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The Role Of Adipose Tissue In Glucose Homeostasis

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Abstract: It is today established that adipose tissue subserves not only in the storage of excess energy but it is also an organ that regulates immune response, metabolic and endocrine functions as well. Broadly, there are three types of adipose tissue - the white adipose tissue (WAT) the brown adipose tissue (BAT) and the brite adipose tissue. Brown adipose tissue expends energy and generates heat. It is however the WAT that truely relates to the traditional belief that adipose tissue stores excess energy. This review takes a step further in revealing that healthy WAT secretes adipokines which are molecular proteins that regulates glucose homeostasis. However, when healthy WAT is transformed into an inflamed WAT as in obesity, there is perturbation in the glucose homeostasis which further leads to the development of metabolic disease. This review also explores the trend that is now followed in reversing the inflammation of WAT by administration of drugs like thiazolidinediones, statins and aspirin. The replenishment of WAT by transplantation of embryonic BAT is also highlighted as one of the promising methods to reverse inflammation in WAT and correct perturbation of glucose homeostasis.

Keywords: White adipose tissue (WAT), Brown adipose tissue (BAT), Adiponectin, Leptin, Tumor Necrotic Factor α (TNFα), Thiazolidinediones.

Introduction: The Adipose tissue biology

It is said that adipose tissue has evolved mainly to store excess energy. According to the first law of thermo-dynamics, energy consumption equals the sum of energy expended and energy stored. The energy stored is the excess energy, which causes increase in adipose tissue mass and results in obesity. As the burden of obesity rises to 1.9 billion obese adults in 2014,[1] studies related to obesity are also rising and there is a great interest emerging in this field and in finding the role of adipose tissue in obesity and in the control of glucose homeostasis. These studies, have today strongly implicated that adipose tissue is not just a storage organ but an organ dealing with immune response, metabolic, and endocrine functions as well.

Adipocyte is a specialized cell that can condense and store more energy per unit mass anhydrously in the form of fat. Glycogen on the other hand has only half the energy content per unit of pure mass as it has to be stored hydrously which therefore reduces its energy storage efficiency [2]. Adipose depots that includes areas like fat pads of the heels, fingers, toes, the periorbital area and skin have been termed as subcutaneous fat. Depots within body cavities, like surrounding the heart and other organs, depots associated with intestinal mesentery and depots in the retroperitoneum are all together termed as visceral fat. Of the two, visceral fat is linked to many morbidities associated with obesity which include T2D (Type 2 Diabetes) and cardiovascular disease.

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Adipose tissue can also be broadly classified into white and brown fat, chiefly due to morphological appearance and similarly in accordance to the origin and function. White adipose tissue (WAT) is made up of adipocytes that contains large unilocular lipid droplets whereas in brown adipose tissue (BAT), the adipocytes contains multiple smaller (multilocular) lipid droplets and numerous mitochondria. WAT is found throughout the body and consists of both the visceral fat and the subcutaneous fat. BAT however is located in depots that are highly innervated and vascularized. As far as rodents are concerned, the brown adipose tissue are located in the interscapular, sub-scapular, cervical regions of the upper anterior side of the trunk and neck and it also grows around parts of the aorta and kidneys. BAT stored in these areas are called classical BAT to differentiate it from brown- adipocyte like cells which are located within some of the WAT called the Brite adipocytes [3]. WAT and BAT are diametrically opposed in function and in the regulation of energy homeostasis. WAT is concerned with storage of energy whereas BAT expends energy and generates heat by a process known as adaptive thermogenesis. The generation of heat in BAT is mediated by the uncoupling protein -1(UCP-1) present in the inner membrane of mitochondria which uncouples oxidative phosphorylation by permitting reentry of protons into the mitochondrial matrix without involving ATP synthase, thereby producing heat only and not ATP [4]. Fedorenko and others, who investigated the functioning of UCP-1, found that UCP-1 is a fatty acid anion/H+ symporter [5] . BAT recovers the energy expended by increasing the uptake of glucose and fatty acid on stimulation as evident from studies done in rodents [4]. Observation in mice have shown that lack of BAT results in reduced energy expenditure and an inclination to develop diet induced obesity[6,7]. However, lack of UCP-1 do not result in obesity but makes the mice become cold-sensitive[7]. This probably lead to an inference that BAT regulates energy metabolism through UCP-1 in a manner not fully comprehensed [8]. It is important to mention here of a third type of adipocyte called as Brite adipocyte or sometimes known as beige or inducible brown which co-exists among classical white adipocytes. Morphologically, brite adipocyte is indistinguishable from white adipose tissue when unstimulated. However, on chronic cold exposure brite adipocytes transform itself into an adipocyte that is multilocular and that is expressing UCP-1 which makes it similar to BAT morphologically[9,10,11,12]. In mice, it is estimated that the maximum capacity of brite adipocyte to generate heat is only around 10% of the maximum capacity of the classical brown adipocyte. This can probably be because of the lower number of UCP-1 expressed in brite than the number of UCP-1 expressed in brown fat[13]. Since the brite adipose tissue lie within the white adipose tissue and differentiate when exposed to cold, it has been proposed that brite adipocytes arises from existing mature white adipocytes by the process of transdifferentiation. Another model proposed that brite adipocytes takes origin from distinct precursor cells [14,15].

Though brite adipocytes are morphologically similar to brown adipocytes, however, the origin of brown adipocytes is altogether a different story. The BAT shares a common origin with skeletal muscle as they both arises from a distinct mesenchymal precursor cells. As for the origin of white adipocytes, the story is complex and hazy [3]. Lineage tracing analysis have indicated that all white adipocytes originated from a Myf5-negative (myogenic factor -5) precursors. However, some recent studies have shown that the subsets of white adipocytes also arises from Myf5-Cre-expressing precursors [3].

Adipose tissue in the control of glucose homeostasis

Excess fat as in obesity or less fat as in lipodystrophy, are both conditions that are associated with hyperglycemia and insulin resistance. This is an implication that any

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alteration in the adiposity can affect the control of glucose homeostasis, and it also implies that adipose tissue is important in the control of glucose homeostasis. Moreover, adipose tissue is where most PPAR-ɤ are found on which antidiabetic drug such as thiazolidinedione (TZD) can effectively act. As a complex and highly active endocrine organ, the white adipose tissue secretes hormones which influences physiological functions including nutrient metabolism, angiogenesis, satiety and immune response [2]. The principal hormones that are also referred to as adipokines are adiponectin and leptin which are important controllers of metabolic homeostasis[2].

Adiponection which was identified by various workers under different names such as apM1, GBP28, AdipoQ and ACR 30, is well known for its insulin sensitizing effects on peripheral tissues. This protein secreted in micromolar amount acts on receptors, such as AdipoR1, AdipoR2 and T Cadherin, stimulates AMP which in turn activates protein kinase and also enhance the activity of peroxisome proliferator-activated receptor- ɤ (PPAR-ɤ) pathway in liver and skeletal muscle [2,16]. In this way, adiponectin increases fatty acid oxidation, inhibits gluconeogenesis and improves insulin sensitivity. It is interesting to know that adiponectin also has anti-inflammatory and anti-atheroselerotic effects suggesting that it is an overall health promoting adipokine [16]. As for its effect on insulin, adiponectin may improve sensitivity to insulin but it has no control on insulin secretion as far as healthy mice or humans are concerned [17]. However in mice with diet-induced obesity, adiponectin enhances glucose-stimulated insulin secretion[17].

Leptin, is another adipokine secreted by WAT which has a wide spectrum of functions. Leptin is well known for its role in energy balance, its central effects on reducing appetite and food intake, its peripheral effects in increasing fat oxidation in the liver, the adipose tissue itself and also in the skeletal muscle. Leptin's effect on glucose homeostasis is seen in obese ob/ob mice where it reverses hyperglycemia even before the body weight is corrected [2,18]. In some cases of obesity, though leptin level is high yet hyperglycemia remains uncorrected due to leptin resistance [19,20]. Leptin also corrects hyperglycemia in lipodystrophy in both mice and humans[21,22]. It was through cross circulation experiments between the ob/ob and the db/db mice, that Coleman suggested that ob/ob mice were leptin deficient whereas db/db mice suffered from a disrupted leptin receptor function[23]. Leptin was discovered only in 1994 when the ob gene was identified[24]. A single nonsense mutation in the ob gene, as in ob/ob mice, leads to the generation of a truncated form of leptin which cannot be detected in circulation and resulting in a condition of leptin deficiency [24]. Soon after leptin was discovered, the leptin receptor (Lepr) was also identified and the db gene encoding it, was also discovered[25]. By encoding an alternatively spliced transcript, db gene generated six leptin receptor isoforms denoted as lepr-a to lepr-f [26]. Failure of the normal splicing of lepr-b isoform can occur when there is insertion mutation in the db gene, as in db/db mice, resulting in the truncation of the intracellular signaling domain of Leptin receptor. This is an implication that the isoform lepr-b is mainly responsible for facilitating the action of leptin[26].

Both the ob/ob and db/db mice express phenotype which is similar to T2D, consisting of obesity, hyperglycemia, hyperinsulinemia and insulin resistance. Some workers have suggested that the peturbation of glucose homeostasis in both leptin and leptin receptor defficiency is secondary to obesity and hyperphagia[27]. But several workers have shown evidence that the control of glucose homeostasis by leptin is independent and is not affected by leptin's effect on food intake and body weight [27]. Some studies have shown that leptin administration in ob/ob mice reduces circulating insulin and glucose levels and that this indicates an increased in insulin sensitivity, which is far

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more effective than pair feeding. These observations are implying that leptin actions on glucose homeostasis is not caused by a reduced food intake [28,29]. Other studies reported that leptin administration in ob/ob mice lowered circulating insulin and glucose level within a short period of 1 to 2 days. The changes in the level of insulin and glucose occurred before changes in body weight could be observed[30,31]. Moreover, evidences are showing that in leptin deficient animal (ob/ob mice), administration of leptin is more effective on glucose metabolism than on body weight, as low doses of leptin can normalize insulin and glucose levels yet failed to change body weight or even food intake[18,32]. Besides increasing insulin sensitivity, leptin has also been found to lower glucose level by reducing the levels of counter-regulatory hormones like growth hormones, corticosterone and even glucagon in insulin deficient rodents [27,33,34].

Today, we know of many other proteins that are secreted by the adipose tissue such as visfatin, omentin, TNFα and resistin that are linked to the control of glucose homeostasis. Visfatin is a protein which is reported to bind to and activates insulin receptor resulting in facilitating glucose uptake [35]. Omentin works as an insulin sensitizer which also promotes glucose uptake[36]. TNFα, on the other hand, reduces insulin action. Insulin sensitivity is restored when TNFα is blocked by biochemical and genetic modes both in vivo and in vitro[2, 37]. Another protein, which was discovered as a secreted product of adipocytes in mice, is resistin. Resistin appears to be reducing the uptake of glucose by muscle and fat [2,38]. Besides TNFα, other cytokines like IL-1, IL-6 and retinol binding protein -4, which originated from WAT and macrophages embedded there-in, have also been implicated to have direct or indirect influences on glucose homeostasis [2].

Adipose tissue inflammation and the derangement of glucose homeostasis

Increase adiposity leads to obesity, a condition that is today considered as an independent risk factor for T2D, dyslipidemia and cardiovascular disease[39]. It is the central type of obesity that involves accumulation of fat in the viscera that shows increased alteration at the metabolic level. Again, obesity has been recently discovered to be associated with a low – grade chronic inflammation featuring abnormal adipokine production[39]. Some workers have revealed the correlation between Body Mass Index (BMI) and c Reactive Protein (CRP) levels in healthy subjects and have implicated IL.6 for increased CRP in obese subjects [40,41]. However, coming back to TNFα, this molecule is considered to be important in linking inflammation and obesity. In animal models of obesity, WAT has been found to over-expressed TNFα [39]. Some workers have provided evidence that administration of recombinant TNFα results in decrease insulin sensitivity [42,43]. There are suggestions therefore, that implicates over- secretion of TNFα from WAT, in obese animal models, as the cause of insulin resistance[39]. Molecules such as TNFα, interleukin 1 and 6 increases inflammation and this leads to insulin resistance which worsens hyperglycemia and results in T2D. Inflamed WAT also secretes other hyperglycemic adipokines such as resistin and retinol binding protein 4- which can exacerbates the perturbed glucose homeostasis[15]. Pro- inflammatory cytokines increases activation or over-expression of signaling molecules such as Nuclear factor κB(NF-κB) , IκB kinase (IKK), activating protein-1 (AP-1) and c-Jan NH terminal kinase, which are pathways interacting with insulin signaling causing insulin resistance[39]. The production of pro-inflamatory cytokines in obesity has opened up new research questions as well as discussion as to how these molecules are secreted by WAT.

In explanation to this, several studies have indicated that fat cells share some features with macrophages and that the preadipocytes in WAT like the macrophages also have the capability to

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phagocytose [44,45]. Properties such as complement activation and pro inflammatory cytokine production are found to be common to fat cells and immune cells [42,46]. Others have suggested as per their findings, that adipose tissue macrophages have a central role in promoting chronic low-grade inflammation [47,48,49]. In obesity, the macrophages are obstructed from becoming alternatively activated macrophages (AAM) by disrupting the function of nuclear hormone receptor peroxisome proliferator-activated receptor gamma (PPAR-ɤ) and thereby become macrophages that have a classically activated inflammatory phenotype [47,48,49]. Another possibility is the increase infiltration of macrophages in the adipose tissue (WAT) which is seen in obese patient, which has been implicated as the source of pro-inflammatory cytokines and the cause of low-grade inflammation[50,51].

Furthermore, the low-grade inflammation is a result of a number of other factors occurring concomitantly in obesity. Leptin could facilitate migration by promoting diapedesis of macrophages from circulation to WAT. Monocyte chemoattractant protein-1 (MCP-1) secreted by fat cells in obesity is a monocyte recruiting factor. Certain factors again secreted by WAT can activate endothelial cells to increase monocyte adhesion and enhance migration of macrophages [52,53].

Tail-end: Reversing inflamed WAT

Taking into consideration the fact that inflammation of the adipose tissue in obesity causes perturbation of glucose homeostasis and results in metabolic disease, it is therefore important to maintain the health of adipose tissue in order to prevent the unwanted consequences. Reducing inflammation of the white adipose tissue is therefore the key to improving the state of health of adipose tissue and to reverse metabolic diseases such as diabetes mellitus. In targeting inflammation, drugs like thiazolidinediones have been used to reduce adipocyte TNF-α production, to decrease levels of resistin in circulation and in adipose tissue, and to induce adiponectin expression[54]. Statins have also been used to inhibit pro-inflammatory cytokine production, to interfere with the NF-κB pathway, to modulate function's of endothelium and to regulate migration of leukocyte across the endothelium[55]. Aspirin is also anti-inflammatory as it inhibits IKK and JNK pathways. Aspirin prevents occurence of insulin resistance, induced by TNFα, by inhibiting serine/threoxine kinases [56]. Therefore the actions of all these drugs reduces inflammation in adipose tissue and eventually improves insulin sensitivity [54,55,56].

Recovery of adipose tissue from inflammation is also seen in T1D (Type 1 Diabetes) patients who were treated with insulin replacement therapy directly or even through transplantation of insulin secreting tissue. Insulin is therefore important in the maintenance of healthy adipose tissue[57,58].

Today, we see a ray of hope in the restoration of a healthy WAT from an inflamed WAT and even in the effort to reverse T1D without replacement of insulin. The ingenuity of today's research to experiment with subcutaneous BAT transplantation is a step in a new direction in the replenishment of a healthy WAT. Embryonic BAT transplantation in T1D mouse models have shown to remarkably reduce WAT inflammation and to induce proliferation of a healthy subcutaneous WAT. Besides recovery from T1D there is also a significant increase in the levels of adiponectin, leptin, IGF-1 and the suppression of glucagon [59,60,61]

In conclusion, understanding the biology of adipose tissue in health and in disease will certainly help increase the pace in the development of newer and effective methods in the treatment of metabolic disease. However, more in depth studies need to be done to

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understand the adipokines generated by the adipocyte and especially to know how these molecules can be put into application to correct the perturbed glucose homeostasis and to cure or prevent metabolic disease.

References:

1. World Health Organisation. 2016. Obesity and overweight fact sheet updated June, 2016 Media centre.
2. Rosen D. Evan, Spiegelman M. Bruce. 2006. Adipocytes as regulators of energy balance and glucose homeostasis, nature. December 14; 444 (7121): 847-853. Doi: 10.1038/nature 05483.
3. Gurmaches J. Sanchez, Guertin David A. 2014. Adipocyte lineages: tracing back the origins of fat, Biochim Biophys Acta. March; 1842 (3): 340-351. Doi: 10.1016/j.bbadis. 2013. 05.027.
4. Cannon B, Nedergaard J. 2004. Brown adipose tissue: function and physiological significance, physiological reviews.;84:277-359. [Pubmed: 14715917]
5. Fedorenko A, Lishko PV, Kirichok Y. 2012. Mechanism of fatty-acid dependent UCP1 uncoupling in brown fat mitochondria. Cell.; 151: 4000-13. [PubMed: 23063128]
6. Bachman ES, et al. 2002. βAR signaling required for diet-induced thermogenesis and obesity resistance. Science.; 297:843-845. [PubMed: 12161655]
7. Lowell BB, et al. 1993.Development of obesity in transgenic mice after genetic ablation of brown adipose tissue. Nature.; 366:740-742. [PubMed: 8264795]
8. Enerback S, et al. 1997. Mice lacking mitochondrial uncoupling protein are cold-sensitive but not obese. Nature.; 387:90-94. [PubMed: 9139827]
9. Cinti S. 2012. The adipose organ at a glance. Disease models & Mechanisms.; 5:588-594. [PubMed: 22915020]
10. Frontini A, Cinti S. 2010. Distribution and Development of Brown Adipocytes in the Murine and Human Adipose Organ. Cell Metabolism.; 11:253-256. [PubMed:19357407]
11. Cinti S. 2011. Between brown and white: Novel aspects of adipcyte differentiation. Annals of Medicine.; 43: 104 – 115. [PubMed. 21254898]
12. Nedergaard, J.; Bengston, T.; Cannon, B. 2010. Three years with adult human brown adipose tissue. In: Powers, AC.; Ahima, RS., editors. Year in Diabetes and Obesity. Vol. 1212.2010. p. E20-E36.
13. Nedergaard J, Cannon B. 2013. UCP1 mRNA does not produce heat. Biochimica et biophysica acta.
14. Cinti S. 2009. Transdifferentiation properties of adipocytes in the adipoe organ. American Journal of Physiology-Endocrinology and Metabolism,; 297: E977 –E986. [PubMed: 19458063].
15. Vegiopoulus A, Muller-Decker K, Strzoda D, Schmitt I, Chichelnitskiy E, Ostertag A, Berriel Diaz M, Rozman J, Hrabe de Angelis M, Nusing Rm, Meyer CW, Wahli W, Klingenspor M, Herzig S. 2010. Cyclooxygenase-2 controls energy homeostasis in mice by de novo recruitment of brown adipocytes. Science.; 328: 1158 -1161. [PubMed: 20448152]
16. Gunawardana S C, 2014. Benefit of healthy adipose tissue in the treatment of diabetes, World Journal of Diabetes Aug 15: 5 (4): 420-430, doi: 10.4239/wjd.v5.i4.420.
17. Winzell MS, Nogueiras R, Dieguez C, Ahren B. 2004.Dual action of adiponectin on insulin secretion in insulin-resistant mice. Biochem. Biophys. Res, Commun. 321:154-160. [PubMed: 15358228]
18. Pelleymounter MA, et al. 1995. Effects of the obese gene product on body weight regulation in ob/ob mice. Science.; 269: 540 – 543. [PubMed: 7624777]

DOI: 10.18535/ijmsci/v3i9.1

19. Ingalls AM, Dickie MM. Snell GD. 1950. Obese, a new mutation in the house mouse. J Hered; 41: 317-318.
20. Hummel KP, Dickie MM, Coleman DL. 1966. Diabetes, a new mutation in the mouse. Science; 153: 1127-1128.
21. Shimomura I, Hammer RE, Ikemoto S. Brown MS, Goldstein JL. 1999. Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. Nature.; 401:73-76. [PubMed: 10485707]
22. Oral EA, et al. 2002. Leptin-replacement therapy for lipodystrophy. N. Engl. J. Med.; 346:570-578. [PubMed: 11856796]
23. Coleman DL. 1973 Effects of parabiosis of obese with diabetes and normal mice. Diabetologia; 9: 294-298.
24. Zhang Y, Proenca R, Maffei M, et al. 1994. Positional cloning of the mouse obese gene and its human homologue. Nature; 372: 425-432.
25. Tartaglia LA, Dembski M, Weng X, et al. 1995. Identification and expression cloning of a leptin receptor, OB-R. Cell; 83: 1263-1271.
26. Lee GH, Proenca R, Montez JM, et al. 1996. Abnormal splicing of the leptin receptor in diabetic mice. Nature; 379: 632-635.
27. Denroche C. Heather, Frank K. Huynh, Kieffer J. Timothy, 2012. The role of leptin in glucose homeostasis, J Diabetes invest, doi: 10.1111/j.2040-1124.2012.00203.x,)
28. Schwartz MW, Baskin DG, Bukowski TR, et al. 1996. Specificty of leptin action on elevated blood glucose levels and hypothalamic neuropeptide Y gene expression in ob/ob mice. Diabetes; 45: 531-535.
29. Levin N, Nelson C, Gurney A, et al. 1996. Decreased food intake does not completely account for adiposity reduction after ob protein infusion. Proc Natl Acad Sci USA; 93: 1726-1730
30. Seufert J, Kieffer TJ, Habener JF. 1999. Leptin inhibits insulin gene transcription and reverses hyperinsulinemia in leptin-deficient ob/ob mice. Prof Natl Acad Sci USA; 96: 674-679.
31. Lam NT, Lewis JT, Cheung AT, et al. 2004. Leptin increases hepatic insulin sensitivity and protein tyrosine phosphatase 1B expression. Mol Endocrinal; 18: 1333-1345.
32. Hedbacker K, Birsoy K, Wysocki RW, et al. 2010. Antidiabetic effects of IGFBP2, a leptin – regulated gene. Cell Metab; 11:11-22.
33. Yu X, Park BH, Wang MY, et al. 2008. Making insulin deficient type 1 diabetic rodents thrive without insulin. Proc Natl Acad Sci USA; 105: 14070 – 14075.
34. German JP, Thaler JP, Wisse BE, et al. 2010. Leptin Activates a Novel CNS Mechanism for insulin-independent Normalization of Severe Diabetic Hyperglycemia. Endocrinology; 152: 394-404.
35. Stephens JM, Vidal –Puig AJ. 2006. An update on Visfatin/pre-B cell colongy-enhancing factor, an ubiquitously expressed, illusive cytokine that is regulated in obesity. Curr. Opin. Lipidol.; 17:128-131. [PubMed: 16531748]
36. Yang RZ, et al. 2006. Identification of omentin as a novel depot-specific adipokine in human adipose tissue; possible role in modulating insuling action. Am J. Physiol. Endocrinol. Metab.; 290: E1253-E1261. [PubMed: 16521507]
37. Xu H, et al. 2003. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J. Clin. Invest.; 112:1821-1830. [PubMed: 14679177]

DOI: 10.18535/ijmsci/v3i9.1

38. Steppan CM, et al. 2001. The hormone resistin links obesity to diabetes. Nature.; 409: 307-312 [PubMed: 11201732]
39. Bastard J. Philippe., Maachi M, Lagathu C, Kim J. Min, Caron M, Vidal H, Capeau J, Feve B; 2006. Recent advances in the relationship between obesity inflammation, and insulin resistance. Eur. Cytokine Netw Vol. 17 n 1, March. 4-12.
40. Ford ES. 2003. The metabolic syndrome and C-reactive protein, fibrinogen. And leukocyte count: findings from the third National Health and Nutrition Examination Survey. Atherosclerosis; 168:351.
41. Castell JV. Gomez-Lechon MJ. David M. Hirano T, Kishimoto T, Heinrich PC. 1988. Recombinant human interleukin-6 (IL-6/BSF-2/HSF) regulates the synthesis of acute phase proteins in human hepatocytes. FEBS Lett: 232: 347.
42. Hotamisligil GS. Shargill NS. Spiegelman BM, 1993. Adipose expression oh tumor necrosis factor-alpha direct role in obesity-linked insulin resistance Science, 259-87.
43. Uysal KT. Wiesbrock SM, Marino MW, Hotamisligil GS. 1997. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature: 389:610.
44. Cousin B, Munoz O. Andre M, Fontanilles AM. Dani C. Cousin JL. Laharragne P. Casteilla L. Penicaud L. 1999. A role for preadipocytes as macrophage-like cells. FASEB j, 13-305
45. Charriere G. Cousin B. Arnaud E. Andre M. Bacou F, Penicaud L. Casteilla L. 2003. Preadipocyte conversion to macrophage. Evidence of plasticity. J Biol Chem: 278: 9850.
46. Rosen BS. Cook KS. Yaglom J, Groves DL. Volanakis JE. Damm D. White T. Spiegelman BM. 1989. Adipsin and complement factor D activity: an immune-related defect in obesity. Science: 244-1483.
47. Hotamisligil GS, 2006. Inflammation and metabolic disorders. Nature; 2006;444: 860-867. [PubMed: 17167474]
48. Odegaard JI, et al. 2007. Macrophage-specific PPAR-ɤ controls alternative activation and improves insulin resistance. Nature.: 447:1116-1120. [PubMed:17515919]
49. Bouhlel MA, et al. 2007. PPAR-ɤ activation primes human monocytes into alternative M2 macrophages with anti-inflammatory properties. Cell Metab.; 6: 137 -143. [PubMed: 17681149]
50. Wellen KE, Hotamisligil GS. 2003. Obesity-induced inflammatory changes in adipose tissue J Clin invest: 112: 1785.
51. Wellen KE. Hotamisligil GS. 2005. Inflammation stress and diabetes. J Clin Invest. 115: 1111.
52. Curat CA, Miranville A. Sengenes C, Diehl M. Tonus C. Busse R. Bouloumie A. 2004. From blood monocytes to adipose tissue resident macrophages, induction of diapedesis by human mature adipocytes. Diabetes: 53 -1285.
53. Christiansen T. Richelsen B. Bruun JM. 2005. Monocyte chemo attractant protein-1 is produced in isolated adipocytes, associated with adiposity and reduced after weight loss in morbid obese subjects. Int J Obes: 29: 146.
54. Muller DE. Berger JP, 2003. Role of PPAR-ɤ in the regulation of obesity related insulin sensitivity and inflammation. Int J Obes (Suppl 3) : S17.
55. Weitz-Schmidt G. 2002. Statins as anti-inflammatory agents. Trends Pharmacol Sci, 23-482.
56. Hundal RS. Petersen KF. Mayerson AB. Randhawa PS. Inzucchi S. Shoelson SE. Shulman Gl. 2002. Mechanism by which high dose aspirin improves glucose

DOI: 10.18535/ijmsci/v3i9.1

metabolism in type 2 diabtes. J clin Invest: 109 : 1321

57. Conway B, Miller RG, Costacou T, Fried L, Kelsey S, Evans RW, Orchard TJ. 2009. Adiposity and mortality in type 1 diabetes. Int J Obes (Lond); 33: 796-805 [PMID: 19451912 DOI: 10.1038/ijo.2009.75]
58. de Vries L. Bar-Niv M, Lebenthal Y, Tenenbaum A, Shalitin S, Lazar L, Cohen A, Philip M. 2014. Changes in Weight and BMI following the diagnosis of type 1 diabetes in Children and adolescents. Acta Diabetol; 51: 395-402 [PMID :24158774]
59. Gunawardana SC, Piston DW. 2012. Reversal of type 1 diabetes in mice by brown adipose tissue transplant. Diabetes; 61: 674-682 [PMID: 22315305 DOI: 10.2337/db11-0510]
60. Gunawardana SC, 2012. Adipose tissue, hormones, and treatment of type 1 diabetes. Curr Diab Rep; 12: 542-550 [PMID: 22814676 DOI: 10.1007/s11892-012-0300-9]
61. Gunawardana SC, Piston DW. 2013. Insulin-independent reversal of type-1 diabetes with brown adipose tissue transplants: involvement of IGP-1. International pancreas and Islet Transplant Association,: Abstract 244.

DOI: 10.18535/ijmsci/v3i9.1