



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Review article

Adipocytokines: Are they the Theory of Everything?

Pierre S. Maximus (M.D., MSc., PGDD) (Specialist Physician)*, Zeina Al Achkar (M.D.), Pousette F. Hamid (M.D.) (Department of Research), Syeda S. Hasnain (M.D.) (Department of Research), Cesar A. Peralta (M.D.)

California Institute of Behavioral Neurosciences and Psychology, United States

ARTICLE INFO

Keywords:

Adipocytokines
Protective effect
Immunoinflammatory
Pathogenesis
Disease progression

ABSTRACT

Introduction: Adipose tissue secretes various bioactive peptides/proteins, immune molecules and inflammatory mediators which are known as adipokines or adipocytokines. Adipokines play important roles in the maintenance of energy homeostasis, appetite, glucose and lipid metabolism, insulin sensitivity, angiogenesis, immunity and inflammation. Enormous number of studies from all over the world proved that adipocytokines are involved in the pathogenesis of diseases affecting nearly all body systems, which raises the question whether we can always blame adipocytokines as the triggering factor of every disease that may hit the body.

Objective: Our review targeted the role played by adipocytokines in the pathogenesis of different diseases affecting different body systems including diabetes mellitus, kidney diseases, gynecological diseases, rheumatologic disorders, cancers, Alzheimer's, depression, muscle disorders, liver diseases, cardiovascular and lung diseases.

Methodology: We cited more than 33 recent literature reviews that discussed the role played by adipocytokines in the pathogenesis of different diseases affecting different body systems.

Conclusion: More evidence is being discovered to date about the role played by adipocytokines in more diseases and extra research is needed to explore hidden roles played by adipokine imbalance on disease pathogenesis.

1. Introduction

Adipose tissue produces different bioactive substances e.g. peptides/proteins, immune molecules, and inflammatory mediators known as adipokines (if they are only produced by the adipose tissue) or adipocytokines (if mainly, but not only, produced by adipocytes). Adipokines function via autocrine, paracrine, and endocrine pathways [1].

Adipokines are secreted in response to different factors including

gut-derived substances, adipocyte hypoxia/death, and mechanotransduction (a process where the cell responds to mechanical stimuli in the form of electrochemical activity that may occur due to extracellular matrix remodeling) [2].

Inflammation which is associated with metabolic diseases (metainflammation) is reported in many tissues that play a role in nutrient regulation [2]. Xu and the team proved that inflammation of the adipose tissue initiate signaling pathways that were found to disturb the metabolic homeostasis [3]. However, inflammation was found to be

Abbreviations: A β , Amyloid β ; ACPA, Anti-citrullinated protein/peptide antibody; AdipoR 1&2, Adiponectin receptor 1 & 2; AIS, Adolescent idiopathic scoliosis; AMPA, Amino propionic acid receptors; AMPK, Adenosine monophosphate-activated protein kinase; APO-B, Apolipoprotein B; BCL-2, B cell lymphoma 2; c-AMP, Cyclic adenosine monophosphate; CAP-1, Cyclase-associated protein 1; CL-2, Chemokine ligand 2; CCL-4, Chemokine ligand 4; CKD, Chronic kidney disease; CRF, Chronic renal failure; CRP, C-reactive protein; CTRP-3, C1q TNF related protein 3; EPC, Endothelial progenitor cells; FABP-4, Fatty acid-binding protein 4; FGF, Fibroblast growth factor; HDL-C, High-density lipoprotein cholesterol; HOMA2-% β , Homeostatic model assessment- β ; HOMA2-IR, Homeostatic model assessment-insulin resistance; IGF-1, Insulin-like Growth Factor 1; IL-1, Interleukin 1; IL-6, Interleukin 6; IL-8, Interleukin 8; IL-12, Interleukin 12; IL-1 β , Interleukin 1 β ; IPA, Idiopathic pulmonary arterial hypertension; IVDD, Intervertebral disc degeneration; JAK, Janus kinase; LDL-C, Low-density lipoprotein cholesterol; MCP-1, Monocyte chemoattractant protein 1; MMP, Matrix metalloproteinase; MMP/TIMP, Matrix metalloproteinase to tissue inhibitor of metalloproteinase balance; mTOR, Mammalian target of rapamycin; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; NF- κ B, Nuclear factor kappa-light-chain-enhancer of activated B cells; NPY, Neuropeptide Y; PAH, Pulmonary artery hypertension; PAI-1, Plasminogen activator inhibitor 1; RBP4, Retinol binding protein 4; SERCA, Sarcoplasmic/endoplasmic reticulum calcium; STAT, Signal transducer and activator of transcription proteins; sVCAM-1, Soluble vascular cell adhesion molecule 1; TLR-4, Toll-like receptor 4; TNF- α , Tumor necrosis factor alpha; VEGF, Vascular endothelial growth factor.

* Corresponding author.

E-mail address: pmosaadraoof@dha.gov.ae (P.S. Maximus).

<https://doi.org/10.1016/j.cyto.2020.155144>

Received 20 January 2020; Received in revised form 8 May 2020; Accepted 21 May 2020

Available online 16 June 2020

1043-4666/ © 2020 Elsevier Ltd. All rights reserved.

useful for proper adipose tissue expansion and remodeling; which in turn has a useful effect on metabolism. This was proved through in vivo experiments done in three different mouse models under a high-fat diet challenge [4].

Adipokines are classified as either pro-inflammatory or anti-inflammatory. In the case of obesity, pro-inflammatory cytokines were found to be elevated at the expense of the anti-inflammatory cytokines [5], which promotes a persistent, low-grade inflammatory response [6]. This adipokine imbalance is thought to be the link between obesity, and different metabolic disorders or other diseases [5], for example, a chronic state of insulin resistance in obese individuals was found to be triggered by proinflammatory effect of macrophages [7]. For the aforementioned reasons adipokines are described as “regulators” of body homeostasis [6].

Since adipokines play important roles in the maintenance of energy homeostasis, appetite, glucose and lipid metabolism, insulin sensitivity, angiogenesis, immunity, and inflammation [8], a huge number of studies from all over the world proved that adipocytokines are involved in the pathogenesis of diseases affecting nearly all body systems which raises the question whether we can always blame adipocytokines as triggering, catalytic or modulating factors that take part in every disease that may hit the body (see Table 1).

In physics, a Theory of Everything [9] is a hypothetical single, scientific theory in physics that fully explains and links together all physical aspects of the universe [10]. The vast effect of adipocytokines on all body systems and many diseases pushes us to put the same hypothesis: are they the “Theory of Everything”, for medicine?

2. Methodology:

In the coming review, we scan the role played by adipocytokines in the pathogenesis of different diseases affecting different body systems. Data were collected from previous literature reviews run during the year (2019) and chosen through both PubMed and Google scholar search engines (around 33 papers). We excluded literature reviews, of languages other than English.

3. Discussion:

3.1. Adipocytokines and Metabolic Diseases

• Insulin Resistance/Diabetes Mellitus

Tumor necrosis factor α (TNF- α), resistin, and interleukin-6 (IL-6) are immunoinflammatory mediators that cause insulin resistance. On the other hand, adiponectin plays an opposite role by improving insulin sensitivity, increasing glucose uptake and decreasing liver gluconeogenesis, and suppressing pro-inflammatory mediators (IL-6) and TNF- α [11]. Due to obesity and subsequent adipose tissue inflammation, secreted immunoinflammatory cytokines slow down the insulin signaling chain and glucose translocation, leading to the onset of insulin resistance and diabetes [12], while the level of circulating adiponectin is reduced in obesity [13]. Omentin, another adipokine, induces adiponectin expression, resulting in increased insulin-mediated glucose uptake [14], the same effect was found with apelin [15].

Another immunoinflammatory mediator is interleukin-1 (IL-1), which works in two directions: to cause postprandial inflammation and postprandial increase in insulin secretion, besides, it stimulates glucose uptake in immune cells [16].

For resistin, it plays a role in reducing phosphorylation of insulin receptors when these receptors bind to insulin, which finally leads to insulin resistance and ends in blocking glucose translocation and a hyperglycemic state [17]. RBP4 (Retinol binding protein 4) serum level positively correlates with insulin resistance as well [18]. Similarly, leptin was found to affect glucose metabolism through the modulation of glucagon secreted by α -cells of the pancreas [19] while visfatin

concentration was related positively to the presence of diabetes [20] as it increased TNF followed by a TNF-mediated insulin resistance in adipocytes [21]

• Lipid Disorders

Adiponectin was positively and independently associated with higher HDL-C (High-density lipoprotein cholesterol) levels; which confirmed its protective role [22]. Marsche et al. found that hypo adiponectinemia was associated with reduced cholesterol efflux capacity in macrophages in adults, leading to less HDL formation [23]. Higher adiponectin level was also proved to be related to lower triglycerides [24]. On the other side, Singh et al. proved that plasma resistin levels positively correlated with triglycerides and serum apolipoprotein B (Apo B) levels [25], while visfatin correlated positively with total cholesterol, triglycerides and LDL-C (Low-density lipoprotein cholesterol) [26].

3.2. Adipocytokines and Kidney

• Renal Failure

Hyper-resistinemia correlated positively with a reduction in renal function [27]. In the same context, high levels of resistin were found in patients with chronic renal failure (CRF) and/or associated clinical complications [28]. Higher serum resistin levels were observed in elderly patients with advanced chronic kidney disease (CKD), particularly those on hemodialysis [29].

• Diabetic Kidney Disease

Kim et al. postulated that in kidneys of patients with diabetes, the expression of AdipoR1 and AdipoR2 (adiponectin receptors) significantly decreased when compared to those of controls, even at an early stage of chronic kidney disease and this decrease was maintained throughout the progression of all CKD stages compared to non-diabetic kidneys, and they related this down-regulation of adiponectin receptors to the increased insulin resistance in diabetes [30].

However, a marked increase in the level of adiponectin was recorded in patients with either chronic kidney disease (CKD) or end-stage renal disease (ESRD), and this upregulation of circulating adiponectin was explained as a compensatory mechanism to delay further renal injury [31].

3.3. Adipocytokines and Fertility/Gynecology

• Polycystic Ovary Disease

Serum adiponectin concentration in women with polycystic ovary was found to be less than control subjects [32]. Moreover, adiponectin concentration was found to decrease in follicular fluid [33] and granulosa cells [34] of this category of patients.

• Ovarian Cancer

Li et al. explained that epithelial ovarian cancer patients with AdipoR1-positive (Adipocytokines receptor-positive) expression survived longer than those with AdipoR1-negative expression [35]. Another study by Hoffmann et al. showed that adiponectin decreased epithelial ovarian cancer cell proliferation. They also postulated using AdipoR1 as a prognostic factor for the aforementioned epithelial ovarian cancer as it becomes down-regulated in the cells of this malignancy [36].

• Cervical and Endometrial Cancers

Table 1
Protective and Pathological Roles Played by Different Adipocytokines in Different Diseases.

Adipocytokine	Protective effect	Diseases involved
Adiponectin	Insulin resistance, diabetes & obesity [11–13], hyperlipidemia [22], diabetic kidney disease [30], polycystic ovary [32], ovarian cancer, gestational diabetes [39], systemic sclerosis [74], breast cancer [98], lung cancer [99], colon cancer [100], thyroid cancer [106], prostate cancer [108,109], glioblastoma [113], AIS [129], Duchene Muscular Dystrophy [132], pulmonary hypertension [149], obstructive sleep apnea [151], atherosclerosis [11], hypertension [158], preeclampsia [41–44], COVID-19 [164]	Cervical & endometrial cancer [37,38], joint inflammation [64], bone erosion in rheumatoid arthritis [65], SLE with renal involvement [87]
Adipsin		Systemic sclerosis with PAH [83], SLE with renal involvement [87]
Apelin	Insulin resistance, diabetes & obesity [11–13], rheumatoid arthritis [69], systemic sclerosis: protects against cardiac, renal, lung and skin complications [84]	
Chemerin		Systemic sclerosis: skin sclerosis, digital ulcers, kidney failure [79–81]
CTRP-3	Systemic sclerosis: prevents cardiac remodeling [86]	
CCL-2		Atherosclerosis [142]
CCL-4		IVDD [48]
FABP4		Osteoarthritis [72]
Ghrelin		IVDD [47], colon cancer [105]
IL-1		Immunoinflammatory (glucose metabolism) [16]
IL-6		Insulin resistance & diabetes [11,12], psoriasis [89], atherosclerosis [142], COVID-19 [164]
IL-8		Atherosclerosis [142]
IL-12		Immunoinflammatory (insulin resistance)[55]
IL-1β		Insulin resistance & diabetes in rheumatoid arthritis [56], psoriasis [90], atherosclerosis [142]
Interferon-γ		Atherosclerosis [142]
Leptin	Colon cancer [103], Alzheimer's [117], Obesity & lipodystrophy [125], SLE with renal involvement [87]	Osteoarthritis and rheumatoid arthritis [51,53], systemic sclerosis [75], psoriasis [91], hepatic affection [137–140], hypertension [152], atherosclerosis [143], interstitial pulmonary fibrosis [161]
Lipocalin-2		Osteoarthritis [68], psoriasis [94]
MCP-1		Monocytes infiltration (atherosclerosis) [134]
Nesfatn-1		Osteoarthritis [71]
Omentin	Insulin resistance, diabetes & obesity [11–13], rheumatoid arthritis [70], psoriasis [95], SLE [87], atherosclerosis [147]	Systemic sclerosis with PAH [82], increased appetite [126]
PAI-1		Psoriasis [93]
Progranulin		SLE [87], IVDD [45]
RBP4		Insulin resistance & diabetes [18], atherosclerosis [18]
Resistin	Alzheimer's [120]	Insulin resistance & diabetes [11,12], hyperlipidemia [25], kidney failure [27,28], gestational diabetes [40], IVDD [48], rheumatoid arthritis & osteoarthritis [47,58], systemic sclerosis complications: PAH, DVT, PE, digital ulcers [76,77], SLE with renal involvement [87], psoriasis [92], Alzheimer's [118], major depression & bipolar [122,123], NAFLD&NASH [125], diabetic microvascular complications [154], atherosclerosis and cardiovascular disease [155], sepsis [162], acute pancreatitis [163]
TNF-α		Insulin resistance & diabetes [11,12], psoriasis [88], vasoconstriction [156], atherosclerosis [142], coronary artery disease [144,145], COVID-19 [164]
Vaspin	Systemic sclerosis: protective effect against digital ulcers [82]	
Visfatin	Systemic sclerosis [78]	Insulin resistance & diabetes [17], hyperlipidemia [25], IVDD [46], rheumatoid & osteoarthritis [66], joint damage in rheumatoid arthritis [67], atherosclerosis [157], diastolic hypertension [20]

Abbreviations in the table: AIS, Adolescent idiopathic scoliosis; IVDD, Intervertebral disc degeneration; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steato-hepatitis; CTRP-3, C1q tumor necrosis factor related protein 3; FABP4, Fatty acid-binding protein 4; IL-1, Interleukin 1; IL-6, Interleukin 6; IL-8, Interleukin 8; IL-12, Interleukin 12; IL-1β, Interleukin 1β; MCP-1, Monocyte chemoattractant protein 1; PAI-1, Plasminogen activator inhibitor 1; RBP4, Retinol binding protein 4; TNF-α, Tumor necrosis factor alpha; PAH, Pulmonary artery hypertension; DVT, Deep venous thrombosis; PE, Pulmonary embolism; SLE, systemic lupus erythematosus; CCL-2, Chemokine legend 2; CCL-4, Chemokine legend 4.

Xie et al. reported that low adiponectin levels inhibited the proliferation of malignant cells of the cervix, inhibited proto-oncogenes e.g. c-myc, and Bcl-2 and activated apoptosis through enhancing the expression of p53 [37], the same effect was observed with endometrial cancer [38].

• Gestational Diabetes

A meta-analysis done by Bao et al. showed that circulating adiponectin levels during the first or early second trimester of pregnancy were significantly lower in women who developed gestational diabetes mellitus [39]. On the contrary, resistin level is positively correlated to gestational diabetes-related complications [40].

• Preeclampsia

Adiponectin deficiency was found to be involved in the process of preeclampsia and endothelial dysfunction [41]. Adiponectin role is the attenuation of the excessive inflammatory response in the wall of the blood vessels of the placenta through inhibition of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling (it is a protein complex that controls transcription of deoxyribonucleic acid (DNA) and cytokine production), decreasing CRP (C-reactive protein) and increasing nitric oxide [42] via activating endothelial nitric oxide synthase and inhibition of superoxide in endothelial cells [43]. Besides, adiponectin mediated the process of trophoblast invasion by modulation of MMP/TIMP (matrix metalloproteinase to tissue inhibitor of metalloproteinase) balance (this is a ratio between active extracellular

matrix proteolytic enzymes and their inhibitors) [44].

3.4. Adipocytokines and Rheumatology

• Intervertebral Disc Degeneration (IVDD)

It was found that progranulin (an adipokine) expression is increased in peripheral blood sera and disc tissues of patients with intervertebral disc degeneration (IVDD) and its blood levels were positively correlated with clinical symptoms [45]. Shi et al. reported increased levels of visfatin in nucleus pulposus tissue in more severe IVDD grades than less severe grades [46]. Finally, ghrelin similarly is proved to have a role in nuclear pulposus degeneration [47]. Another study by Li and colleagues showed that resistin binds to toll-like receptor 4 (TLR4) that leads to an increase in chemokine ligands 4 (CCL4) expression in nucleus pulposus cells, causing macrophage infiltration [48]. Human resistin also directly binds to adenylyl cyclase-associated protein 1 (CAP1) receptors in monocytes and white adipose tissue (the type of adipose tissue responsible for energy homeostasis) and ends in upregulating the transcription of inflammatory cytokines [49].

• Rheumatoid and Osteoarthritis

A study by Francisco et al. confirmed the expression of leptin receptors in osteoblasts and chondrocytes and described the role of leptin in cartilage catabolism and joint inflammation [50]. In a study by Scotecce et al., higher serum leptin levels have been linked to erosion of cartilage and bone in patients with osteoarthritis [51], while similar relations to synovitis, bone marrow lesions and osteophytes were there [52]. Similarly, a significant positive correlation exists between leptin levels and rheumatoid arthritis activity [53]. There are reports that the production of leptin in obese patients with rheumatoid arthritis was directly proportional to the ACPA (anti-citrullinated protein/peptide antibody) production thus suggesting that leptin may play a role in favor of the humoral response in rheumatoid arthritis [54]. As shown in a meta-analysis by Gajewski and colleagues, levels of circulating leptin are significantly higher in rheumatoid arthritis patients than controls [53]. Leptin plays a proinflammatory role by increasing the production of TNF- α , IL-6, IL-1 β , and IL-12, which, in turn, increase the expression of leptin in adipose tissue [55]. Moreover, IL-1 β is associated with insulin resistance in patients with rheumatoid arthritis. In a study by Ruscitti et al., rheumatoid arthritis patients with type 2 diabetes mellitus, treated with Anakinra- interleukin 1 receptor antagonist – showed a significant improvement in HOMA2-% β , HOMA2 – IR (markers of insulin resistance) and glucagon, in comparison with patients treated with TNF inhibitors. This proves the pathological role played by IL-1 β as a mediator of insulin resistance and type 2 diabetes mellitus in patients with rheumatoid arthritis [56].

Resistin, on the other side, stimulates the migration of endothelial progenitor cells (EPCs) into synovium via promoting vascular endothelial growth factor (VEGF), leading to rheumatoid arthritis angiogenesis [57]. Hyper-resistinemia was detected in patients with either rheumatoid arthritis or osteoarthritis [58] indicating the catabolic role of resistin [59]. Resistin was found to be inversely correlated with bone mineralization in patients with hip or lumbar spine fractures [60]. Leptin was found to increase the secretion of osteocalcin (a hormone that is important for bone mineralization) by osteoblasts while resistin was found to decrease this hormone [60]. The levels of resistin in serum showed a positive and independent association with both cartilage and bone marrow lesions observed on magnetic resonance imaging in patients with knee osteoarthritis [61]. In one study on knee osteoarthritis patients, the synovial fluid resistin level was found to be strongly related to joint dysfunction and weakly related to joint pain [62]. Other positive correlations have been observed between resistin and inflammatory factors (IL-6, matrix metalloproteinase-1 (MMP-1), and matrix metalloproteinase-3 (MMP-3) in synovial fluid of osteoarthritis

patients [63].

Adiponectin was found to induce the production of oncostatin M, a proinflammatory cytokine, in human osteoblasts [64]. On the other side, it increased bone erosions by promoting osteopontin production in the synovial tissue of patients with rheumatoid arthritis; this osteopontin subsequently recruits osteoclasts that end in bone erosion [65]. Regarding visfatin, it was found to be overexpressed in both plasma and synovial fluid of both rheumatoid and osteoarthritis patients [66]. In rheumatoid arthritis, serum visfatin levels correlated with radiographic joint damage [67]. Lipocalin-2, another adipokine in osteoblasts and chondrocytes in osteochondral junctions of osteoarthritis patients is considered a catabolic adipokine [68]. Researchers found a strong negative association between apelin and metalloproteinase-9 (MMP-9) level in patients with rheumatoid arthritis [69] while omentin, was associated with lower levels of MMP-3 in the same group of patients [70], which proves its protective role. Another adipokine, nesfatin-1 showed elevated levels in serum and synovial fluid of patients with knee osteoarthritis and had a significant association with disease severity [71], similarly plasma and synovial fluid levels of fatty acid-binding protein 4 (FABP4) are significantly higher in osteoarthritis patients than in healthy controls [72].

• Systemic Sclerosis

In human skin biopsy, adiponectin activity is measured in fibrotic tissue by measuring cellular phosphorylated adenosine monophosphate-activated protein kinase (AMPK) level, which was considerably decreased in patients with systemic sclerosis compared to healthy control [73]. Adiponectin is an anti-fibrotic molecule, and its decreased level seems to be one of the factors exacerbating fibrosis in the early stage of systemic sclerosis [74]. On the other hand, leptin acts as a chemokine that calls macrophages into adipose tissue, creating a local inflammatory niche in patients with systemic sclerosis [75].

Resistin, on the other side, induces smooth muscle cell proliferation and endothelial cell migration that may end in vasoconstriction in patients with systemic sclerosis. Resistin-induced angiogenesis and immune response potentiated the development of pulmonary artery hypertension (PAH) in this group of patients. Furthermore, there was a positive correlation between the prevalence of digital ulcers in patients with systemic sclerosis and higher resistin level [76]. Also, resistin level may be one of the factors explaining the higher prevalence of deep venous thrombosis and pulmonary thromboembolism in patients with systemic sclerosis than the general population [77]. It has been found also that an increase of visfatin level in serum, induced regression of skin lesions in late-stage diffuse cutaneous systemic sclerosis (i.e. greater than 6 years duration) [78]. Moreover, chemerin recruits dendritic cells and natural killer cells. These cells combat pathogens but may exacerbate inflammation in skin lesions and fibrosis in systemic sclerosis patients [79]. Chemerin seems to be involved in the development of skin sclerosis in the early stage of systemic sclerosis (disease duration < 1 year). There is a reported association between serum chemerin levels and the presence of digital ulcers in patients with systemic sclerosis [80]. As a clue of its effect on internal organs in patients with systemic sclerosis, chemerin level increased in patients with impaired renal function; this can be explained by direct damage of kidneys or reduced chemerin clearance in this group of patients [81]. On the other hand, serum vaspin levels were significantly decreased in systemic sclerosis patients with digital ulcers compared with those without, suggesting that there may be a protective role of vaspin against digital ulcer development [82]. Besides, an elevated serum level of adipisin in systemic sclerosis was associated with vascular involvement, especially pulmonary artery hypertension (PAH), and can be used as a potential biomarker for pulmonary artery hypertension [83]. Other studies reported that apelin may improve renal, myocardial, and lung fibrosis [84]. It was also shown that skin fibrosis is inhibited by apelin and that expression of apelin was significantly reduced in systemic

sclerosis [85]. Omentin level, on the other hand, was positively correlated with disease duration and right ventricular systolic pressure, so that it can be used as a biomarker of pulmonary vessel involvement in systemic sclerosis with pulmonary artery hypertension (PAH) [68]. CTRP-3 (C1q TNF related protein 3), another adipokine, showed a useful effect on the cardiovascular system through improving pathological vascular remodeling [86].

• Systemic Lupus Erythematosus

In a study by Chougule et al., adipokines were found to play a role in low-grade inflammation in systemic lupus erythematosus. There was found a statistically significant elevation in progranulin, adiponectin, and resistin levels in this group of patients compared to the control subjects. However, leptin and omentin showed a significant reduction. In patients with systemic lupus with renal involvement adiponectin, adiponectin, and resistin were significantly elevated, with a significant reduction in leptin. Adiponectin levels positively correlated with disease activity in contrast to leptin [87].

3.5. Adipocytokines and Psoriasis

A positive correlation between TNF- α and psoriasis severity was found [88]. IL-6 also increases in psoriasis [89], while interleukin 1 β (IL-1 β) showed a positive correlation with the psoriasis area and severity index (PASI), before and after treatment [90]. Leptin level [91], resistin level [92] and PAI-1 (plasminogen activator inhibitor-1) [93] increase in psoriasis. A significant increase in tissue lipocalin – 2 levels, but not in serum, was reported in psoriasis [94]. On the contrary lower levels of omentin-1 were reported in psoriasis [95].

3.6. Adipocytokines and Cancers

• Breast Cancer

In breast cancer, there is deregulation of adipokines secretion, so the net result is a reduction in the anti-proliferative effect of adiponectin on breast cells [96]. It was found that adiponectin is also able to regulate breast cancer cell migration and invasion [97]. Many studies recognized adiponectin as an inhibitor of cancer growth in estrogen receptor-negative breast cancers; while adiponectin at lower concentrations might promote tumor growth and progression in estrogen receptor-positive breast cancers [98].

• Lung Cancer

Adiponectin may exert an anti-proliferative effect through CREB down-regulation (CREB is a protein involved in tumorigenesis and stands for: cAMP response element-binding protein). It was proved that physiological concentrations of adiponectin significantly decreased cell proliferation of human lung adenocarcinoma [99].

• Colon Cancer

Low adiponectin serum concentration has been strongly associated with increased risk of colorectal adenoma or early colorectal cancer [100]. AdipoR1 and AdipoR2 are upregulated secondary to low adiponectin in colorectal cancer and are associated with positive lymph node involvement. AdipoR1 expression, specifically, is correlated to tumor size during the early stages of colorectal cancer [101]. Also, Choe and colleagues observed that a high expression level of mRNA of some of the genes related to the adipokine gene family had unfavorable outcomes in colorectal cancer patients and was related to the staging and mortality of this type of cancer [102].

Similarly, Paik and colleagues showed that a low tissue leptin expression in colorectal cancer tissue samples is associated with a more

advanced disease while a high tissue leptin expression is associated with a favorable overall survival and diseases free survival [103]. Jeong and the team also found that leptin expression was inversely associated with the lymph node stage [104], while ghrelin and its receptor were significantly higher in cancer cell lines and colorectal cancer tissue [105].

• Thyroid Cancer

A Study by Dossus and the team reported that low levels of circulating adiponectin which usually accompanies obesity, are associated with higher thyroid cancer risk [106]. The mechanism of this was discussed in an in vivo study performed on the thyroid cancer mouse model. In this study high fat diet was found to increase cell proliferation in the thyroid by two main mechanisms: either increasing cyclin D1 (a protein involved in enhancing cell cycle progression) and retinoblastoma protein phosphorylation (retinoblastoma protein is a tumor suppressor protein that is inhibited by phosphorylation) or chronic activation of JAK2/STAT3 signaling pathway (a chain of interactions between cell proteins involved in processes such as immunity, cell division, cell death and tumor formation) [107].

• Prostate Cancer

Several studies highlighted the inverse association between adiponectin and risk of prostate cancer or high-grade prostate cancer including a study by Tan and colleagues [108] and a meta-analysis by Liao and team [109]. Adiponectin was found to play a role in blocking carcinogenesis through inhibiting proliferation and promoting apoptosis. Adiponectin also inhibits vascular endothelial growth factor- α , thus inhibiting cancer neovascularization [110]. Adiponectin was also found to have anti-proliferation effects on prostatic cancer cells [111]. Adiponectin induces cell cycle arrest of prostatic epithelial and stromal cell lines and induces apoptosis by increasing caspase-3 and down-regulating of Bcl2 (B cell lymphoma) gene [112].

• Other Tumors

Porcile and colleagues showed that adiponectin inhibited cell proliferation of human glioblastomas cell lines, by inducing growth arrest within G1-phase. Moreover, they observed that adiponectin negatively regulated Insulin-like Growth Factor 1 (IGF-1) action abolishing the IGF-1-induced proliferation of glioblastoma cell lines [113].

4. Adipocytokines and Central Nervous System

• Effect on Hippocampus

Irving and Harvey investigated treating cultured hippocampal neurons with leptin and found that leptin has distinct effects on different AMPA receptor subunits (these are amino propionic acid receptors which are subtypes of glutamate receptors that act through affecting the flow of calcium and sodium ions, therefore responsible for fast synaptic transmission) [114]. Leptin is also involved in regulating neuronal morphology [115]. Alterations in hippocampal neuron morphology have also been reported in vivo following dietary changes in leptin levels [116].

• Effect on Alzheimer's Disease

Research tackling Alzheimer's disease indicates that leptin prevents the destructive effects of amyloid β ($A\beta$) plaque aggregation on hippocampal synaptic plasticity and glutamate receptor trafficking (receptor trafficking involves the intracellular movement of receptors from sites of synthesis to the plasma membrane, where they function). Furthermore, treatment with leptin prevents $A\beta$ -driven internalization

of the AMPA receptor subunit [117]. On the other side, High resistin levels were detected in the plasma of patients with Alzheimer's disease [118]. Increased activity of toll-like receptor 4 (TLR4), a resistin receptor, was observed both in the initial neurodegenerative processes in Alzheimer's disease and during disease progression [119]. However, neuroprotective effects of resistin in Alzheimer's disease were observed as well, including its role in avoiding oxidative stress, mitochondrial dysfunction, and cell vulnerability to stress [120].

• *Effect on Depressive Mood*

Disturbances in adipokine secretion play a role in the pathogenesis and clinical outcome of mental disorders in psychiatric patients, particularly with mood disorders [121]. Higher resistin levels in blood accompanied melancholic subtypes of major depressive disorders [122] and bipolar disorders [123] via inhibition of norepinephrine and dopamine release in the hypothalamus [124].

4.1. *Adipocytokines and Appetite*

Leptin was found to play a great role in controlling the fat content in the human body so that low leptin effect due to the mutant leptin gene or mutant leptin receptor gene, can end in obesity; moreover, some patients with obesity may have resistance to leptin action or relative leptin deficiency. Similarly, patients with lipodystrophies have low leptin levels. Leptin acts as an anti-obesity hormone that suppresses the appetite and hunger response through controlling the hypothalamus; meanwhile, it increases energy expenditure and has a potentiating effect on the thyroid axis and sympathetic activity. All of these mechanisms end in decreasing obesity and body fat [125]. On the other side, omentin expression in both visceral and subcutaneous adipose tissue was found to have a positive correlation with the expression of neuropeptide Y (NPY), the most potent appetite-stimulating peptide, suggesting that omentin may play a role in appetite modulation [126].

4.2. *Adipocytokines and Muscles*

Adiponectin has been shown to influence calcium entry in cardiomyocytes through the regulation of sarcoplasmic reticulum calcium ATPase (SERCA) function. This proves that adiponectin may be linked to muscle contractile function [127]. Moreover, adiponectin appears to play a role in regulating muscle mass and acts as a critical signal for muscle regeneration and suppression of proteolysis [128]. In a study of adolescent idiopathic scoliosis (AIS), a common form of spinal deformity, it was mentioned that adiponectin deficiency was involved in unequal bilateral development of the paravertebral muscles that ended in the development of lateral curvatures of the spine [129].

It has been highlighted that reductions in adiponectin and/or adiponectin signaling could mediate deleterious effects on skeletal muscle through decreasing autophagy, which is the natural way of degradation of the unnecessary or dysfunctional cellular components [130].

Adiponectin potentiates satellite cells, a population of stem cells involved in adult skeletal muscle regeneration following trauma [131]. Another study by Lecompte and colleagues proved that human dystrophic myotubes in Duchene muscular dystrophy show a local decrease in adiponectin secretion; also, they proved the presence of an anti-inflammatory effect of adiponectin in skeletal muscle [132].

The effect of training on skeletal muscles was discussed as well. It was found that training has a significant effect in reducing circulating CRP, leptin, and resistin levels. In a study by Marcelino-Rodriguez and the team, the risk of elevated serum resistin concentrations was lower in subjects who spent more than 20 min/day engaging in physical activity while the risk was higher in subjects with a more sedentary lifestyle [133].

Besides, significant correlations were observed between changes in abdominal fat mass after training and corresponding changes in MCP-

1(monocyte chemoattractant protein-1: a chemokine that regulates migration and infiltration of monocytes during infection), leptin, adiponectin, and resistin levels [134].

4.3. *Adipocytokines and Liver Diseases*

Dysfunction of adipocytes that occurs in obesity ends in the release of a large number of pro-inflammatory factors including leptin [135]. Leptin causes free fatty acids to move to the liver and skeletal muscles [136]; which in turn causes hepatic oxidative stress [137], inflammation [138], fibrosis [139] and hepatocyte apoptosis [140]. Resistin also plays a role in the pathogenesis of the non-alcoholic fatty liver disease (NAFLD) and its advanced variant, non-alcoholic steatohepatitis (NASH), through its role in inducing hepatic necro-inflammation and steatosis. For the aforementioned reasons resistin is considered a good predictive marker of NAFLD and NASH and is found to be strongly associated with the severity of hepatic inflammation and fibrosis [141].

4.4. *Adipocytokines and Cardiovascular Diseases:*

• *Atherosclerosis*

Beinsberger and colleagues suggested many immunopathogenic mechanisms that explain the role of systemic inflammation and adipocytokines in atherosclerosis. They highlighted an increase in endothelial-activating cytokines: interleukin IL-1 β , IL-6, tumor necrosis factor TNF- α , and interferon- γ ; this is followed by binding of neutrophils, monocytes, and platelets to the cytokine-activated endothelium leading to their activation. They added that this binding and activation of these 3 types of cells is potentiated by the neutrophil and monocyte chemokines, IL-8 and CCL2 (Chemokine ligand 2). All these reactions end in the formation of a proinflammatory medium that facilitates the formation of pro-atherogenic oxidized low-density lipoprotein [142]. Ghanous and colleagues clarified that leptin promotes hypertension, angiogenesis, and atherosclerosis [143]. A study by Kumari et al. showed a high TNF- α level in coronary artery disease [144]. Moreover, another study lead by the same author showed that TNF- α /IL-10 ratio may also be responsible for coronary artery disease in the north Indian population [145]. Aroor and colleagues highlighted that IL-6, through its inflammatory effect, plays a role in the endothelial cell damage within blood vessels that ends in vascular dysfunction and atherosclerosis [146]. Omentin, on the contrary, was found to have cardiovascular protective effect by slowing the atherosclerotic lesion formation [147].

• *Pulmonary Hypertension*

Adiponectin suppresses smooth muscle cell proliferation and migration. This occurs by the inhibition of the AMPK (5' AMP-activated protein kinase) activation and mTOR (mammalian target of rapamycin) activity; both are needed to boost cell growth and proliferation. The mTOR pathway promotes the induction of growth factors including fibroblast growth factor (FGF) that ends in vascular smooth muscle cell proliferation [148]. In the same context, a significant increase in adiponectin level was observed in patients with idiopathic pulmonary arterial hypertension (IPAH) than control subjects. Similarly, a significant correlation has been reported between serum adiponectin concentration and pulmonary vascular resistance [149], which was justified by the reflex increase in adiponectin level due to adiponectin resistance in this group of patients [150]. The same concept was proved by Domagała-Kulawik and colleagues who found that the median serum adiponectin levels were significantly reduced in obstructive sleep apnea patients compared to healthy subjects [151]. Other adipocytokines that were found to play a role in PAH accompanying systemic sclerosis include resistin [76], omentin [82], and adipisin [83].

• Other Vessels

Elevated levels of leptin are associated with hypertension; this was justified by chronic activation of the sympathetic nervous system by high levels of leptin [152]. Moreover, leptin resistance was documented in obesity-related hypertension due to reduced leptin receptor expression and altered signal transduction pathways especially in the elderly [153].

On the other side, elevated serum levels of resistin are associated with diabetic microvascular complications mediated by its role in causing endothelial dysfunction [154], besides, it has a significant role in atherosclerosis and cardiovascular disease occurrence [155]; this is explained as resistin mediates different molecular pathways e.g. angiogenesis, thrombosis migration, proliferation of the vascular smooth muscle cells and increasing MCP-1 and sVCAM-1 (soluble vascular cell adhesion molecule-1) expression in vascular endothelial cells [40]. TNF- α , another adipocytokine, has been shown to induce impairment of nitric oxide-mediated vasodilatation in the small arteries found in the visceral fat of obese patients, which ends in vasoconstriction [156]. RBP4 (retinol-binding protein 4) serum level also, positively correlates with pro-atherogenic conditions [18], while visfatin is markedly elevated during atherosclerosis and its elevation was associated with decreased levels of L-arginine and nitric oxide [157] and associated with higher diastolic blood pressure [20]. Finally, adiponectin was found to lower serum triglyceride levels that lead to improving endothelial dysfunction [24]; higher adiponectin meant less atherosclerosis and vascular disorders [11]. Besides, adiponectin inhibited the harmful effect of the renin-angiotensin system on the vascular system, ending in controlled blood pressure [158].

4.5. Adipocytokines and Interstitial Pulmonary Fibrosis

In idiopathic pulmonary fibrosis, measuring adiponectin/leptin ratio is helpful to assess the course of the disease and predict the intensity of fibrosis [159]. Leptin per se induces human lung fibroblasts to transdifferentiate into myofibroblasts, which are responsible for collagen production [160]. Also, leptin promotes pulmonary fibrosis by inhibiting autophagy [161].

4.6. Adipocytokines and Other Diseases

Higher resistin was associated with sepsis, septic shock [162], and acute pancreatitis (as a part of sepsis progression) [163] including disease severity, tissue necrosis, and clinical outcome.

4.7. Adipocytokines and COVID-19

A recent review from Italy following the COVID-19 pandemic highlighted the role played by both IL-6 and TNF- α as proinflammatory cytokines that may exacerbate the condition of the patient infected with COVID-19 through what is known as “cytokine storm”. This finding encouraged the use of IL-6 and TNF- α inhibitors as a possible mode of treatment for this group of patients. Besides, the study highlighted the role played by adiponectin to prevent the infection and improve the outcome of the patients through downregulating the inflammatory response and decreasing the production of IL-6 and TNF- α . The study indicated that during the cytokine storm there will be a decrease in adiponectin level and that diet containing ω 3- polyunsaturated fatty acid can increase the level of adiponectin, thus favors the resolution of inflammation [164].

5. Conclusion

In summary, adipose tissue can be recognized as an active endocrine organ. More adipocytokines are being discovered and considered as an important surrogate marker to reflect cardiovascular risk and other

metabolic abnormalities. Besides, they can be regarded as a good biomarker in atherosclerosis, systemic inflammation, obesity, and diabetes. It regulates inflammation from anti-inflammatory to pro-inflammatory state with immunomodulatory properties; in addition to playing an essential role in rheumatology and cancers. Association of adipocytokines with insulin resistance, obesity, lipid profile, tumor pathogenesis, endothelial dysfunction, etc. highlights the active role played by these factors in the pathophysiology of a wide spectrum of diseases and open a new window for novel clinical diagnostic and therapeutic options, which require larger clinical trials to explore all these implications. However, further and prolonged research is needed to answer the question of our article: if adipocytokines are the hidden theory behind every disease that may affect our body.

CRedit authorship contribution statement

Pierre Samir Maximus: Conceptualization, Methodology, Resources, Writing - original draft, Visualization. **Zeina Al Achkar:** Resources, Visualization. **Pousette F. Hamid:** Writing - review & editing, Supervision. **Syeda S. Hasnain:** Writing - review & editing, Project administration. **Cesar A. Peralta:** Resources.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] D. Azamar-Llamas, G. Hernández-Molina, B. Ramos-Ávalos, J. Furuzawa-Carballeda, Adipokine contribution to the pathogenesis of osteoarthritis, *Mediators Inflamm.* 2017 (2017) 1–26.
- [2] S. Reilly, A. Saltiel, Adapting to obesity with adipose tissue inflammation, *Nat. Rev. Endocrinol.* 13 (2017) 633–643.
- [3] X. Xu, A. Grijalva, A. Skowronski, M. van Eijk, M. Serlie, A. Ferrante Jr., Obesity activates a program of lysosomal-dependent lipid metabolism in adipose tissue macrophages independently of classic activation, *Cell Metab.* 18 (2013) 816–830.
- [4] I. Wernstedt Asterholm, C. Tao, T. Morley, Q. Wang, F. Delgado-Lopez, Z. Wang, P. Scherer, Adipocyte inflammation is essential for healthy adipose tissue expansion and remodeling, *Cell Metab.* 20 (2014) 103–118.
- [5] R. Shibata, N. Ouchi, K. Ohashi, T. Murohara, The role of adipokines in cardiovascular disease, *J. Cardiol.* 70 (4) (2017) 329–334.
- [6] N. Ouchi, J. Parker, J. Lugus, K. Walsh, Adipokines in inflammation and metabolic disease, *Nat. Rev. Immunol.* 11 (2) (2011) 85–97.
- [7] Y. Lee, P. Li, J. Huh, I. Hwang, M. Lu, J. Kim, M. Ham, S. Talukdar, A. Chen, W. Lu, G. Bandyopadhyay, R. Schwendener, J. Olefsky, J. Kim, Inflammation is necessary for long-term but not short-term high-fat diet-induced insulin resistance, *Diabetes* 60 (2011) 2474–2483.
- [8] A. Aguilar-Valles, W. Inoue, C. Rummel, G. Luheshi, Obesity, adipokines and neuroinflammation, *Neuropharmacology* 96 (2015) 124–134.
- [9] F. De Aquino, *Theory of Everything, Collected Articles* (1999).
- [10] S. Weinberg, *Dreams of a final theory: The scientist's search for the ultimate laws of nature*, Knopf Doubleday Publishing Group, 2011.
- [11] J. Petto, E. Santos, M. Motta, R. Teixeira-Filho, G. Santo, J. Ribas, A. Ladeia, Adiponectin: characterization, metabolic and cardiovascular action, *Int. J. Cardiovasc. Sci.* 28 (5) (2015) 424–432.
- [12] M. Lacerda, G. Malheiros, A. Abreu, Tecido adiposo, uma nova visão: as adipocinas e seu papel endócrino, *Rev. Cient FMC* 11 (2) (2016) 25–31.
- [13] A. Ghadge, A. Diwan, A. Harsulkar, A. Kuvalekar, Gender dependent effects of fasting blood glucose levels and disease duration on biochemical markers in type 2 diabetics: A pilot study, *Diabetes Metab. Syndr.* 11 (2017) 481–489.
- [14] C. Herder, D. Ouwens, M. Carstensen, B. Kowall, K. Huth, C. Meisinger, W. Rathmann, M. Roden, B. Thorand, Adiponectin may mediate the association between omentin, circulating lipids and insulin sensitivity: results from the KORA F4 study, *Eur. J. Endocrinol.* 172 (4) (2015) 423–432.
- [15] S. Xu, P. Tsao, P. Yue, Apelin and insulin resistance: Another arrow for the quiver? *J. Diabetes* 3 (2011) 225–231.
- [16] E. Dror, E. Dalmas, D. Meier, S. Wuest, J. Thévenet, C. Thienel, K. Timper, T. Nordmann, et al., Postprandial macrophage-derived IL-1 stimulates insulin, and both synergistically promote glucose disposal and inflammation, *Nat. Immunol.* 18 (3) (2017) 283–292.
- [17] W. Pinto, A função endócrina do tecido adiposo, *Rev. Fac. Ciênc. Med.* 16 (3) (2014) 111–120.
- [18] J. Mohapatra, M. Sharma, A. Acharya, G. Pandya, A. Chatterjee, R. Balaraman, M. Jain, Retinol-binding protein 4: a possible role in cardiovascular complications,

- Br. J. Pharmacol. 164 (8) (2011) 1939–1948.
- [19] K. Rehman, M. Akash, Z. Alina, Leptin: a new therapeutic target for treatment of diabetes mellitus, *J. Cell. Biochem.* 119 (7) (2018) 5016–5027.
- [20] C. Robinson, L. Tsang, A. Solomon, A. Woodiwiss, S. Gunter, M. Mer, et al., Nsfatin-1 and visfatin expression is associated with reduced atherosclerotic disease risk in patients with rheumatoid arthritis, *Peptides* 102 (2018) 31–37.
- [21] E. Gouranton, B. Romier, J. Marcotorcino, F. Tourniaire, J. Astier, F. Peiretti, J.-F. Landrier, Visfatin is involved in TNF α -mediated insulin resistance via an NAD (+)/Sirt1/PTP1B pathway in 3T3-L1 adipocytes, *Adipocytes* 3 (3) (2014) 180–189.
- [22] Y. Tomono, C. Hiraishi, H. Yoshida, Age and sex differences in serum adiponectin and its association with lipoprotein fractions, *Ann. Clin. Biochem.* 55 (2018) 165–171.
- [23] G. Marsche, S. Zelzer, A. Meinitzer, S. Kern, S. Meissl, G. Pregartner, D. Weghuber, G. Almer, H. Mangge, Adiponectin predicts high-density lipoprotein cholesterol efflux capacity in adults irrespective of body mass index and fat distribution, *J. Clin. Endocrinol. Metab.* 102 (2017) 4117–4123.
- [24] M. Kajikawa, T. Maruhashi, T. Matsumoto, Y. Iwamoto, A. Iwamoto, N. Oda, S. Kishimoto, S. Matsui, Y. Aibara, T. Hidaka, et al., Relationship between serum triglyceride levels and endothelial function in a large community-based study, *Atherosclerosis* 249 (2016) 70–75.
- [25] A. Singh, S. Tiwari, A. Gupta, K. Shukla, K. Chhabra, A. Pandey, A. Pant, Association of resistin with insulin resistance and factors of metabolic syndrome in north Indians, *Indian J. Clin. Biochem.* 30 (2015) 255–262.
- [26] S. Penumarthi, G. Penmesta, S. Mannem, Assessment of serum levels of triglycerides, total cholesterol, high density lipoprotein cholesterol, and low density lipoprotein cholesterol in periodontitis patients, *J. Indian Soc. Periodontol.* 17 (2013) 30–35.
- [27] M. Jamaluddin, S. Weakley, Q. Yao, C. Chen, Resistin: Functional roles and therapeutic considerations for cardiovascular disease, *Br. J. Pharmacol.* 165 (2012) 622–632, <https://doi.org/10.1111/j.1476-5381.2011.01369.x>.
- [28] C. Menzaghi, L. Salvemini, G. Fini, R. Thompson, D. Mangiacotti, R. Di Paola, E. Morini, M. Giorelli, C. De Bonis, S. De Cosmo, A. Doria, V. Trischitta, Serum resistin and kidney function: a family-based study in non-diabetic, untreated individuals, *PLoS ONE* 7 (2012) e38414.
- [29] A. Marouga, M. Dalamaga, A. Kastania, C. Kroupis, M. Lagiou, K. Saounatsou, K. Dimas, D. Vlahakos, Circulating resistin is a significant predictor of mortality independently from cardiovascular comorbidities in elderly, non-diabetic subjects with chronic kidney disease, *Biomarkers* 21 (2016) 73–79.
- [30] Y. Kim, J. Lim, M. Kim, E. Kim, H. Yoon, S. Shin, B. Choi, Y. Kim, Y. Chang, C. Park, The adiponectin receptor agonist AdipoRon ameliorates diabetic nephropathy in a model of type 2 diabetes, *JASN* 29 (2018) 1108–1127.
- [31] C. Lim, B. Teo, E. Tai, S. Lim, C. Chan, S. Sethi, T. Wong, C. Sabanayagam, Elevated serum leptin, adiponectin and leptin to adiponectin ratio is associated with chronic kidney disease in Asian adults, *PLoS ONE* 10 (2015).
- [32] S. Li, X. Huang, H. Zhong, Q. Peng, S. Chen, Y. Xie, X. Qin, A. Qin, Low circulating adiponectin levels in women with polycystic ovary syndrome: An updated meta-analysis, *Tumour Biol.* 35 (2014) 3961–3973.
- [33] T. Artimani, M. Saidijam, R. Aflatoonian, M. Ashrafi, I. Amiri, M. Yavangi, S. SoleimaniAsl, N. Shabab, J. Karimi, M. Mehdizadeh, Downregulation of adiponectin system in granulosa cells and low levels of HMW adiponectin in PCOS, *J. Assist. Reprod. Genet.* 33 (2016) 101–110.
- [34] R. Dehghan, M. Saidijam, M. Mehdizadeh, N. Shabab, M. Yavangi, T. Artimani, Evidence for decreased expression of APPL1 associated with reduced insulin and adiponectin receptors expression in PCOS patients, *J. Endocrinol. Investig.* 39 (2016) 1075–1082.
- [35] X. Li, Z. Yu, L. Fang, F. Liu, K. Jiang, Expression of adiponectin receptor-1 and prognosis of epithelial ovarian cancer patients, *Med. Sci. Monit.* 23 (2017) 1514–1521.
- [36] M. Hoffmann, J. Gogola, A. Ptak, Adiponectin reverses the proliferative effects of estradiol and IGF-1 in human epithelial ovarian cancer cells by downregulating the expression of their receptors, *Horm. Cancer* 9 (2018) 166–174.
- [37] L. Xie, Y. Wang, S. Wang, N. Wu, Y. Chen, J. Yan, Adiponectin induces growth inhibition and apoptosis in cervical cancer HeLa cells, *Biologia* 66 (2011) 712–720.
- [38] H. Moon, J. Chamberland, K. Aronis, S. Tseleni-Balafouta, C. Mantzoros, Direct role of adiponectin and adiponectin receptors in endometrial cancer: In vitro and ex vivo studies in humans, *Mol. Cancer Ther.* 10 (2011) 2234–2243.
- [39] W. Bao, A. Baecker, Y. Song, M. Kiely, S. Liu, C. Zhang, Adipokine levels during the first or early second trimester of pregnancy and subsequent risk of gestational diabetes mellitus: A systematic review, *Metabolism* 64 (2015) 756–764.
- [40] P. Codoner-Franch, E. Alonso-Iglesias, Resistin: insulin resistance to malignancy, *Clin. Chim. Acta* 438 (2015) 46–54.
- [41] Y. Song, J. Gao, Y. Qu, S. Wang, X. Wang, J. Liu, Serum levels of leptin, adiponectin and resistin in relation to clinical characteristics in normal pregnancy and preeclampsia, *Clin. Chim. Acta* 458 (2016) 133–137.
- [42] K. Miehle, H. Stepan, M. Fasshauer, Leptin, adiponectin and other adipokines in gestational diabetes mellitus and pre-eclampsia, *Clin. Endocrinol. (Oxf.)* 76 (2012) 2–11.
- [43] W. Zhu, K. Cheng, P. Vanhoutte, K. Lam, A. Xu, Vascular effects of adiponectin: Molecular mechanisms and potential therapeutic intervention, *Clin. Sci. (Lond.)* 114 (2008) 361–374.
- [44] N. Eleuterio, A. Palei, J. Rangel Machado, J. Tanus-Santos, R. Cavalli, V. Sandrim, Relationship between adiponectin and nitrite in healthy and preeclampsia pregnancies, *Clin. Chim. Acta* 423 (2013) 112–115.
- [45] S. Wang, J. Wei, Y. Fan, H. Ding, H. Tian, X. Zhou, L. Cheng, Progranulin is positively associated with intervertebral disc degeneration by interaction with IL-10 and IL-17 through TNF pathways, *Inflammation* 41 (2018) 1852–1863.
- [46] C. Shi, H. Wu, D. Du, H. Im, Y. Zhang, B. Hu, H. Chen, X. Wang, Y. Liu, P. Cao, et al., Nicotinamide phosphoribosyltransferase inhibitor APO866 prevents IL-1-induced human nucleus pulposus cell degeneration via autophagy, *Cell. Physiol. Biochem.* 49 (2018) 2463–2482.
- [47] W. Li, X. Wu, R. Qu, W. Wang, X. Chen, L. Cheng, Ghrelin protects against nucleus pulposus degeneration through inhibition of NF- κ B signaling pathway and activation of Akt signaling pathway, *Oncotarget* 8 (2017) 91887–91901.
- [48] Z. Li, X. Wang, H. Pan, H. Yang, X. Li, K. Zhang, H. Wang, Z. Zheng, H. Liu, J. Wang, Resistin promotes CCL4 expression through toll-like receptor-4 and activation of the p38-MAPK and NF- κ B signaling pathways: implications for intervertebral disc degeneration, *Osteoarthritis Cartilage* 25 (2) (2017) 341–350.
- [49] S. Lee, H. Lee, Y. Kwon, S. Lee, Y. Cho, J. Kim, S. Lee, J. Kim, et al., Adenylyl cyclase-associated protein 1 is a receptor for human resistin and mediates inflammatory actions of human monocytes, *Cell Metab.* 19 (3) (2014) 484–497.
- [50] V. Francisco, J. Pino, V. Campos-Cabaleiro, C. Ruiz-Fernández, A. Mera, M. Gonzalez-Gay, R. Gómez, O. Gualillo, Obesity, fat mass and immune system: Role for leptin, *Front. Physiol.* 9 (2018) 640.
- [51] M. Scotece, J. Conde, V. Lopez, F. Lago, J. Pino, J. Gomez-Reino, O. Gualillo, Adiponectin and leptin: New targets in inflammation, *Basic Clin. Pharmacol. Toxicol.* 114 (2014) 97–102.
- [52] C. Karvonen-Gutierrez, S. Harlow, J. Jacobson, P. Mancuso, Y. Jiang, The relationship between longitudinal serum leptin measures and measures of magnetic resonance imaging-assessed knee joint damage in a population of mid-life women, *Ann. Rheum. Dis.* 73 (2014) 883–889.
- [53] Y. Lee, S. Bae, Circulating leptin level in rheumatoid arthritis and its correlation with disease activity: A meta-analysis, *Z für Rheumatol.* 75 (2016) 1021–1027.
- [54] E. Gómez-Bañuelos, R. Navarro-Hernández, F. Corona-Meraz, P. Madrigal-Ruiz, B. Martín-Marquez, O. Pizano-Martinez, et al., Serum leptin and serum leptin/serum leptin receptor ratio imbalance in obese rheumatoid arthritis patients positive for anti-cyclic citrullinated peptide antibodies, *Arthritis Res Ther* 17 (1) (2015), <https://doi.org/10.1186/s13075-015-0850-8>.
- [55] M. Gajewski, J. Gajewska, P. Rzodkiewicz, E. WojteckaLukasik, Influence of exogenous leptin on redox homeostasis in neutrophils and lymphocytes cultured in synovial fluid isolated from patients with rheumatoid arthritis, *Reumatologia* 54 (3) (2016) 103–107.
- [56] P. Ruscitti, F. Ursini, P. Cipriani, M. Greco, S. Alvaro, L. Vasiliki, P. Di Benedetto, F. Carubbi, O. Berardicurti, E. Gulletta, G. De Sarro, R. Giacomelli, IL-1 inhibition improves insulin resistance and adipokines in rheumatoid arthritis patients with comorbid type 2 diabetes: An observational study, *Medicine* 98 (7) (2019) e14587.
- [57] C. Su, C. Hsu, C. Tsai, C. Huang, S. Wang, C. Tang, Resistin promotes angiogenesis in endothelial progenitor cells through inhibition of microRNA206: Potential implications for rheumatoid arthritis, *Stem Cells* 33 (2015) 2243–2255.
- [58] M. Filkova, M. Haluzik, S. Gay, L. Senolt, The role of resistin as a regulator of inflammation: implications for various human pathologies, *Clin. Immunol.* 133 (2009) 157–170.
- [59] T. Poonpet, S. Honsawek, Adipokines: Biomarkers for osteoarthritis? *World J. Orthop.* 5 (2014) 319–327.
- [60] A. Fisher, W. Srikusalanukul, M. Davis, P. Smith, Interactions between serum adipokines and osteocalcin in older patients with hip fracture, *Int. J. Endocrinol.* 2012 (2012) 684323.
- [61] K. Wang, J. Xu, J. Cai, S. Zheng, X. Yang, C. Ding, Serum levels of resistin and interleukin-17 are associated with increased cartilage defects and bone marrow lesions in patients with knee osteoarthritis, *Mod. Rheumatol.* 27 (2) (2016) 339–344.
- [62] J. Calvet, C. Orellana, N. Albinana Gimenez, A. Berenguer-Llergo, A. Caixas, M. Garcia-Manrique, C. Galisteo-Lencastre, et al., Differential involvement of synovial adipokines in pain and physical function in female patients with knee osteoarthritis. A cross-sectional study, *Osteoarthritis Cartilage* 26 (2) (2018) 276–284.
- [63] A. Koskinen, K. Vuolteenaho, T. Moilanen, E. Moilanen, Resistin as a factor in osteoarthritis: Synovial fluid resistin concentrations correlate positively with interleukin 6 and matrix metalloproteinases MMP-1 and MMP-3, *Scand. J. Rheumatol.* 43 (2014) 249–253.
- [64] C. Su, W. Lee, C. Hsu, T. Lu, L. Wang, G. Xu, C. Tang, Adiponectin induces oncostatin M expression in osteoblasts through the PI3K/Akt signaling pathway, *Int. J. Mol. Sci.* 17 (2016) 29.
- [65] J. Qian, L. Xu, X. Sun, Y. Wang, W. Xuan, Q. Zhang, et al., Adiponectin aggravates bone erosion by promoting osteopontin production in synovial tissue of rheumatoid arthritis, *Arthritis Res. & Therapy* 20 (1) (2018) 26.
- [66] M. Laigouillon, X. Houard, C. Bougault, M. Gosset, G. Nourissat, A. Sautet, C. Jacques, F. Berenbaum, J. Sellam, Expression and function of visfatin (Nampt), an adipokine-enzyme involved in inflammatory pathways of osteoarthritis, *Arthritis. Res. Ther.* 16 (2014) R38.
- [67] M. Nourbakhsh, M. Nourbakhsh, Z. Gholinejad, M. Razzaghy-Azar, Visfatin in obese children and adolescents and its association with insulin resistance and metabolic syndrome, *Scand. J. Clin. Lab. Invest.* 75 (2) (2015) 183–188.
- [68] A. Villalvilla, A. Garcia-Martin, R. Largo, O. Gualillo, G. Herrero-Beaumont, R. Gomez, The adipokine lipocalin-2 in the context of the osteoarthritic osteochondral junction, *Sci. Rep.* 6 (2016) 29243.
- [69] S. Gunter, A. Solomon, L. Tsang, A. Woodiwiss, C. Robinson, A. Millen, G. Norton, P. Dessein, Apelin concentrations are associated with altered atherosclerotic plaque stability mediator levels and atherosclerosis in rheumatoid arthritis, *Atherosclerosis* 256 (2017) 75–81.
- [70] C. Robinson, L. Tsang, A. Solomon, A. Woodiwiss, S. Gunter, A. Millen, G. Norton,

- M. Fernandez-Lopez, I. Hollan, P. Desseign, Omentin concentrations are independently associated with those of matrix metalloproteinase-3 in patients with mild but not severe rheumatoid arthritis, *Rheumatol. Int.* 37 (2017) 3–11.
- [71] Y. Zhang, X. Shui, X. Lian, G. Wang, Serum and synovial fluid nesfatin-1 concentration is associated with radiographic severity of knee osteoarthritis, *Med. Sci. Monit.* 21 (2015) 1078–1082.
- [72] C. Zhang, T. Li, K. Chiu, C. Wen, A. Xu, C. Yan, FABP4 as a biomarker for knee osteoarthritis, *Biomark. Med.* 12 (2018) 107–118.
- [73] R. Marangoni, Y. Masui, F. Fang, B. Korman, G. Lord, J. Lee, K. Lakota, J. Wei, P. Scherer, L. Otvos, T. Yamauchi, N. Kubota, T. Kadowaki, Y. Asano, S. Sato, W. Tourtellotte, J. Varga, Adiponectin is an endogenous anti-fibrotic mediator and therapeutic target, *Sci. Rep.* 7 (2017) 4397.
- [74] K. Lakota, J. Wei, M. Carns, M. Hinchcliff, J. Lee, M. Whitfield, S. Sodin-Semrl, J. Varga, Levels of adiponectin, a marker for PPAR-gamma activity, correlate with skin fibrosis in systemic sclerosis: potential utility as biomarker, *Arthritis. Res. Ther.* 14 (2012) R102.
- [75] L. Dib, M. Ortega, T. Melgarejo, S. Chapes, Establishment and characterization of DB-1: a leptin receptor-deficient murine macrophage cell line, *Cytotechnology* 68 (2016) 921–933.
- [76] Y. Masui, Y. Asano, K. Akamata, N. Aozasa, S. Noda, T. Taniguchi, T. Takahashi, Y. Ichimura, T. Toyama, H. Sumida, Y. Kuwano, K. Yanaba, Y. Tada, M. Sugaya, S. Sato, T. Kadono, Serum resistin levels: a possible correlation with pulmonary vascular involvement in patients with systemic sclerosis, *Rheumatol. Int.* 34 (2014) 1165–1170.
- [77] W. Chung, C. Lin, F. Sung, W. Hsu, W. Yang, C. Lu, C. Kao, Systemic sclerosis increases the risks of deep vein thrombosis and pulmonary thromboembolism: a nationwide cohort study, *Rheumatology* 53 (2014) 1639–1645.
- [78] Y. Masui, Y. Asano, S. Shibata, S. Noda, K. Akamata, N. Aozasa, T. Taniguchi, T. Takahashi, Y. Ichimura, T. Toyama, H. Sumida, K. Yanaba, Y. Tada, M. Sugaya, S. Sato, T. Kadono, A possible contribution of visfatin to the resolution of skin sclerosis in patients with diffuse cutaneous systemic sclerosis via a direct anti-fibrotic effect on dermal fibroblasts and Th1 polarization of the immune response, *Rheumatology* 52 (2013) 1239–1244.
- [79] M. Ah Kioon, C. Tripodo, D. Fernandez, K. Kirou, R. Spiera, M. Crow, J. Gordon, F. Barrat, Plasmacytoid dendritic cells promote systemic sclerosis with a key role for TLR8, *Sci. Transl. Med.* 10 (423) (2018) eam8458.
- [80] K. Akamata, Y. Asano, T. Taniguchi, T. Yamashita, R. Saigusa, K. Nakamura, S. Noda, N. Aozasa, T. Toyama, T. Takahashi, Y. Ichimura, H. Sumida, Y. Tada, M. Sugaya, T. Kadono, S. Sato, Increased expression of chemerin in endothelial cells due to Fl11 deficiency may contribute to the development of digital ulcers in systemic sclerosis, *Rheumatology* 54 (2015) 1308–1316.
- [81] S. Zylla, R. Rettig, H. Volzke, K. Endlich, M. Nauck, N. Friedrich, Serum chemerin levels are inversely associated with renal function in a general population, *Clin. Endocrinol. (Oxf.)* 88 (2018) 146–153.
- [82] S. Miura, Y. Asano, R. Saigusa, T. Yamashita, T. Taniguchi, T. Takahashi, Y. Ichimura, T. Toyama, Z. Tamaki, Y. Tada, M. Sugaya, S. Sato, T. Kadono, Serum omentin levels: a possible contribution to vascular involvement in patients with systemic sclerosis, *J. Dermatol.* 42 (2015) 461–466.
- [83] B. Korman, R. Marangoni, M. Hinchcliff, S. Shah, M. Carns, A. Hoffmann, R. Ramsey-Goldman, J. Varga, Brief report: association of elevated adipisin levels with pulmonary arterial hypertension in systemic sclerosis, *Arthritis. Rheumatol.* 69 (2017) 2062–2068.
- [84] S. Huang, L. Chen, L. Lu, L. Li, The apelin-APJ axis: a novel potential therapeutic target for organ fibrosis, *Clin. Chim. Acta* 456 (2016) 81–88.
- [85] Y. Yokoyama, A. Sekiguchi, C. Fujiwara, A. Uchiyama, A. Uehara, S. Ogino, R. Torii, O. Ishikawa, S. Moteji, Inhibitory regulation of skin fibrosis in systemic sclerosis by apelin/APJ signaling, *Arthritis. Rheumatol.* 70 (2018) 1661–1672.
- [86] M. Sawicka, J. Janowska, J. Chudek, Potential beneficial effect of some adipokines positively correlated with the adipose tissue content on the cardiovascular system, *Int. J. Cardiol.* 222 (2016) 581–589.
- [87] D. Chougule, M. Nadkar, K. Venkataraman, A. Rajadhyaksha, N. Hase, T. Jamale, S. Kini, P. Khadilkar, V. Anand, M. Madkaikar, V. Pradhan, Adipokine interactions promote the pathogenesis of systemic lupus erythematosus, *Cytokine* 111 (2018) 20–27.
- [88] A. Dilek, N. Dilek, Y. Saral, D. Yuksel, The relationship between severity of the disease and circulating nucleosomes in psoriasis patients, *Arch. Dermatol. Res.* 305 (2013) 483–487.
- [89] M. Rajappa, S. Rathika, M. Munisamy, L. Chandrashekar, D. Thappa, Effect of treatment with methotrexate and coal tar on adipokine levels and indices of insulin resistance and sensitivity in patients with psoriasis vulgaris, *J. Eur. Acad. Dermatol. Venereol.* 29 (2015) 69–76.
- [90] E. Tamilselvi, D. Haripriya, M. Hemamalini, G. Pushpa, S. Swapna, Association of disease severity with IL-1 levels in methotrexate-treated psoriasis patients, *Scand. J. Immunol.* 78 (2013) 545–553.
- [91] R. Robati, M. Partovi-Kia, H. Haghhighatkah, S. Younespour, F. Abdollahimajid, Increased serum leptin and resistin levels and increased carotid intima-media wall thickness in patients with psoriasis: is psoriasis associated with atherosclerosis? *J. Am. Acad. Dermatol.* 71 (2014) 642–648.
- [92] P. Gisondi, V. Lora, C. Bonauguri, A. Russo, G. Lippi, G. Girolomoni, Serum chemerin is increased in patients with chronic plaque psoriasis and normalizes following treatment with infliximab, *Br. J. Dermatol.* 168 (2013) 749–755.
- [93] G. Sigurdardottir, A. Ekman, M. Stahle, C. Bivik, C. Enerback, Systemic treatment and narrowband ultraviolet B differentially affect cardiovascular risk markers in psoriasis, *J. Am. Acad. Dermatol.* 70 (2014) 1067–1075.
- [94] H. El-Hadidi, N. Samir, O. Shaker, S. Oth, Estimation of tissue and serum lipocalin-2 in psoriasis vulgaris and its relation to metabolic syndrome, *Arch. Dermatol. Res.* 306 (2014) 239–245.
- [95] H. Turan, K. Yaykasli, H. Soguktas, E. Yaykasli, C. Aliagaoglu, T. Erdem, M. Karkucak, E. Kaya, T. Ucgun, A. Bahadir, Omentin serum levels and omentin gene Val109Asp polymorphism in patients with psoriasis, *Int. J. Dermatol.* 53 (2014) 601–605.
- [96] K. Avgerinos, N. Spyrou, C. Mantzoros, M. Dalamaga, Obesity and cancer risk: Emerging biological mechanisms and perspectives, *Metabolism* 92 (2018) 121–135.
- [97] Z. Jia, Y. Liu, S. Cui, Adiponectin induces breast cancer cell migration and growth factor expression, *Cell Biochem. Biophys.* 70 (2014) 1239–1245.
- [98] S. Andò, L. Gelsomino, S. Panza, C. Giordano, D. Bonfiglio, I. Barone, S. Catalano, Obesity, leptin and breast cancer: Epidemiological evidence and proposed mechanisms, *Cancers* 11 (2019) 62.
- [99] M. Illiano, E. Nigro, L. Sapio, I. Caiafa, A. Spina, O. Scudiero, A. Bianco, S. Esposito, F. Mazzeo, P. Pedone, A. Daniele, S. Naviglio, Adiponectin down-regulates CREB and inhibits proliferation of A549 lung cancer cells, *Pulm. Pharmacol. Ther.* 45 (2017) 114–120.
- [100] J. Saetang, T. Boonpipattanapong, A. Palanusont, W. Maneechay, S. Sangkhathat, Alteration of leptin and adiponectin in multistep colorectal tumorigenesis, *Asian Pac. J. Cancer Prev.* 17 (2016) 2119–2123.
- [101] C. Tae, S. Kim, S. Jung, Y. Joo, K. Shim, H. Jung, T. Kim, M. Cho, K. Kim, J. Kim, Involvement of adiponectin in early stage of colorectal carcinogenesis, *BMC Cancer* 14 (2014) 811.
- [102] E. Choe, J. Yi, Y. Chai, K. Park, Upregulation of the adipokine genes ADIPOR1 and SPPI1 is related to poor survival outcomes in colorectal cancer, *J. Surg. Oncol.* 117 (2018) 1833–1840.
- [103] K. Paik, I. Lee, Y. Lee, N. Sung, T. Kwon, Clinical implications of systemic inflammatory response markers as independent prognostic factors in colorectal cancer patients, *Cancer Res. Treat* 46 (1) (2014) 65–73.
- [104] W. Jeong, S. Baek, M. Kim, S. Kwon, H. Kim, Prognostic significance of tissue leptin expression in colorectal cancer patients, *Ann. Coloproctol.* 31 (6) (2015) 222–227.
- [105] A. Liu, C. Huang, J. Xu, X. Cai, Lentivirus-mediated shRNA interference of ghrelin receptor blocks proliferation in the colorectal cancer cells, *Cancer Med.* 5 (9) (2016) 2417–2426.
- [106] L. Dossus, S. Franceschi, C. Biessy, A. Navionis, R. Travis, E. Weiderpass, A. Scalbert, I. Romieu, A. Tjønneland, A. Olsen, et al., Adipokines and inflammation markers and risk of differentiated thyroid carcinoma: The EPIC study, *Int. J. Cancer* 142 (2018) 1332–1342.
- [107] N. Mitsiades, K. Pazaitou-Panayiotou, K. Aronis, H.-S. Moon, J. Chamberland, X. Liu, K. Diakopoulos, V. Kytarris, V. Panagiotou, G. Mylvaganam, et al., Circulating adiponectin is inversely associated with risk of thyroid cancer: In vivo and in vitro studies, *J. Clin. Endocrinol. Metab.* 96 (2011) E2023–E2028.
- [108] W. Tan, L. Wang, Q. Ma, M. Qi, N. Lu, L. Zhang, B. Han, Adiponectin as a potential tumor suppressor inhibiting epithelial-to-mesenchymal transition but frequently silenced in prostate cancer by promoter methylation, *Prostate* 75 (2015) 1197–1205.
- [109] Q. Liao, C. Long, Z. Deng, X. Bi, J. Hu, The role of circulating adiponectin in prostate cancer: a meta-analysis, *Int. J. Biol. Markers* 30 (2015) e22–31.
- [110] Q. Gao, X. Yao, J. Zheng, MiR-323 inhibits prostate cancer vascularization through adiponectin receptor, *Cell. Physiol. Biochem.* 36 (2015) 1491–1498.
- [111] Q. Gao, J. Zheng, Adiponectin-induced antitumor activity on prostatic cancers through inhibiting proliferation, *Cell Biochem. Biophys.* 70 (2014) 461–465.
- [112] S. Fu, H. Xu, M. Gu, C. Liu, Q. Wang, X. Wan, Y. Chen, Q. Chen, et al., Adiponectin deficiency contributes to the development and progression of benign prostatic hyperplasia in obesity, *Sci. Rep.* 7 (2017) 43771.
- [113] C. Porcile, E. Di Zazzo, M. Monaco, G. D'Angelo, D. Passarella, C. Russo, A. Di Costanzo, A. Pattarozzi, M. Gatti, A. Bajetto, et al., Adiponectin as novel regulator of cell proliferation in human glioblastoma, *J. Cell. Physiol.* 229 (2014) 1444–1454.
- [114] A. Irving, J. Harvey, Leptin regulation of hippocampal synaptic function in health and disease, *Philos. Trans. R Soc. Lond. B* 369 (2014) 20130155.
- [115] M. Dhar, M. Zhu, S. Impey, T. Lambert, T. Bland, I. Karatsoreos, T. Nakazawa, S. Appleyard, G. Wayman, Leptin induces hippocampal synaptogenesis via CREB-regulated microRNA-132 suppression of p250GAP, *Mol. Endocrinol.* 28 (2014) 1073–1087.
- [116] I. Valladolid-Acebes, A. Fole, M. Martín, L. Morales, M. Cano, M. Ruiz-Gayo, N. Del Olmo, Spatial memory impairment and changes in hippocampal morphology are triggered by high fat diets in adolescent mice. Is there a role of leptin? *Neurobiol. Learn. Mem.* 106 (2013) 18–25.
- [117] Y. Malekizadeh, A. Holiday, D. Redfearn, J. Ainge, G. Doherty, J. Harvey, A leptin fragment mirrors the cognitive enhancing and neuroprotective actions of leptin, *Cereb. Cortex* 27 (10) (2016) 4769–4782.
- [118] W. Hu, D. Holtzman, A. Fagan, L. Shaw, R. Perrin, S. Arnold, M. Grossman, C. Xiong, R. Craig-Schapiro, C. Clark, E. Pickering, M. Kuhn, Y. Chen, V. Van Deerlin, L. McCluskey, L. Elman, J. Karlawish, A. Chen-Plotkin, H. Hurtig, A. Siderowf, F. Swenson, V. Lee, J. Morris, J. Trojanowski, H. Soares, Alzheimer's disease Neuroimaging Initiative, 2012. Plasma multi-analyte profiling in mild cognitive impairment and Alzheimer's disease, *Neurology* 79 (2012) 897–905.
- [119] S. Walter, M. Letiembre, Y. Liu, H. Heine, B. Penke, W. Hao, B. Bode, N. Manietta, J. Walter, W. Schulz-Schuffer, K. Fassbender, Role of the toll-like receptor 4 in neuroinflammation in Alzheimer's disease, *Cell. Physiol. Biochem* 20 (2007) 947–956.
- [120] M. Kizilarslanoglu, O. Kara, Y. Yeşil, M. Kuyumcu, Z. Ozturk, M. Cankurtaran, S. Rahatli, N. Pakashticali, E. Cinar, M. Halil, B. Sener, E. Cankurtaran, S. Ariogul, Alzheimer disease, inflammation, and novel inflammatory marker: resistin,

- Turkish J. Med. Sci. 45 (2015) 1040–1046.
- [121] A. Wędrychowicz, A. Zajac, M. Pilecki, B. Kościelniak, P. Tomasik, Peptides from adipose tissue in mental disorders, *World J. Psychiatry* 4 (2014) 103–111.
- [122] B. Weber-Hamann, J. Kratzsch, D. Kopf, F. Lederbogen, M. Gilles, I. Heuser, M. Deuschle, Resistin and adiponectin in major depression: the association with free cortisol and effects of antidepressant treatment, *J. Psychiatr. Res.* 41 (2006) 344–350.
- [123] M. Yumru, H. Savas, E. Kurt, M. Kaya, S. Selek, E. Savas, E. Oral, I. Atagun, Atypical antipsychotics related metabolic syndrome in bipolar patients, *J. Affect. Disord.* 98 (2007) 247–252.
- [124] L. Brunetti, G. Orlando, L. Recinella, B. Michelotto, C. Ferrante, M. Vacca, Resistin, but not adiponectin, inhibits dopamine and norepinephrine release in the hypothalamus, *Eur. J. Pharmacol.* 493 (2004) 41–44.
- [125] J. Flier, Starvation in the midst of plenty: Reflections on the history and biology of insulin and leptin, *Endocr. Rev.* 40 (1) (2019) 1–16.
- [126] N. Nway, C. Sitticharoon, S. Chatree, P. Maikaew, Correlations between the expression of the insulin sensitizing hormones, adiponectin, visfatin, and omentin, and the appetite regulatory hormone, neuropeptide Y and its receptors in subcutaneous and visceral adipose tissues, *Obesity Res. & Clin. Practice* 10 (3) (2016) 256–263.
- [127] W. Yan, F. Zhang, R. Zhang, X. Zhang, Y. Wang, F. Zhou, Y. Xia, P. Liu, C. Gao, H. Wang, et al., Adiponectin regulates SR Ca (2+) cycling following ischemia/reperfusion via sphingosine 1-phosphate-CaMKII signaling in mice, *J. Mol. Cell. Cardiol.* 74 (2014) 183–192.
- [128] Y. Tanaka, S. Kita, H. Nishizawa, S. Fukuda, Y. Fujishima, Y. Obata, H. Nagao, S. Masuda, Y. Nakamura, Y. Shimizu, et al., Adiponectin promotes muscle regeneration through binding to T-cadherin, *Sci. Rep.* 9 (2019) 16.
- [129] H. Jiang, F. Yang, T. Lin, W. Shao, Y. Meng, J. Ma, C. Wang, R. Gao, X. Zhou, Asymmetric expression of H19 and ADIPOQ in concave/convex paravertebral muscles is associated with severe adolescent idiopathic scoliosis, *Mol. Med.* 24 (2018) 48.
- [130] Y. Liu, R. Palanivel, E. Rai, M. Park, T. Gabor, M. Scheid, A. Xu, G. Sweeney, Adiponectin stimulates autophagy and reduces oxidative stress to enhance insulin sensitivity during high-fat diet feeding in mice, *Diabetes* 64 (2015) 36–48.
- [131] L. Giordani, A. Parisi, F. Le Grand, Satellite cell self-renewal, *Curr. Top. Dev. Biol.* 126 (2018) 177–203.
- [132] S. Lecompte, M. Abou-Samra, R. Boursereau, L. Noel, S. Brichard, Skeletal muscle secretome in Duchenne muscular dystrophy: A pivotal anti-inflammatory role of adiponectin, *Cell. Mol. Life Sci.* 74 (2017) 2487–2501.
- [133] I. Marcelino-Rodriguez, D. Almeida Gonzalez, J. Aleman-Sanchez, B. Brito Diaz, M. Rodriguez Perez, F. Gannar, S. Dominguez Coello, F. Cuevas Fernandez, A. Cabrera de Leon, Inverse association of resistin with physical activity in the general population, *PLoS One* 12 (2017), <https://doi.org/10.1371/journal.pone.0182493>, e0182493.
- [134] J. Ihalainen, M. Schumann, D. Eklund, M. Hamalainen, E. Moilanen, G. Paulsen, K. Hakkinen, A. Mero, Combined aerobic and resistance training decreases inflammation markers in healthy men, *Scand. J. Med. Sci. Sports* 28 (2018) 40–47.
- [135] T. Wang, C. He, Pro-inflammatory cytokines: The link between obesity and osteoarthritis, *Cytokine Growth Factor Rev.* 44 (2018) 38–50.
- [136] F. Bessone, M. Razoni, M. Roma, Molecular pathways of nonalcoholic fatty liver disease development and progression, *Cell. Mol. Life Sci.* (2018) 1–30.
- [137] S. Spahis, E. Delvin, J. Borys, E. Levy, Oxidative stress as a critical factor in nonalcoholic fatty liver disease pathogenesis, *Antioxid. Redox Signal.* 10 (2017) 519–541.
- [138] W. Liu, R. Baker, T. Bhatia, L. Zhu, S. Baker, Pathogenesis of nonalcoholic steatohepatitis, *Cell. Mol. Life Sci.* 73 (10) (2016) 1969–1987.
- [139] P. Dulai, S. Singh, J. Patel, M. Soni, L. Prokop, Z. Younossi, G. Sebastiani, M. Ekstedt, et al., Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis, *Hepatology* 65 (5) (2017) 1557–1565.
- [140] T. Kanda, S. Matsuoka, M. Yamazaki, T. Shibata, K. Nirei, H. Takahashi, T. Kaneko, M. Fujisawa, et al., Apoptosis and non-alcoholic fatty liver diseases, *World J. Gastroenterol.* 24 (25) (2018) 2661–2672.
- [141] C. Shen, C. Zhao, W. Wang, Y. Wang, H. Sun, W. Cao, W. Yu, L. Zhang, R. Ji, M. Li, J. Gao, The relationship between hepatic resistin overexpression and inflammation in patients with nonalcoholic steatohepatitis, *BMC Gastroenterol.* 14 (2014) 39.
- [142] J. Beinsberger, J. Heemskerck, J. Cosmans, Chronic arthritis and cardiovascular disease: Altered blood parameters give rise to a prothrombotic propensity, *Seminars Arthritis Rheumatism* 44 (3) (2014) 345–352.
- [143] C. Ghantous, Z. Azrak, S. Hanache, W. Abou-Kheir, A. Zeidan, Differential Role of Leptin and Adiponectin in Cardiovascular System, *Int. J. Endocrinol.* 2015 (2015) 534320.
- [144] R. Kumari, S. Kumar, M. Ahmad, R. Singh, S. Kant Kumar, A. Pradhan, S. Chandra, S. Kumar, Promoter variants of TNF- α rs1800629 and IL-10 rs1800871 are independently associated with the susceptibility of coronary artery disease in north Indian, *Cytokine* 110 (2018) 131–136.
- [145] R. Kumari, S. Kumar, M. Ahmad, R. Singh, A. Pradhan, S. Chandra, S. Kumar, TNF- α /IL-10 ratio: An independent predictor for coronary artery disease in North Indian population, *Diabetes Metab. Syndr.* 12 (3) (2018) 221–225.
- [146] A. Aroor, S. McKarns, V. DeMarco, G. Jia, J. Sowers, Maladaptive immune and inflammatory pathways lead to cardiovascular insulin resistance, *Metabolism* 62 (11) (2013) 1543–1552.
- [147] M. Hiramatsu-Ito, R. Shibata, K. Ohashi, Y. Uemura, N. Kanemura, T. Kambara, et al., Omentin attenuates atherosclerotic lesion formation in apolipoprotein E-deficient mice, *Cardiovasc. Res.* 110 (1) (2016) 107–117.
- [148] M. Civelek, A. Lulus, Systems genetics approaches to understand complex traits, *Nat. Rev. Genet.* 15 (2014) 34–48.
- [149] E. Kochetkova, L. Ugai, Y. Maistrovskaia, V. Nevzorova, Adipokines: A possible contribution to vascular and bone remodeling in idiopathic pulmonary arterial hypertension, *Calcif. Tissue Int.* 100 (2017) 325–331.
- [150] M. Santos, A. Reis, F. Goncalves, M. Ferreira-Pinto, S. Cabral, S. Torres, A. Leite-Moreira, T. Henriques-Coelho, Adiponectin levels are elevated in patients with pulmonary arterial hypertension, *Clin. Cardiol.* 37 (2014) 21–25.
- [151] J. Domagała-Kulawik, I. Osńska, A. Piechuta, P. Bielicki, T. Skirecki, T. B, and NKT cells in systemic inflammation in obstructive sleep apnea, *Mediators Inflamm* 2015 (2015) 161579.
- [152] R. Zeng, C. Xu, Y. Xu, Y. Wang, M. Wang, Association of leptin levels with pathogenetic risk of coronary heart disease and stroke: a meta-analysis, *Arquivos Brasileiros de Endocrinologia & Metabologia* 58 (8) (2014) 817–823.
- [153] M. Balasko, S. Soos, M. Szekely, E. Petervari, Leptin and aging: review and questions with particular emphasis on its role in the central regulation of energy balance, *J. Chem. Neuroanat.* 61–62 (2014) 248–255.
- [154] K. Blaslov, T. Bulum, L. Duvnjak, The role of endothelial dysfunction driven by adipocytokines in the development and progression of microvascular complications in patients with type 1 and type 2 diabetes, *Med. Hypotheses* 84 (6) (2015) 593–595.
- [155] M. Jamaluddin, S. Yan, J. Lu, Z. Liang, Q. Yao, C. Chen, Resistin increases monolayer permeability of human coronary artery endothelial cells, *PLoS ONE* 8 (2013) e84576.
- [156] A. Virdis, E. Duranti, C. Rossi, U. Dell'Agnello, E. Santini, M. Anselmino, M. Chiarugi, S. Taddei, A. Solini, Tumour necrosis factor- α participates on the endothelin-1/nitric oxide imbalance in small arteries from obese patients: role of perivascular adipose tissue, *Eur. Heart J.* 36 (13) (2014) 784–794.
- [157] Z. Kusku-Kiraz, S. Genc, S. Bekpinar, Y. Unlucerci, V. Olgac, M. Uysal, F. Gurdol, Circulating levels of apelin, glucagon-like peptide and visfatin in hypercholesterolemic-hyperhomocysteinemic guinea pigs: their relation with NO metabolism, *Mol. Cell. Biochem.* 400 (1–2) (2015) 69–75.
- [158] C. van Stijn, J. Kim, G. Barish, U. Tietge, R. Tangirala, Adiponectin expression protects against angiotensin II-mediated inflammation and accelerated atherosclerosis, *PLoS ONE* 9 (1) (2014) e86404.
- [159] F. Malli, P. Georgoulas, Leptin and adiponectin levels in idiopathic pulmonary fibrosis: association with hypoxia, *J. Obes. Weight Loss Ther.* 5 (6) (2015) 1000284.
- [160] B. Chen, Q. Lyu, M. Zhang, M. Zhang, W. Liu, S. Zhu, Leptin induces human lung fibroblast to Trans-differentiate into myofibroblast. *Xi bao yu fen zi mian yi xue za zhi*, *Chin. J. Cell Mol. Immunol.* 31 (2015) 199–202.
- [161] X. Gui, H. Chen, H. Cai, L. Sun, L. Gu, Leptin promotes pulmonary fibrosis development by inhibiting autophagy via PI3K/Akt/mTOR pathway, *Biochem. Biophys. Res. Commun.* 498 (2018) 660–666.
- [162] A. Koch, O. Gressner, E. Sanson, F. Tacke, C. Trautwein, Serum resistin levels in critically ill patients are associated with inflammation, organ dysfunction and metabolism and may predict survival of non-septic patients, *Crit. Care* 13 (2009) R95.
- [163] A. Schaffler, O. Hamer, J. Dickopf, A. Goetz, K. Landfried, M. Voelck, H. Herfarth, A. Kopp, C. Buchler, J. Scholmerich, T. Brunnler, Admission resistin levels predict peripancreatic necrosis and clinical severity in acute pancreatitis, *Am. J. Gastroenterol.* 105 (2010) 2474–2484.
- [164] G. Messina, R. Polito, V. Monda, L. Cipolloni, N. Di Nunno, G. Di Mizio, P. Murabito, et al., Functional role of dietary intervention to improve the outcome of COVID-19: A hypothesis of work, *Int. J. Mol. Sci.* 21 (2020) 3104.