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The Physiological Roles of Adipokines and Their Pathological Interventions

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ABSTRACT
The persistent increase in the global prevalence of obesity and associated co-morbidities has led to a great deal of research into the biology of adipocytes, the events that take place in them and in the physiological undertakings of people with obesity. There is significant evidence that a state of prolonged low-grade inflammation brought on in obesity triggers an occurrence of systemic metabolic dysfunction and other critical disorders. The primary organ for the storage of fats in the body is the adipose tissue. In addition to its role as an organ that stores energy, the adipose tissue also undertakes the function of secreting a number of adipokines which include cytokines, hormones and other inflammatory mediators, which exhibit both local and systemic effects, thereby serving as an endocrine organ. Leptin, adiponectin, resistin, chemerin, omentin, vaspin and visfatin are among some of the most prominently studied adipokines. The implications of these adipokines have been seen in various diseases such as obesity, cardiovascular dysfunctions,Type2 Diabetes Mellitus, autoimmune diseases and various other pathological conditions. The current review will shed light on the roles these adipokines play in normal physiological conditions and their involvement in pathophysiology of various metabolic, cardiovascular and inflammatory disorders.
Keywords:*Adipokines, Adiponectin, Leptin, Omentin, Obesity, Type 2 Diabetes Mellitus,*

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INTRODUCTION

Obesity and overweight, according to the WHO is defined as an abnormal accumulation of fats in the body. As per reports from the WHO, the number of individuals contracting with obesity has increased drastically in the past few decades. [1] Obesity has drawn a great deal of attention across the globe due to the contributions it can make in the pathogenesis of serious diseases like Type2 Diabetes Mellitus, hypertension, cancer and many more.[2]Obesity, which is characterized by astate of consistent positive energy balance, can occur due to various factors including genetic predisposition, environmental, social and physiological factors.[3] The excess nutrients in the body gets stored in the form of droplets of triglycerides in the adipose tissues, which ultimately results in the adipocyte hypertrophy, to an extent that the adipocytes become saturated and lose their ability to expand any further.[4]Paracrine substances secreted by the hypertrophic adipocytes, such as hormones and cytokines, aid in the assignment of the preadipocytes and encourage their differentiation into mature fat cells . [5]

By morphology, adipose tissue can be divided into subsets that are white, brown, beige and pink,each exhibiting a specialized function on the basis of their physiological distinction. Additionally, the white adipose tissue can generically be categorized according to the region it is situated, with subcutaneous and visceral being the two primary categories.[6] The pathogenic expansion and energy overload of white adipose tissue eventually leads to an increased accumulation of macrophages and proinflammatory agents into the adipocytes, all of which contribute to the clinical complications of obesity[7]suchas hyperlipidemia, insulin resistance[8], infiltration of inflammatory mediators [9]and increased risk of atherogenesis in patients.[10]

Although the fat tissue is the primary organ which stores energy in the body, it also functions as an endocrine organ, secreting several hormones, cytokines and chemokines(collectively termed as the adipokines) that undertake the regulation of distinct mechanisms including feeding behavior in the body. [11] The adipokines, a group of bioactive polypeptides which operate as paracrine and endocrine hormones, are produced by adipocytes. Their activity has been seen in several organs and they havea crucial role in managing a number of physiological activities, including blood pressure, endothelial

function, fat distribution, hunger and satiety, and inflammation. [12] The adipokines include adiponectin, chemerin, C1q/TNF-related protein (CTRPs) family with sequence similarity to 19 member A5 (FAM19A5), follistatin like-1, leptin, lipocalin-2, Nesfatin, omentin, Progranulin, resistin, retinol binding protein-4, secreted frizzled-related protein 5, secreted protein acidic and rich in cysteine (SPARC), vaspin, visfatin/PBEF/NAMPT, wingless-type inducible signaling pathway protein-1. [13].

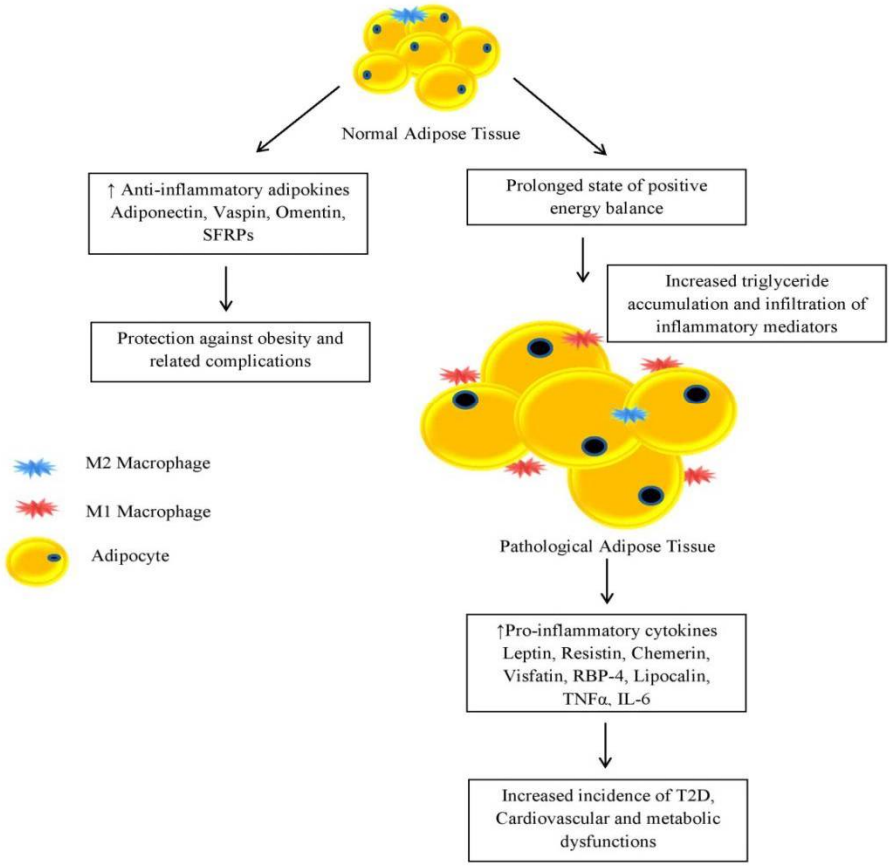

Fig: 1: Pathological changes in adipose tissue and the release of adipokines

LEPTIN

Leptin is a polypeptide hormone of molecular weight 160kDa,[14] which is produced mainly by the adipocytes in response to the extent offats accumulating in them. The discovery of leptin was done in the late 90's by the scientists Doug Coleman and Jeffery Friedmann. Doug Coleman in 1970's through a parabiotic study concluded the existence of a circulating satiety factor [15]and Friedmann in 1990's, cloned the *ob* geneusing positional cloning and identified the gene product which could potentially lower food intake and promote energy expenditure.[16] Friedmann then named this protein product 'leptin'(Greek: '*Leptos*':'thin'). [17]

The main site for leptin action and its anti-obesity effect lies in the hypothalamic regions, likearcuate nucleus, and dorsomedial hypothalamus. [18] Leptin exerts its action on two sets of neurons having potentially antagonistic action, first set being the Proopiomelanocortin neurons (POMC) and cocaine and amphetamine regulated transcript neurons (CART) and second set being the Neuropeptide (NPY) and agouti-related peptide neurons (AgRP), which exhibit anorexigenic and orexigenic actions respectively. [19]

The Proopiomelanocortin is a precursor protein, which yields Melanocyte stimulating hormone, β-endorphins and corticotrophins. By binding to the melanocortin receptors in the brain, melanocyte stimulating hormone and corticotrophins tend to be regulate appetite and food consumption. [20]The intervention of leptin in obesity is associated not just with a petite regulation, but with the regulation of energy expenditure in the body by sympathetic modulations and brown adipose tissue thermogenesis too. [21] Leptin exerts its action mainly by acting on the long-form leptin receptor-b (LepRb). [22] Other forms include the short isoform (LepRa, LepRc, LepRd, LepRf) and the soluble isoform (LepRe). [23]Once bound to its receptor leptin exerts action by variousintracellular signaling pathways like theInsulin

Receptor Substrate-1 (IRS-1), JAK2/STAT3 pathways, Wingless type (Wnt)/ β-Cantenin and Transforming growth factor-βto regulate appetite, energy expenditure, glucose homeostasis and other inflammatory responses.[24][25] Leptin signaling lowers food intake while enhancing energy expenditure in leptin-sensitive people to maintain the energy reserve sizes', however, low levels of leptin result in an increase in food intake while reducing energy usage.[26]Despite higher levels of leptin in obese people, leptin's anorexigenic impact is less effective. This is often due to the acquirement of resistance to leptin in circulation. Genetic mutations, impaired leptin delivery across the BBB (Blood Brain Barrier), attenuated downstream signaling, inflammatory mediators [25][27] or a dysfunction in the leptin receptor structure can also result inleptin insensitization and further aggravation of obesity. [28]

Though leptin was first identified as a crucial metabolic regulator, it has also been implicated in immunity and inflammatory responses. Leptin in conditions like obesity contributes to an inflammatory state, particularly a low grade one and aggravates the likelihood of contracting obesity related comorbidities. [29]The role of leptin has been seen in various autoimmune disorders like systemic lupus erythematous, [30]rheumatoid arthritis,[31] osteoarthritis, [32]multiple sclerosis,[33][34] asthma,[35][36]Parkinson' disease.[37]and breast cancer.[38]The potential role that leptin can play in the development of breast cancers was studied in leptin deficient mice, wherein the results indicated that lack of leptin could prevent tumor growth. [39][40] Insulin sensitivity is greatly affected by the levels of circulating leptin and people with genetic deficiency or mutation of leptin are seen to be contracting with insulin resistance and intolerance to glucose, implicating the part leptin playsin the progression of Type2 Diabetes Mellitus. Elevated leptin levels result in a low-grade systemic inflammation which in turn leads to a diversity of cardiovascular diseases such as dilated cardiomyopathy, coronary heart disease and congestive heart failure, however, the part that leptin plays in cardiovascular abnormalities is still controversial. [41]

ADIPONECTIN

Adiponectin is a proteinaceous adipokine consisting 244 amino acids, and a molecular weight of 30kDa. It is also known as "the adipocyte compliment related protein" and is coded by the AdipoQ gene, which is located at thechromosome locus 3q27. The fat tissues are the main secretors of adiponectin, however other cell types like the myocytes, endothelial cells, osteoblasts, placental tissue and liver parenchymal tissue are also seen to be eliciting this function. Several membrane proteins associated with the endoplasmic reticulum, such as thedisulfide-bond anoxidoreductase-like protein (DsbA-L),Endoplasamic reticulumoxidoreductase 1-La (Ero1-La) and Endoplasmic Reticulum resident protein 44 (ERp44), strictly regulate the production and release of adiponectin from adipose tissue. [42] AdipoR1, AdipoR2and T-cadherin are the main receptors identified for adiponectin action, of which the AdipoR1 receptors are expressed in all tissues but majorly in skeletal muscles while AdipoR2expressed mostly by the liver. T-cadherin is found to be binding high molecular weight adiponectin and is seen to be exhibiting cardioprotective activity. Activation of pathways like the AMPK, SIRT-1, PPARα and intracellular calcium pathways are seen as a result of adiponectin binding to its receptor which modulate glucose tolerance, insulin sensitivity and exercise endurance. [43]

Low level of adiponectin has been reported in people with obesity. Moreover, adiponectin is seen to be exhibiting a protective action in type2 diabetes mellitus and other cardiac, hepatic and renal disorders. Adiponectin, by its renal action, was seen to be improving conditions of albuminuria and diabetic nephropathy and ameliorating harmful effects of angiotensin II. Adiponectin in the liver by inhibiting sterol regulatory element binding transcription factor-1 (SREBP-1) and activation of PPARα led to decreased triglyceride accumulation and incidence of hepatic steatosis.[44] The cardioprotective effect of adiponectinwas associated with the reduction of ROS and TNF levels, as well as the activation of AMPK and COX-2. Under physiological conditions, adiponectin causes eNOS to produce more NO, which has a positive impacton cardiac function, but under pathological conditions, which reduces NO release, encouraging heart damages. Low levels of adiponectin have been implicated in obesity, type2 diabetes mellitus, ovarian and prostate cancer. Administration of recombinant adiponectin resulted in improved levels of circulating insulin indicating improvements in insulin production and secretion. Adiponectin also is seen to be correcting states of resistance to insulin and also insulin sensitivity by elevating hepatic expression of enzymes involved in gluconeogenesis like glucose-6-phosphate. Fatty acid translocase production is stimulated by adiponectin, which promotes the transport of fatty acids into muscle cells. Adiponectin regulates lipid metabolism by enhancing fatty acid transport and β-oxidation in muscle cells, suppressing hepatic lipogenesis, and boosting adipose tissue's storage function. As a result, it causes a drop in circulating lipid levels and lowers lipid levels in the body. Adiponectin also has ability to ameliorate the differentiation of cells in pancreatic and colon cancer. [45]

RESISTIN-

During his research on the anti-diabetic drugs 'the glitazones,'Steppan et al. made the discovery of resistin."Resistance to insulin" is where the word "resistin" comes from.Various cells involved in immunity like the macrophages, granulocytes and monocytes are seen to be producing resistin. Additionally, hematopoietic stem cells, the skeletal muscle system, the spleen, digestive system, pancreas, thymus, uterus, and placenta were all found to have this protein. By controlling the expression of the signal pathway inhibitor, resistin affects how leptin function is inhibited. There is proof that adipose tissue with increased concentrations of this protein develops insulin resistance. Patients with T2D have higher resistin mRNA levels than healthy individuals. Resistin has the capacity to bind the JAK-STAT signal pathway's antagonistic regulators, the suppressor of cytokine signal proteins (SOCS). Resistin has an effect on insulin activity in adipocytes, and SOCS may promote insulin resistance by inducing resistin.The contributions of resistin was also reported in the etiology of several cardiovascular diseases and resistin also serves as a potential biomarker for diseases like atherosclerosis, Ischemic heart disease and atrial fibrillation. Other implications of resistin have been in renal function impairment, Asthma, Crohn's disease and stromal tumor in breast cancer. [46]

CHEMERIN-

Chemerin is an inflammatory chemokine which exhibits in-vivo autocrine, paracrine and also endocrine activities. The Retinoic acid receptor responder 2 or the Rarres2 encodes this protein and it was identified for the first time in the retinoic acid-responsive gene in psoriatic lesions of the skin which indicated the immunomodulatory effect of chemerin. Previously, a precursor of 163 amino acids called chemerin was produced in mammalian cells. The C-terminal cleavage leads to the activation and deactivation of the protein. Three major receptor types have been identified for the action of chemerin: two GPCR receptors: CMKLR1 and GPR1 receptor, and the Chemokine [C-C motif] receptor like-2 (Ccrl-2), a silent, non-signalling chemokine receptor. Chemerin has higher affinity for the CMKLR-1 receptor than the GPR1 receptor. The Ccrl-2 is involved in concentrating chemerin for CMKLR1 interaction. The presence of these receptors has been seen in the brain, cardiovascular and reproductive systems, indicating the involvement chemerin has in diverse physiological functioning's of the body and also in disease states. The concentration of chemerin is found to be greater in the white adipocytes rather than the brown adipocytes which states that adipogenesis is affected by chemerin and not thermogenesis. A significant relation between levels of chemerin in increased BMI and hip-waist ratio has also been observed which indicates that chemerin is associated with visceral fat accumulation and resistance to insulin. Chemerin also contributes to obesity associated hypertension by its action on CMKLR1 receptors which bring about vasoconstriction and the promotion of vascular smooth muscle cell proliferation. [47]

VASPIN-

The visceral adipose tissue derived serpine is a 45kDa protein which is coded by the SERPINA12 gene present on chromosome 14 (14q32.1). It is made up of 395 amino acids and is expressed in the visceral and subcutaneous fat tissue, pancreas, stomach, cerebrospinal fluid, hypothalamus and ovaries. Vaspin has binding affinity to the cell surface glucose-regulated protein-GRP78 (78kDa) and under endoplasmic reticulum stress the GRP78 is translocated from the Endoplasmic reticulum to the plasma membrane. Both intracellular and cell surface receptors were identified, of which the intracellular receptors facilitate polypeptide transfer, maintain calcium ion homeostasis and regulate the efflux of these ions from the endoplasmic reticulum to mitochondria. The cell surface receptors are seen to be involved in the proliferation of cells and their survival. Increased expression of vaspin and increased serum concentration is seen in insulin resistance and obesity. The level of vaspin is also influenced by other hormones. Women tend to exhibit higher vaspin levels than men and their level in pubertal girls has also been reported to be higher. Studies involving the expression and activity of vaspin in the hypothalamus and pituitary indicate that vaspin brings about asuppression of appetite by the inhibition of neuropeptide Yneurons and upregulation of the Proopiomeanocortin neurons. Vaspin affects the adipose tissue and causes a decrease in leptin, resistin and TNF-α level but increases the GLUT4 and adiponectin expression. It also causes for an increase in the preadipocytes differentiation and lipid accumulation by increasing expression of PPARγ, C/EBPα ad C/EBPβ. Vaspin increases the m-RNA expression of IRS-2(insulin receptor substrat-2) and also enhances insulin secretion. It tends to downregulate NFκB and prevents the inflammation of pancreatic cells. Due to its serpin activity, vaspin also prevents insulin degradation by inhibiting kallikrien7. The involvement of vaspin has also been implicated in male germ cell steroidogenesis, oocyte maturation, PCOS, Gestational Diabetes Mellitus, hypo and hyperthyroidism. [48]

VISFATIN-

Visfatin is a 52kDa protein and an adipocytokine which is derived from the Pre-B-cell-colony enhancing factor gene (PBEF). It is widely expressed in the visceral fat tissue, leucocyte of peripheral blood cells, adipose tissue macrophage, hepatocyte and skeletal muscles. Visfatin is a proinflammatory adipocytokine,

and the adipose tissue macrophages are predominant secretors of visfatin. Through a process dependent on HIF1a (hypoxia-inducible factor 1a), obesity associated hypoxia increases visfatin levels in adipocytes. HIF1a is a transcription factor that accumulates in hypoxia and is crucial for hypoxic state adaption. Visfatin's two HREs (hypoxia response elements) are bound by HIF1a, which causes an increase in Visfatin expression. Visfatin has also been indicated in childhood obesity and has been reported to have beneficial effects on lipid profile. Visfatin has affinity for the insulin receptors, and exhibits non-competitive insulin mimetic activity by binding to a site different on the insulin receptor and thereby contributes to the regulation of serum glucose levels. [49]

OMENTIN-

Omentin is a 313 amino acid containing 34kDa protein which exists in two homologs forms, with Omentin-1 being the one with greater clinical significance. Omentin is coded by genes situated on the chromosome 1q21.3 and its expression is seen mainly in the visceral andepicardial fat tissues and additionally in the small intestine, intestinal Paneth cells, the colon, thymus, airway and intestinal goblet cells, ovary, and testis. Not sufficient information about the omentin receptors and the signaling cascades that follow them are available, however it is postulated that the cell surface receptor might either be of carbohydrate or glycolipid nature. A negative correlation has been stated between the levels of omentin-1 and resistance to insulin, haemoglobin A1c body mass index, saturated fat intake, serum total cholesterol and leptin levels systolic blood pressure, while adiponectin levels, very low-density lipoprotein particle size and high-density lipoprotein cholesterol concentrations, are seen to be positively correlated. Omentin also exhibits protective effect against atherosclerosis and myocardial hypertrophy and also brings about vasodilation by activation of eNOS. Omentin-1 expression in gastric cancer is related with decreased degree of invasion and metastasis, but not with the size or the location of these tumors. However, positive relation between tumor differentiation, the expression of a gene responsible for tumor suppression‘the CDX2’ (a homebox transcription factor) and levels of omentin is seen. Omentin-1's elevated expression in gastric cancer is thus intimately linked to its clinicopathological characteristics and may prove to be a helpful marker for the prognosis of gastric cancer. Omentin-1 concentrations are also seen to be low in women with Gestational diabetes and preeclampsia. [50]

Other Adipokines-

Several other adipokines such as the FSTL-1, SPARC, SFRP5, CTRPS, FAM19A5, WISP1, Progranulin, Lipocalin, Nesfatin, RBP-4 and PAI-1 have been stated in obesity and other related metabolic diseases.

SPARC- The 32-kDa matricellular glycoprotein Secreted protein acid and rich in cysteine, which binds calcium,is encoded by the SPARC gene at the location of 5q31-q33 on the human chromosome. It is also sometimes referred to as BM-40 or osteonectin and is mostly expressed when tissues go through changes such as tissue repair and remodeling. Adipose tissue and skeletal muscles are two tissues where SPARC is expressed, and it affects a number of metabolic and remodeling processes. The SPARC gene is identified to be an exercise-induced gene and it has been noted that SPARC deficiency is associated with lower physical activity and reduced mobility related energy expenditure. SPARC plays a crucial part of the extracellular matrix; its lack decreases the extracellular matrix (mesangial cells) rigidity and would result in extracellular matrix remodelling (SPARC-deficiency-induced extracellular matrix remodelling) that would increase the adipocytes' capacity to grow. This is particularly in the subcutaneous adipose cells where SPARC expression is rather prominent than within the visceral adipose tissue. Since the SPARC has tendency to bind to various extracellular matrix components like vitronectin and collagen type IV and undertake extracellular matrix remodeling tissues like the cardiac tissue, peripheral neurons, and lungs and even in tumors, it can serve as a target for regulating related pathologies and developing potential therapeutics. [51]

FOLLISTATIN LKE-1-Follistatin like-1 (FSTL-1), found insubcutaneous fat tissues, heart and lungs is a glycoprotein belonging to the SPARC family. FSTL-1 is seen to be acting ona variety of receptors including the DIP2A (disco-interacting protein 2 homologue A) receptors. Implications of FSTL-1 have been seen in cardiovascular pathologies like myocardial infarction, acute coronary disease, in inflammatory conditions such as Sjorgen’s syndrome and in asthma. FSTL-1 levels are seen to be elevated in overweight and obesity. [52]

WISP1- the wingless-type inducible-signaling pathway protein-1 is largely the subset of "matricellular proteins," which are extracellular matrix proteins with major modulatory rather than structural roles in cell growth. The fat tissues along with other tissue types like the neuronal cells, myocytes, hepatocytes, lungs and osteoblasts express this protein. Studies have stated the part WISP1 plays in a wide range of diseases, such as T2DM, and in obesity, both of which exhibited elevated concentration of WISP1 in the circulation. WISP1 also serves are an indicator for systemic inflammation, adipogenesis and tissue inflammation. [53]

SFRP-5 –The next set of adipokine, the secreted frizzled-related protein-5, possesses an affinity for the frizzled transmembrane receptor family. The protein acts as by competitively inhibiting the Wnt5a (wingless type family member 5a) which plays a part in inflammatory responses, and cellular function like proliferation and differentiation. The SFRP5 are expressed in the duodenum, pancreas, stomach, gall bladder, adrenal and prostate glands.Studies have stated that decreased plasma levels of SFRP-5 are implicated in obesity and cardiovascular diseases and that SFRP5 plays role in insulin sensitization and restoration of pancreatic islet-β cell function. [54]

LIPOCALIN-2 –Lipocalin-2, also referred to as siderocalin,uterocalin or neutrophil gelatinase-associate lipocalin is novel glycoprotein adipokine which is contains 198 amino acids and a gene on chromosome 9 at locus 9q34.11 codes for the same.LCN-2 was first isolated at inflammation sites from the neutrophil granules and later the expression was studied in various healthy tissues, including the thymus, prostate, small intestine, lung, kidney, bone marrow, liver and non-cancerous breast duct. LCN-2 is expressed in the diseased condition while not being present in the healthy the colon, testes, ovary, brain, heart, skeletal muscle, or spleen. Though a clear mechanism linking LCN-2 with obesity and diabetes are not yet derived, LCN-2 is seen to play roles in adipogenesis and insulin resistivity and also in energy metabolism. Moreover, obese and diabetic individuals exhibit elevated levels of plasma LCN-2. [55]

NESFATIN-1 –Obtained from Nucleobindin, the precursor protein, Nesfatin-1 is an 82 amino acid protein, which was first detected in the paraventricular nucleus of the brain. Later the presence of the protein was studied in other peripheral regions like the ovaries, adipose tissue, cardiomyocytes, pancreatic beta cells of which the stomach was the most abundant source. Nesfatin through its central action on the various brain regions has shown to be an effective anorexigenic agent. Nesfatin also exhibits positive implication in obesity such as reduction of weight gain due to increased expression of the UCP-1and reduction in gastric emptying time. Nesfatin also leads to an increase in levels of GLP-1 resulting in reduced blood glucose levels. In the cardiovascular system Nesfatin is seen to be play a role increased incidence of hypertension and reduced cardiac contractility. [56]

PROGRANULIN- Progranulin (PGRN; molecular weight of 88 kDa with 593 amino acid) also known by the names granulin, proepithelin, acrogranin or PC cell-derived growth factor (PCDGF), is a secretory glycoprotein and is coded by a gene on human chromosome 17q21.32. Epithelial cells, neurons, microglial cells, macrophages, neutrophils, and dendritic cells all produce PGRN and it is minimally expressed by non-proliferating epithelial cells like lung or kidney epithelial cells but strongly expressed in rapidly dividing epithelial cells like keratinocytes and intestinal crypt epithelial cells.Numerous chronic inflammatory and autoimmune disorders, including rheumatoid arthritis, COPD, psoriasis, inflammatory bowel disease, systemic lupus,systemic sclerosis exhibit increased local PGRN expression and its serum levels. Inherited deficiency of progranulin is also implicated as a causative for dementia in Alzheimer's disease. Expression of progranulin following a high-fat containing diet administration was seen to be increased in the liver and fat tissues. Progranulin is indicated in insulin resistance occurring due to obesity, and it is also seen to be leading to an increase in the expression of enzymes for gluconeogenesis like phosphoenolpyruvate-carboxykinase and glucose-6-phosphatase. Progranulin is also expressed in the hypothalamic nuclei wherein it causes a suppression of the orexigenic AgRP and neuropeptide Ythat reduce food intake, indicating its role in obesity. [57]

RBP-4 - Retinol binding protein-4 is a basically a protein for the transport of hydrophobic molecules majorly retinol or vitamin A. This protein is made up of 201 amino acids and possesses a molecular weight of 21kDa. The expression of the protein is seen to be the highest in the liver followed by the fat tissues. Two major cell surface receptors, the STRA6 ('stimulated by retinoic acid6') and STRA6-L('stimulated by retinoic acid 6 like') have been identified for the action of RBP4, which bring about the bi-directional transport of retinol across the cell membrane. Since RBP-4 is associated with the transport of retinol, its deficiency can result in vision disturbance and impairment of embryonic development. As an adipokine, the expression of RBP-4 was seen to be elevated in visceral fat tissue in obesity and increased RBP-4 is seen to be associated with reduced insulin sensitivity. Adipose tissue lipolysis is also facilitated by RBP-4 expressed in the adipocytes which enhances the level of circulating fatty acids and contributes to hepatic steatosis. Studies have also indicated positive correlation between levels of RBP-4 and systolic and diastolic blood pressure. Antagonizing RBP-4 had effects on its secretion of hepatic cells and also improved insulin sensitivity. [58]

FAM19A5- FAM19A5 (Family with sequence similarity to member A5) was identified initially as a secretory product from the brain however; later studies proved that the adipose tissues showed a greater expression of FAM19A5 than the brain, indicating its adipokine nature. Significant evidence correlating immune responses and FAM19A5 levels are available. Inflammation induced TNFα levels tend to downregulate the levels of FAM19A5. FAM19A5 also been studied for its inhibitory effects on RANKL-

osteoclastogenesis. However, the role of FAM19A5 in obesity and other metabolic dysfunctions still remains contradictory. [59]

CTRP- CTRP or the C1q/TNF related proteins are a family of 15 member proteins secreted by the adipocytes. The CTRP share great structural similarity with adiponectin of which CTRP 9 shares the greatest homology. Implications of the CTRP's have been studied in various pathologies. It has been stated that the CTRP's play a positive role in T2DM by improving sensitivity to insulin, enhancing glucose uptake by GLUT4 translocation and AMPK activation. The involvmentof CTRP in cardiovascular and metabolic diseases still remain to be elicited where over expression of certain CTRP's like CTRP5, CTRP6, CTRP7 showed detrimental effects in obesity and cardiovascular diseases whereas others like CTRP9 exhibit cardioprotective action. [60]

CONCLUSION

Adipokines, the polypeptide secretory product of the adipose tissue have been subjected to extensive research in the past few years. The pleiotropic actions of these adipokines were seen to be having both beneficial and detrimental effects in various metabolic, cardiovascular and immune disorders. However, our knowledge of the exact relationships and mechanisms underlying these effects is still at infancy and further research in this direction can facilitate the identification of potential biomarkers, therapeutic and diagnostic agents for the management and treatment of a broad spectrum of diseases and disorders.

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