regard to adipocyte maturation and energy regulation (adipsin, ASP, C3a, C5a) [43]. In contrast, increased complement action can contribute to metabolic pathology.

In the pancreas, complement activation can contribute to  $\beta$ -cell apoptosis in T1DM [44,45] and T2DM [46]. In obesity, anaphylatoxins promote leukocyte recruitment to the AT, thereby facilitating inflammation and the associated insulin resistance [39, 47].

Obesity-activated adipocytes release adipocytokines, which induce the secretion of pro-inflammatory cytokines, resulting in vascular endothelial dysfunction and organ injury. C3a is a candidate to induce tissue inflammation [48].

Adipose tissue synthesizes complement proteins and is a target of complement activation. C3a-desArg/acylation-stimulating protein stimulates lipogenesis and affects lipid metabolism. The C3a receptor and C5aR are involved in the development of adipocytes' insulin resistance through macrophage infiltration and the activation of adipose tissue. As a mediator of the effects of the terminal complement complex C5b-9, RGC-32 has an impact on energy

expenditure as well as lipid and glucose metabolic homeostasis. All of this evidence, taken together, indicates an important role for complement activation in metabolic diseases [49].

In fenton j et el, (2009) it was reported that diet-induced obese may lead to an inflammatory state characterized as a shift towards a T helper lymphocyte type 1-skewed responsiveness. The demonstration of differential adipokine, cytokine and chemokine protein profile in control, lean and diet-induced obese mice may have implications for immune responsiveness and risk of disease [50].

Sharp JA et al., (2015) reported that, the complement system has been increasingly recognized to play a pivotal role in a variety of inflammatory and autoimmune diseases. Consequently, therapeutic modulators of the classical, lectin and alternative pathways of the complement system are currently in pre-clinical and clinical development [51].

The complement system has been implicated in obesity, fatty liver, diabetes and cardiovascular disease (CVD). Complement links adipose tissue inflammation to systemic metabolic derangements, such as low-grade inflammation, insulin resistance and dyslipidaemia. C3 concentrations are associated with insulin resistance, liver dysfunction, risk of the metabolic syndrome, type 2 diabetes and CVD. The available human data suggest a complex and potentially causal role for the complement system in human cardiometabolic disease[52].

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### **References:-**

1. M. M. Finucane, G. A. Stevens, M. J. Cowan et al., "National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants," *The Lancet*, vol. 377, no. 9765, pp. 557–567, 2011. View at Publisher · View at Google Scholar · View at Scopus
2. National Institutes of Health, Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, U.S. Department of Health and Human Services, Bethesda, Md, USA, 1998.
3. P. M. Ridker, J. E. Buring, J. Shih, M. Matias, and C. H. Hennekens, "Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women," *Circulation*, vol. 98, no. 8, pp. 731–733, 1998. View at Google Scholar · View at Scopus
4. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. *Annu Rev Immunol.* 2011;29:415-45.
5. Heriberto Rodríguez-Hernández,<sup>1,2</sup> Luis E. Simental-Mendía, Gabriela Rodríguez-Ramírez, and Miguel A. Reyes-Romero: Obesity and Inflammation: Epidemiology, Risk Factors, and Markers of Inflammation. *International Journal of Endocrinology* Volume 2013 (2013), Article ID 678159, 11 pages.
6. M. S. Kaplan, N. Huguét, J. T. Newsom, B. H. McFarland, and J. Lindsay, "Prevalence and correlates of overweight and obesity among older adults: findings from the Canadian National Population Health Survey," *Journals of Gerontology A*, vol. 58, no. 11, pp. 1018–1030, 2003. View at Google Scholar · View at Scopus
7. Maria E. Ramos-Nino: The Role of Chronic Inflammation in Obesity-Associated Cancers. *ISRN Oncology*, Volume 2013 (2013), Article ID 697521, 25 pages.
8. Amanda J Cox, Nicholas P West, Allan W Cripps: Obesity, inflammation, and the gut microbiota. *The Lancet Diabetes & Endocrinology*, Volume 3, No. 3, p207–215, March 2015
9. Dixit VD. Adipose-immune interactions during obesity and caloric restriction: reciprocal mechanisms regulating immunity and health span. *J Leukoc Biol.* 2008 Oct;84(4):882-92.
10. Womack J, Tien PC, Feldman J, et al. Obesity and immune cell counts in women. *Metabolism.* 2007 Jul;56(7):998-1004.
11. X Xu, S Su, X Wang, V Barnes, C De Miguel, D Ownby, J Pollock, H Snieder, W Chen and X Wang: Obesity is associated with more activated neutrophils in African American male youth. *International Journal of Obesity* (2015) 39, 26–32; doi:10.1038/ijo.2014.194

12. VirginieMansuy-Aubert, Qiong L. Zhou, XiangyangXie, Zhenwei Gong, Jun-Yuan Huang, Abdul R. Khan, Gregory Aubert, Karla Candelaria, Shantele Thomas, Dong-Ju Shin, Sarah Booth, Shahid M. Baig, Ahmed Bilal, Daehee Hwang, Hui Zhang, Robin Lovell-Badge, Steven R. Smith, Fazli R. Awan, Zhen Y. Jiang. Imbalance between Neutrophil Elastase and its Inhibitor  $\alpha$ 1-Antitrypsin in Obesity Alters Insulin Sensitivity, Inflammation, and Energy Expenditure. *Cell Metabolism*, 2013; 17 (4): 534 DOI: 10.1016/j.cmet.2013.03.005
13. Targher G, Day CP, and Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med*. 2010;363:1341-1350.
14. Veronelli A, Laneri M, Ranieri R, et al. White blood cells in obesity and diabetes: effects of weight loss and normalization of glucose metabolism. *Diabetes Care*. 2004;27:2501-2502.
15. Talukdar S, Oh DY, Bandyopadhyay G, et al. Neutrophils mediate insulin resistance in mice fed a high-fat diet through secreted elastase. *Nat Med*. 2012;18:1407-1412.
16. KassemMakki,PhilippeFroguel, and Isabelle Wolowczuk: Adipose Tissue in Obesity-Related Inflammation and Insulin Resistance: Cells, Cytokines, and Chemokines. *ISRN Inflammation*, Volume 2013 (2013), Article ID 139239, 12 pages
17. N. Ouchi, J. L. Parker, J. J. Lugus, and K. Walsh, "Adipokines in inflammation and metabolic disease," *Nature Reviews Immunology*, vol. 11, no. 2, pp. 85–97, 2011. View at Publisher · View at Google Scholar · View at Scopus
18. Karen E. Inouye<sup>1</sup>, Hang Shi<sup>1</sup>, Jane K. Howard<sup>1</sup>, Christine H. Daly<sup>2</sup>, Graham M. Lord<sup>3</sup>, Barrett J. Rollins<sup>2</sup> and Jeffrey S. Flier: Absence of CC Chemokine Ligand 2 Does Not Limit Obesity-Associated Infiltration of Macrophages Into Adipose Tissue. *diabetesjournals.org* on 1 May 2007. DOI: 10.2337/db07-0425.
19. H. Kitade, K. Sawamoto, M. Nagashimada, et al., "CCR5 plays a critical role in obesity-induced adipose tissue inflammation and insulin resistance by regulating both macrophage recruitment and M1/M2 status," *Diabetes*, vol. 61, pp. 1680–1690, 2012. View at Google Scholar
20. J. Huber, F. W. Kiefer, M. Zeyda et al., "CC chemokine and CC chemokine receptor profiles in visceral and subcutaneous adipose tissue are altered in human obesity," *Journal of Clinical Endocrinology and Metabolism*, vol. 93, no. 8, pp. 3215–3221, 2008. View at Publisher · View at Google Scholar · View at Scopus
21. S. Talukdar, Y. Oh da, G. Bandyopadhyay, et al., "Neutrophils mediate insulin resistance in mice fed a high-fat diet through secreted elastase," *Nature Medicine*, vol. 18, pp. 1407–1412, 2012. View at Google Scholar
22. Fenton JI, Nuñez NP, Yakar S, Perkins SN, Hord NG, Hursting SD. Author information: Diet-induced adiposity alters the serum profile of inflammation in C57BL/6N mice as measured by antibody array. *DiabetesObesMetab*. 2009 Apr;11(4):343-54.
23. M. M. Finucane, G. A. Stevens, M. J. Cowan et al., "National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9.1 million participants," *The Lancet*, vol. 377, no. 9765, pp. 557–567, 2011. View at Publisher · View at Google Scholar · View at Scopus
24. National Institutes of Health, *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*, U.S. Department of Health and Human Services, Bethesda, Md, USA, 1998.
25. P. M. Ridker, J. E. Buring, J. Shih, M. Matias, and C. H. Hennekens, "Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women," *Circulation*, vol. 98, no. 8, pp. 731–733, 1998. View at Google Scholar · View at Scopus
26. M. S. Kaplan, N. Huguét, J. T. Newsom, B. H. McFarland, and J. Lindsay, "Prevalence and correlates of overweight and obesity among older adults: findings from the Canadian National Population Health Survey," *Journals of Gerontology A*, vol. 58, no. 11, pp. 1018–1030, 2003.
27. C.-Y. Yeung, A. W.-K. Tso, A. Xu et al., "Pro-inflammatory adipokines as predictors of incident cancers in a chinese cohort of low obesity prevalence in Hong Kong," *PLoS ONE*, vol. 8, no. 10, Article ID e78594, 2013. View at Publisher · View at Google Scholar · View at Scopus
28. Un Ju Jung and Myung-Sook Choi: Obesity and Its Metabolic Complications: The Role of Adipokines and the Relationship between Obesity, Inflammation, Insulin Resistance, Dyslipidemia and Nonalcoholic Fatty Liver Disease. *Int J Mol Sci*. 2014 Apr; 15(4): 6184–6223.
29. KassemMakki,PhilippeFroguel, and Isabelle Wolowczuk: Adipose Tissue in Obesity-Related Inflammation and Insulin Resistance: Cells, Cytokines, and Chemokines. *ISRN Inflammation*, Volume 2013 (2013), Article ID 139239, 12 pages

30. PramodNehete, Elizabeth R. Magden, BhartiNehete, Patrick W. Hanley, and Christian R. Abee: Obesity Related Alterations in Plasma Cytokines and Metabolic Hormones in Chimpanzees. *International Journal of Inflammation*, Volume 2014 (2014), Article ID 856749, 11 pages
31. Zhan YT, An W. Roles of liver innate immune cells in nonalcoholic fatty liver disease. *World J Gastroenterol*. 2010;16:4652–4660. [PMC free article] [PubMed]
32. Donath MY, Boni-Schnetzler M, Ellingsgaard H, Ehses JA. Islet inflammation impairs the pancreatic beta-cell in type 2 diabetes. *Physiology (Bethesda)* 2009;24:325–331. [PubMed]
33. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol*. 2011;11:98–107.
34. Choy LN, Rosen BS, Spiegelman BM. Adipsin and an endogenous pathway of complement from adipose cells. *J Biol Chem*. 1992;267:12736–12741. [PubMed]
35. Wilkison WO, Min HY, Claffey KP, Satterberg BL, Spiegelman BM. Control of the adipsin gene in adipocyte differentiation. Identification of distinct nuclear factors binding to single- and double-stranded DNA. *J Biol Chem*. 1990;265:477–482. [PubMed]
36. Choy LN, Spiegelman BM. Regulation of alternative pathway activation and C3a production by adipose cells. *Obes Res*. 1996;4:521–532. [PubMed]
37. Peake PW, O'Grady S, Pussell BA, Charlesworth JA. Detection and quantification of the control proteins of the alternative pathway of complement in 3T3-L1 adipocytes. *Eur J Clin Invest*. 1997;27:922–927.[PubMed]
38. Paglialunga S, Schrauwen P, Roy C, Moonen-Kornips E, Lu H, Hesselink MK, et al. Reduced adipose tissue triglyceride synthesis and increased muscle fatty acid oxidation in C5L2 knockout mice. *J Endocrinol*. 2007;194:293–304.
39. Fisette A, Munkonda MN, Oikonomopoulou K, Paglialunga S, Lambris JD, Cianflone K. C5L2 receptor disruption enhances the development of diet-induced insulin resistance in mice. *Immunobiology*. 2013[PubMed]
40. Lim J, Iyer A, Suen JY, Seow V, Reid RC, Brown L, et al. C5aR and C3aR antagonists each inhibit diet-induced obesity, metabolic dysfunction, and adipocyte and macrophage signaling. *Faseb J*. 2013;27:822–831. [PubMed]
41. Ahren B, Havel PJ, Pacini G, Cianflone K. Acylation stimulating protein stimulates insulin secretion. *Int J ObesRelatMetabDisord*. 2003;27:1037–1043. [PubMed]
42. Martinez A, Pio R, Lopez J, Cuttitta F. Expression of the adrenomedullin binding protein, complement factor H, in the pancreas and its physiological impact on insulin secretion. *J Endocrinol*. 2001;170:503–511.[PubMed]
43. Faraj M, Sniderman AD, Cianflone K. ASP enhances in situ lipoprotein lipase activity by increasing fatty acid trapping in adipocytes. *J Lipid Res*. 2004;45:657–666. [PubMed]
44. Conroy SJ, Abdel-Wahab YH, Caraher EM, Byrne PM, Murphy E, Nolan J, et al. Evidence for complement-dependent and -independent inhibition of insulin secretion from clonal beta-cells incubated in the presence of sera of newly diagnosed IDDM patients. *J Endocrinol*. 2000;164:139–147.
45. Lin M, Yin N, Murphy B, Medof ME, Segerer S, Heeger PS, et al. Immune cell-derived c3 is required for autoimmune diabetes induced by multiple low doses of streptozotocin. *Diabetes*. 2010;59:2247–2252.
46. Sjolander J, Westermark GT, Renstrom E, Blom AM. Islet amyloid polypeptide triggers limited complement activation and binds complement inhibitor C4b-binding protein, which enhances fibril formation. *J Biol Chem*. 2011;287:10824–10833.
47. Mamane Y, Chung Chan C, Lavallee G, Morin N, Xu LJ, Huang J, et al. The C3a anaphylatoxin receptor is a key mediator of insulin resistance and functions by modulating adipose tissue macrophage infiltration and activation. *Diabetes*. 2009;58:2006–2017.
48. Fujita T, Hemmi S, Kajiwara M, Yabuki M, Fuke Y, Satomura A, Soma M.: Complement-mediated chronic inflammation is associated with diabetic microvascular complication. *DiabetesMetab Res Rev*. 2013 Mar;29(3):220-6. doi: 10.1002/dmrr.2380.
49. Sonia I. Vlaicu, Alexandru Tatomir, Dallas Boodhoo, Stefan Vesa, Petru A. Mircea, Horea Rus: The role of complement system in adipose tissue-related inflammation. *Immunologic Research* pp 1-12 online: 11 January 2016
50. Fenton JINuñezNPYakarSPerkinsSNHordNGHursting SD: Diet-induced adiposity alters the serum profile of inflammation in C57BL/6N mice as measured by antibody array. *DiabetesObesMetab*. 2009 Apr;11(4):343-54.
51. Sharp JA, Hair PS, Pallera HK, Kumar PS, Mauriello CT, Nyalwidhe JO, et al. (2015) Peptide Inhibitor of Complement C1 (PIC1) Rapidly Inhibits Complement Activation after Intravascular Injection in Rats. *PLoS ONE* 10(7): e0132446. doi:10.1371/journal.pone.0132446
52. Rio de Janeiro: XXV International Complement Workshop September 14-18, 2014 -, Brazil. *Molecular Immunology*, Volume 61, Issue 2, October 2014, Pages 135–148