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Review Article

Current Understanding of Adipokines and Adipose Tissue: Roles and Functions

Jennifer J Brown[1,2]* and Vanessa Fiaud[3]

[1]*Elizabeth City State University, Elizabeth City, North Carolina, United States*

[2]*Old Dominion University, Norfolk, Virginia, United States*

[3]*West Texas A&M University, Canyon, Texas, United States*

***Corresponding Author:** Jennifer J Brown, Elizabeth City State University, Elizabeth City, North Carolina, United States.

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Abstract

Obesity rates and cardiometabolic diseases are on the rise in developing countries, giving cause for concern as metabolic syndrome and type 2 diabetes are becoming more prevalent. Changes in the roles of adipose tissue paired with sharp increases in BMI have drawn attention to the secretory effects of adipocytes and adipokines on human physiology. This new realm of research targets revealing relationships between adipose tissue and its function as an endocrine organ and processes relating to inflammation, disease, and health. Research on adipose tissue storage locations, commonly studied adipokines and their affects, and novel peptides are presented. Nutrition, medication, and exercise as potential interventions are discussed.

Keywords: *VAT; SAT; Beige (Brite) Adipose Tissue; Adipokines; Adiponectin; FGF21; IL-6; Leptin; Nesfatin; Resistin; Retinol Binding Protein-4 (RBP4); TNF-α; Visfatin; Omentin; Apelin; Chemerin*

Adipose tissue as an endocrine organ

More than a century ago, increased weight status was viewed as a sign of wealth and health status, while recent studies from the second half of the century have revealed strong links between this "once elite" status and chronic illnesses [1,2]. Although those more recent studies have highlighted the unhealthy effects of obesity, Hippocrates (460 BC-370 BC) had already drawn attention to the relation between obesity, infertility and early mortality [3]. Developed countries are experiencing epidemic growth rates in obesity and increased weight status, giving rise to a need to address this Increasing health concern [4]. Numerous reports and publications have been released since the publication of The Surgeon General's Call To Action To Prevent and Decrease Overweight and Obesity in 2001 to attempt to stimulate healthy behaviors in the population. The Surgeon General's Vision for a Healthy and Fit Nation (2010) [5,6] describes the health consequences of obesity, especially when present in early life. Risks associated with increased weight status include metabolic syndrome, insulin resistance, cardiovascular disease, liver issues, high blood pressure, lipid disorders, cancer, and impeded immune function [7-11]. Adipose tissue (AT) was once thought to be an inert, inactive tissue, that stored triacylglycerol and provided protection from heat loss [2]. Research indicates that AT dynamically and multi-functionally secretes biologically active peptides (adipokines) which exert physiological effects on endocrine, paracrine, and autocrine functions [8,12]. Major physiological effects are enacted through secretory products and include influences on lipid metabolism, energy storage and homeostasis [1,7,13]. Additional effects include impact on bone metabolism, steroid hormone conversion, coagulation, fibrinolysis hematopoiesis, immune system modulation, angiogenesis, kidney function, sexual

maturation, vasoconstriction, and vasorelaxation [1,7,13]. AT dysfunction initiates processes in the human body that set the stage for the development of these disease progressions, particularly insulin resistance, leading to type 2 diabetes, hypertension, and cardiovascular disease [14].

AT has now been studied and proven to contain many biologically active peptides [1] which have varying roles including pro and anti-inflammatory effects, insulin sensitizing effects, insulin resistance promoters, and other roles yet to be fully determined. Cytokines and associated proteins are of great interest and their research includes the study of peptides such as leptin, TNF-α (tumor necrosis factor a), interleukin-6 (IL-6), IL-8, IL-10 and MCP-1, the PAI proteins within the clotting system, ASP (acylation stimulating protein), adiponectin, adipsin and their associated proteins within the components of the complement system [2,8]. The reaching effects of AT extend into the proteins of the renin-angiotensin system, as demonstrated in angiotensinogen [1]. Lipid transport and metabolism regulation proteins, in addition to lipids themselves are also targets of the actions of AT as lipoprotein lipase, cholesteryl ester transfer protein and apolipoprotein E have been found to be affected by its actions. Resistin, apelin, and visfatin are affected as hormonally active proteins [15]. While not comprehensive by any means, the growing list of researched factors also encompasses RBP4, TGFβ, RANTES, and enzymes related to steroid hormone metabolism, as would be the case with P450, 17B-HSD, and 11B-HSD1 [8,16,17]. This paper reviews the fascinating information surrounding AT storage depots, the roles of white, brown, and beige (brite) AT, adipokines, adiponectin, FGF21, interleukin-6 (IL-6), leptin, nesfatin, resistin, retinol binding protein-4 (RBP4), TNF-α, visfatin, omentin, apelin and chemerin.

Storage depots and adipose tissue types

Storage depots

Body fat storage is variable from one individual to the next, but is divided into types generally known as subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT), with VAT known as ectopic fat and correlated with metabolic dysfunction [12]. VAT is further divided into 2 subcategories, omental adipose tissue (OAT) and mesenteric adipose tissue (MAT). VAT and VAT play key roles in health due to anatomical locations, even though their total depots combined only account for 15% of the body's fat storage [7,13]. If VAT, OAT and MAT dominate the midsection of an individual, the AT may encompass organs by covering and attaching in these localized areas, even sharing common vasculature, thus drainage into the liver may occur and products may be released into the hepatic portal vein, increasing the likelihood of developing conditions such as nonalcoholic steatohepatitis, known as NASH [18]. Secretions of "sick fat" influence processes such as glycogenesis, gluconeogenesis, and VLDL synthesis. Subcutaneous adipose tissue (SAT) accounts for approximately 85% of body fat but is spread all throughout the body, right underneath the skin. Obesity disrupts SAT's primary function and designs to act as a metabolic sink and free fatty (FFA) acids pool. This dysfunction is termed as lipodystrophy. Thus, increases in weight status may negatively affect the expression of SAT's abilities to act angiogenically. Perivascular fat is AT with endothelial anti-contractile properties and is considered ectopic fat that responds to nitric oxide availability. This dependence on endothelial pathways is correlated with reduced influence in obese states [12]. Adipocytes may double in size in response to excess energy intake, and as excess is accumulated, secretions from adipocytokines mediate a low grade inflammatory response, particularly within the liver and skeletal muscle [8]. The physiological effects created by increased, inflamed AT are termed adiposopathy, which has been linked to the negative cardiometabolic outcomes associated with AT that has become dysfunctional [7,13,19]. Booth., *et al.* points out that storage of extra AT within lower body compartments has been associated with protective effects within the body. Sanchez-Gurmaches and Guertin discuss similar findings and thus, when considering the impact of increased body mass due to AT [10]. In addition, Baltieri., *et al*. have discussed the protective role of perivascular adipose tissue through the control of endothelial function [20]. As such it would be wise to consider the regions where AT has accumulated rather than just total fat mass, since some areas seem to have more favorable metabolic effects [10]. Distinct types of adipose cells have been distinguished: white adipose cells (WAT), brown adipose cells (BAT) and brown in WAT (beige or brite), each with functional differences from the other [11].

White adipose tissue

White adipose tissue (WAT) has few thermogenic properties but provides shock absorption, is extensively distributed throughout the body, and acts both as a thermal insulator and temperature maintenance regulator [11]. WAT, in healthy individuals, is found distributed subcutaneously, within organs and muscle tissues throughout the body. This tissue type is unusually capable of accumulating excess energy and releasing it again when needed, growing to twice its size in order to accommodate excess fuel storage [2]. However, if the storage capacity is exceeded, as a result of chronical conditions, triglycerides may be deposited ectopically [21]. WAT's role in endocrine function relates to the influence of regulation of appetite, arterial blood pressure, clotting and fibrinolysis systems and insulin sensitivity [1]. Composed of a nucleus and cytoplasm which surrounds a large droplet, these adipocytes store and release free fatty acids.

Brown adipose tissue

Brown adipose tissue (BAT) is associated with thermogenesis and largely found in infants at birth [2]. Adults rarely exhibit these smaller diameter adipocytes, which tend to have densely packed mitochondria and extensively vascularized properties, from which they obtain their distinctive? color [2]. However, in recent studies, functional and inducible BAT, primarily located in the cervical, axillary, paraspinal regions and representing only 1 - 2% of the total fat, have been identified [22,23]. BAT has recently gained attention for its capacity beyond thermogenesis, with greater focus on its role as an endocrine organ [11]. Villarroya suggests that BAT's endocrine role is still somewhat of a mystery at this point but points out the apparent effects created in paracrine/autocrine functions that suggest an endocrine role. Transplantation of BAT offers notable evidence for consideration regarding the role it plays within the endocrine system by the targeted endocrine signals it releases, which was demonstrated by Gunawardana and Piston with rodent research that reversed symptoms of type 1 diabetes and normalized glucose levels [24].

Beige fat

This brown in white AT type represents a type of AT that is somewhat in between the other two types, and may have intermediate thermogenic phenotype properties [12,25]. Current research suggests increases metabolic health status with an increase in active beige or brite adipocytes, and therefore, interest has risen in recruiting and activating these thermogenic adipocytes. Vosselman and fellow researchers submit that stimulating the development of hyperplasia and hypertrophy in these cells may show promise in addressing obesity concerns and metabolic diseases [25,26].

Adipokines

General information

These peptides have a unique history and role in AT as an endocrine organ in that they were one of the leading factors in the field that led the way towards acceptance of this new role for fat tissue. Scherer., *et al.* and Zhang., *et al.* both performed research which highlighted the enriched expression of adipokines in AT, leading towards the affirmation of its new status [27,28]. This research highlights adipokine functional relationships with and between key organs that go well beyond skeletal muscle and into the realm of the liver, pancreas, brain, and other vasculature within the body. Its metabolic influence was established to key processes that are of great interest, including coagulation, blood pressure regulation, carbohydrate metabolism, lipid metabolism, inflammation, and relationships relating to eating and energy expenditure [16,27]. Some researchers would claim that the role of adipokines has become established, while others would claim that the mechanisms by which they maneuver their effect still remains unclear [17], yet links for adipokines within research would suggest key influences in vascular and inflammatory disorders, type 2 diabetes (T2DM), metabolic syndrome and cardiometabolic health disorders, all of which pave a path towards coronary heart disease. The major adipokines of study would include adiponectin, leptin, resistin, and retinol binding protein 4 (RBP4), increased release of inflammatory cytokines, tumor necrosis factor alpha (TNFα) and interleukin 6 (IL6).

When viewing the effects of these adipokines, it is the dysregulation of them that promotes unwanted side effects within the human body as they act upon key organs [16]. The hypothalamus, pancreas, liver, skeletal muscle, and overall vasculature of the human body respond to dysfunctional levels of adipokine release, leading the way towards overeating, inactivity, and systemic insulin resistance and dysfunctional cardiometabolic factors [19,29].

Adiponectin

Since adiponectin's discovery in scientific literature in 1995 by Scherer, much has transpired to define and redefine its physiological function both in healthy and obese human and animal studies [27]. It is structurally related to the complement 1q superfamily is composed of a carboxyl-terminal globular domain and amino-terminal collagenous domain and is related to collagen VIII and X [1,4,27]. Adiponectin's secretion and release is controlled by proteins EPp4 and Ero1-1Lx (and is almost exclusively secreted by AT [1,4]. This adipokine has been highlighted as a nuclear factor Kappa-light-chain-enhancer of active β-cells and a tumor necrosis factor inhibitor [16]. Positive roles have been established as it has an insulin sensitizing effect, working inversely of the processes that cause cardiometabolic health issues [30]. Adiponectin contrasts leptin in that it is expressed less in obese individuals than in lean individuals [1] with a strong negative correlation between its expression and fat mass, with the exceptions of newborns and under nutritioned individuals [4]. Adiponectin also varies in its expression depending on the sex (women tend to express higher levels than males), and adipose tissue depot location (visceral fat tends to have lower expression than subcutaneous) [31,32]. Weight loss generally increases levels and the expression of adiponectin. Plasma levels are typically lower in men than in women, in individuals with coronary artery disease, T2DM, and those experiencing essential hypertension. AdipoR1 and adipoR2 function as adiponectin's receptors, negotiating anti-inflammatory, anti-atherogenic and insulin sensitization properties and are expressed in tissue specific ways [1,2,4]. Both receptors are expressed in skeletal muscle, liver, and AT [33], but AdipoR2 has more dominant expression within the liver. Blood concentration levels of adiponectin do not fluctuate, suggesting that its levels are established by long-term changes within metabolism rather than acute events. It is unknown how leptin reaches the brain, but this energy expenditure regulator activates AMPK within the hypothalamus, and works with the leptin receptor ObR, affecting the stimulation of appetite and reduction of energy expenditure. Research indicates that adiponectin and leptin work reciprocally to create homeostasis within the body [2].

Fibroblast growth factor 21 (FGF21)

Formed in pre-adipocytes, and part of the FGF superfamily, this adipokine plays a role in adipogenesis [17,34]. Circulating levels of FGF21 show a negative correlation when examined with BMI; however levels are likely to be affected by exercise intervention or pharmacologically administration [35]. Several sites of FGF21 production include the pancreas, skeletal muscles, and the liver identified as the primary source of circulation. BAT has recently emerged as a production site for FGF21 and this information proves to be some of the most important evidence that is currently available to support BAT's place as an endocrine organ [11]. This powerful component of the FGF family promotes the oxidation of glucose in several sites within the human body such as the liver, WAT, pancreas, and limited activity in the CNS. Villarroya reports that, in rodent research, FGF21 has emerged as a protective factor, metabolically fighting against obesity and type 2 diabetes. Thermogenic activation appears to be the inducing factor to cause the production of FGF21 in brown fat. Inducement of restrictive diets such as fasting diets, ketogenic diets, or protein restrictive diets, along with bariatric surgery seems to favor the circulation of FGF21 in the liver [36]. Increased concentrations of FGF21 have been reported in research involving both children and adults who are obese [34], but this is somewhat puzzling due to contradictions in some research findings. Some propose that FGF21 predominantly asserts expression through autocrine means in WAT [11] and that FGF21 is most intensely expressed in beige or brite adipose tissue which is a bit of a mystery when higher expressions are present in obese individuals, as Bergmann and Sypniewska state [34].

Interleukin-6

The interleukin-6 (IL-6) adipokine has different roles it plays within AT and insulin secretion. Its levels are elevated in individuals with increased body mass, and a correlational relationship has been established between IL-6 and free-fatty acid concentrations in circulating plasma [4,37]. IL-6 is formed within AT itself and then launched into circulation within the body [16]. WAT is responsible for approximately one third of the production of IL-6, but stromal vascular cells play key roles, as these are where the majority of IL-6 is derived from. SAT produces 2 to 3-fold lower levels of IL-6 than omental fat [38]. Early research suggested that IL-6 acted as an insulin inhibitor by up-regulating SOCS3 expression and interfering with the regulated signal pathways for insulin secretion [39,40]. New research on IL-6's role in skeletal muscle reveals that it can enhance fatty acid oxidation and positively affect glucose uptake while improving and enhancing insulin [4,41]. Harwood reports that levels of VAT are the main contributing factor to the development of plasma concentrations in individuals facing extreme obesity [16]. Research suggests that IL-6 asserts a deregulatory role in carbohydrate and lipid substrate utilization, possibly creating greater risk for cardiometabolic disorders. These contrasts in research leave scholarly readers with a diverse pack of research to comprehend and mixed roles to sort through.

Leptin

The protein leptin, discovered in 1994, is a small peptide that is an inflammatory cytokine dominantly produced by AT and is often referred to as the "satiety hormone" [1,2]. Individuals who tend to be extremely obese with added hyperglycemia and extreme insulin resistance often also demonstrate a lack of leptin or leptin receptor [42]. Studies on leptin's structure and composition identify it as a class I cytokine, with six isoform receptors (ObR) spanning ObRa-ObRf, inclusive of long, short forms and unique termini [43]. OBRb takes action within the hypothalamus, where it helps to regulate energy homeostasis [2]. This process sets off a chain of events that activates proopiomelanocortin neurons, thereby initiating the release of a-melanocyte-stimulating hormone [1]. This creates the activation of type 4 melanocortin receptors (MC-4R) and is presumed to stimulate increased energy expenditure and promote reduced food intake, thereby contributing to weight management [1,2]. Leptin's key roles in literature focus on the regulation of appetite, food intake and energy expenditure, however, there are other roles that leptin is presumed to take part in. Examples of such roles include fertility, bone metabolism and expression in relationship to the hypothalamic-pituitary-gonadal axis [1].

The receptor for leptin is expressed in various systems in the body such as the central nervous system, peripheral tissues (hematopoietic and immune cells), which leads researchers to hypothesize of influences it may have that are not related to energy balance [2]. Leptin levels are thought to be positively correlated with levels of AT. Leptin levels rise in the human body as AT increases as an influence and are lower accordingly in more lean individuals or when fasting is present [44]. Morioka found that leptin had an independent association with flow-mediated dilation measures in overweight individuals, but not in the lean group that was studied. Leptin's expression relates to insulin production, rising and falling accordingly with high or low levels of insulin, or responding with increases to glucocorticoids, acute infections, and proinflammatory cytokines. Decreases in leptin may occur when exposed to cold, adrenergic stimulation, growth hormone, and melatonin or in smokers. Leptin may participate in the development of cardiovascular disease through the pathogenesis of atherogenesis, inflammation, endothelial dysfunction, stimulated platelet aggregation, vascular smooth muscle cell proliferation and migration [1,44]. Produced in greater amounts by SAT rather than VAT, higher levels of leptin are usually found in females who tend to carry additional SAT in comparison to VAT. An alternate explanation for high levels of leptin include advanced kidney disease, which often produces four times the normal level of leptin, even after adjusting for age, race, sex, smoking, alcohol, BMI, diabetes, hypertension, and cholesterol [44].

Nesfatin

The adipokine Nesfatin is secreted in brain tissue, β−cells and AT and acts centrally to produce reductions in appetite, influences glucose metabolism, obesity, and is supposed to affect gonadal function [8,45,46]. Nesfatin decreases with increased weight status, obesity,

T2DM, polycystic ovary syndrome (PCOS), and generalized anxiety disorders [45,47]. Recent research has highlighted the benefits of exercise to increase the levels of Nesfatin-1 [48,49]. As energy expenditure regulation is critical for weight management, nesfatin-1 seems to play an important role in the process [50]. Incidentally, Yuan and colleagues, *et al*. have shown that an increase in core body temperature resulted from an increase in nesfatin-1 through the uncoupling protein 1 (UCP1) located in the brown adipose tissue [51]. While UCP1 is mainly found in infants and almost undetectable in adults, the activation of this protein, either through temperature or diet modifications, appears to play a role in thermal regulation more than body composition. In research, reduced levels of nesfatin are present in people with higher BMI and higher body fat percentages [52].

Resistin is a small polypeptide with structure similar to adiponectin and is secreted by macrophages in WAT, immune cells and in other sites within the body [7,8]. Increased expression occurs when inflammation is present and it is stimulated by lipopolysaccharides, Il-6, hyperglycemia, and hormones relating to growth and the gonads [2] and this peptide is associated with impaired glucose tolerance and insulin action [7]. This adipocytokine increases insulin resistance by acting on adipocytes themselves while also promoting increased hepatic gluconeogenesis [2]. A key point to consider is that circulating resistin does not seem to directly relate to actual weight or BMI, but instead, this adipokine is likely to be more highly expressed in inflamed states [7]. Resistin stimulates the production of vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1) and monocyte chemoattractant protein-1(MCP-1) [2,16], thereby promoting endothelial dysfunction, which is likely why researchers suggest that it contributes to chronic low-grade inflammation [7].

Retinol-binding protein-4 (RBP4)

RBP4 is a member of the lipocalin transport protein family and is primarily secreted in the liver and secondarily, in AT [17]. This blood protein transports retinal and was reported in 1995 to act in the same manner as a WAT adipokine by acting as a signal transmitter to vital tissues, including the liver [11]. Retinol plays a key role with this protein, as 90% of the amount available for circulation is bound to it and 10% remains present in unbound form [17]. It is not uncommon for RBP4 to be elevated in those with increased weight or obesity conditions within mouse model research and expression of this protein is regulated by macrophage and adipocyte factors. TNF-α imposes a down-regulation effect on this protein in humans, while leptin is likely to cause increases in RBP4. Controversy has risen within research regarding the role RBP4 plays due to new findings related to activation of expression in association with thermogenic activity in BAT. Villarroya reports that the role of RBP4 is not completely established, but former suppositions of links to reductions in insulin sensitivity are not likely [11].

TNF-α

This adipocytokine, first described in 1993, is primarily categorized in literature as pro-inflammatory and historically, was the first factor derived from adipocytes that led researchers to link increased weight status, T2DM, and inflammation [16,30], with upregulation of the amounts of this peptide forming in higher levels in AT as adiposity onsets [17]. There are, however, tissue specific roles that TNFα may play as an anti-inflammatory agent, and such may be the case in muscle tissue and its role in regeneration. Researchers originally thought that this cytokine was formed from adipocytes; however, it is now apparent that macrophages are responsible for the majority of TNFα secretion [8]. It exerts an immunomodulatory influence within the human body [16], and increases in TNFα are correlated with increases in weight status and insulin resistance markers and decrease accordingly with decreases in weight [8,17,30]. The release in the liver and skeletal muscles promotes insulin resistance through the activation of the hormone sensitive lipase (HSL) by the TNFα [53]. Research reports that the deletion or blockade of TNFα in rodents or associated receptors benefits insulin sensitivity and improvements in metabolic profile, but similar results have not been reproduced within obese humans with T2DM [17,54].

Visfatin, also known as pre-β cell colony-enhancing factor (PBEF), is produced by visceral fat tissue or VAT, and SAT in smaller quantities [2,8]. Its major functions relate to energy metabolism and immunity. It is currently viewed as a pro-inflammatory adipocytokine, as its properties stimulate the expression of TNF-α and Il-6 and leukocytes. Involved in NAD biosynthesis, it exerts influence on NAD+/NADH

dependent enzymes and cell energy metabolism [2]. It exerts influence on insulin properties by acting as an insulin mimetic and binding to insulin receptors to activate them [16]. Circulating levels of Visfatin increase when kidney dysfunction occurs [1]. Mixed research findings cloud the role of this adipokine as some literature suggests associations with β-cell deterioration [55] and others report reverted β-cell dysfunction [17, 56].

New adipokines to consider

Omentin

This adipokine is secreted by omental AT and has been found to increase insulin sensitivity, but decreases in expression with the onset of obesity [8,16,46]. Due to its positive effects as an anti-inflammatory agent and glucose homeostasis, omentin has gained attention more recently in research [12]. It exists in known research in two isoforms: omentin 1 and omentin 2, with omentin 1 representing the circulating form of this adipokine that reported to positively affect insulin sensitivity [8,57]. This peptide is suggested to be an anti-inflammatory adipokine which acts positively in the body by inhibiting the expression of TNFα's influence on the formation of adhesion molecules in endothelial tissue and inhibition of p38 and JNK pathways [58,59]. Research thus far indicates a similar role for omentin as for adiponectin; as weight is reduced, circulating omentin levels rise much in the same way [60]. Thus, reported effects in research suggest a positive role in inflammation reduction at this point in time.

Apelin and chemerin

Apelin is produced in a wide range of tissues, and is reported to have positive influence on important processes such as insulin sensitivity, glucose uptake, and lipolysis (within skeletal muscle) [8,61]. Human studies have shown an apelin increase with obesity and decreases with subsequent weight loss, suggesting resistance to apelin in study findings, which some researchers parallel to leptin and insulin [8]. Mice studies suggest that apelin increases complete fatty acid oxidation and mitochondrial oxidative capacity, while positively impacting the muscle of insulin-resistant mice [61] and some proport that this small peptide produces potent effects, some of which may be able to target T2D treatment [62]. Converse to some positive findings, apelin has also been implicated with a pro-inflammatory role, demonstrating close relationships with TNFα [63]. Chemerin is secreted by WAT and suggested to play a role in adipogenesis, adipocyte metabolism, and glucose homeostasis however, inflammatory qualities of this novel cytokine link it to TNFa and other pro-inflammatory actions such as macrophage adhesion [8,64]. Further investigation into literature links chemerin to positive findings, which indicates chemerin's relationship with markers of inflammation such as TNFa, IL-6, CRP, leptin, and resistin [65] but not as a cardiovascular risk factor. In contrast, Ali and Hadidi, found chemerin to be a predictor of atherosclerosis in Saudi subjects with metabolic syndrome and T2DM [66] and Rhee suggests that chemerin may link inflammation and atherosclerosis through its potential role in vascular remodeling, alteration of insulin sensitivity and potentially, a direct relationship on the inflammatory process by increasing nitric production [67].

Apelin and chemerin have been studied recently as novel cytokines, but not enough research exists to definitively state roles at present. Yu., *et al.* examined relationships between chemerin, apelin and found that their levels correlated with IR [68], but the possibility of compensatory reactions within the body exist and are suggested. Yu., *et al.* suggests that these high *in vivo* levels of these two cytokines could improve IR, however, even within Yu., *et al.*'s research, apelin has exhibited some insulin limiting properties, which could play a role in health concerns related to glucose metabolism. Researchers hypothesize that with the cooperation of other factors, apelin and chemerin may, indeed, have a hand in causing IR, rather than helping it. Support for this exists in Yu., *et al.*'s findings, where the two peptides correlated with oxidative stress inflammation, indicating potential involvement in the development of atherosclerosis, pathophysiology of obesity and T2D.

Possible interventions: Nutrition, medication and exercise

Nutrition

One potential intervention to interrupt the inflammatory process that occurs in AT includes examining and redefining nutrition to impact gut bacteria [8]. Piya points out that lower glycemic diets have been established in literature as viable means to reduce both the glucose absorption into the G.I. tract and subsequent glucose transport into body tissues, thus slowing the process and reducing hyperinsulinemia conditions within the body and creating an environment in which to calm inflammatory conditions. Studies examining dietary changes such as high fiber diet adherence have indicated positive impacts on glucose levels and subsequently lowered insulin levels, which in turns feeds the effect of lowering overall inflammation within the body systems [69,70]. Yu's research team found that the antioxidant effects of intravenous lipoic acid in concentrations of 600 mg daily created a reduction in serum levels of chemerin, apelin, and TNF-α in T2DM and T1DM subjects [68].

Medication

High lipid counts through lipotoxicity increase risk for cardiovascular events and conversely, addressing the problems through cholesterol lowering medication aid in reducing adipokine inflammation and cardiovascular risk [71]. Pioglitazone has proven to be more effective in comparison to Metformin in some research with T2DM patients [68]. The use of DM medications within the context of targeting the relief of the effects of sick fat should be considered if nutritional, lifestyle, and physical activity interventions are unsuccessful [19,29]. This includes anti-hypertensive agents, lipid altering drugs, PPAR-y, and anti-platelets, if nutritional, lifestyle interventions and physical activity are not successful.

Exercise

Reduced weight status has its own rewards, as with it a decrease in inflammation processes will occur if exercise is part of the weight reduction process. Kim., *et al*. and Oh., *et al.* report positive changes in inflammatory markers with a reduction in BMI [72-74]. Kim., *et al.* reports that both low and high intensity exercise creates an effective influence that reduces DM mediated inflammation processes in rat models, while also specifically causing a reduction of inflammatory markers such as IL-6, TNF-α and IL-1β in tissue-specific areas such as muscles [74]. Exercise has also been reported to remarkably increase adiponectin levels in individuals with obesity-related liver diseases within the context of a 12-week training program with no diet restrictions, ultimately reducing inflammation factors within the liver [72]. The effect of exercise itself is reported to have remarkable impact on reducing inflammation factors in individuals who undertake a long-term intervention, even if weight loss is not achieved [73]. This is especially something to consider in metabolic syndrome obesity-related conditions where treatments are needed to reduce chronic inflammation.

Conclusion

AT is an incredibly complex set of tissues which secrete a large variety of influencing factors that affect the human body in a multitude of ways. This endocrine organ responds to conditions with the body system in a dysfunctional fashion as AT grows in quantity, particularly in anatomical sites such as the midsection, where VAT is stored and imposes inflammatory influences on local organs such as the liver. When left undeterred and without intervention, AT easily takes on the qualities of "sick fat", producing larger amounts of inflammatory cytokines and by the dysfunctional state of obesity, will often lower production of protective factors. Literature is divided on many fronts regarding the roles of these biologically active peptides, but researchers seem to agree on certain common themes; the importance of researching the effects of AT, inflammation is linked to disease, and higher amounts of VAT places individuals at risk for cardiometabolic disease. Additionally, while each peptide is not currently confirmed to a precise pattern, the acknowledgment of their importance suggests that their place in future studies are likely, secure.

Nutrition, medication, and exercise are all likely to be effective in addressing the issues of "sick fat", each in their own way. Research supports the notion that we can make a difference in our health by adjusting nutritional habits, taking appropriate medications, and applying exercise. Low or high intensity aerobic activity resistance training should be implemented as personal interventions in healthy participants and individuals facing serious metabolic issues such as in DM, metabolic syndrome, and other cardiometabolic challenges.

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