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REVIEW

Effect of Leptin on Chronic Inflammatory Disorders: Insights to Therapeutic Target to Prevent Further Cardiovascular Complication

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Abstract: In response to obesity-associated chronic inflammatory disorders, adipose tissue releases a biologically active peptide known as leptin. Leptin activates the secretion of chemical mediators, which contribute to the pathogenesis of chronic inflammatory disorders, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and psoriasis. Conversely, adiposity and obesity are the major aggravating risk factors in the pathogenesis of metabolic syndrome (MetS), including type II diabetes mellitus and obesity-associated hypertension. Elevated level of leptin in obesity-associated hypertension causes an increase in the production of aldosterone, which also results in elevation of arterial blood pressure. Hyperleptinemia is associated with the progress of the atherosclerosis through secretion of pro-inflammatory cytokines, like interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), IL-17, and other cytokines to promote inflammation. The release of those cytokines leads to chronic inflammatory disorders and obesity-associated MetS. Thus, the aberrant leptin level in both MetS and chronic inflammatory disorders also leads to the complication of cardiovascular diseases (CVD). Therapeutic target of leptin regarding its pro-inflammatory effect and dysregulated sympathetic nervous system activity may prevent further cardiovascular complication. This review mainly assesses the mechanism of leptin on the pathogenesis and further cardiovascular risk complication of chronic inflammatory disorders.

Keywords: leptin, chronic inflammatory disorders, cardiovascular

Introduction

Adipose tissue is the major organ to produce and release leptin.[1] Leptin was discovered on animal models by Friedman in 1994.[2] At the time of discovery, treatment of obesity was hopeful on this active adipokine molecule. However, hyperleptinemia was seen in obese individuals after it was found.[3] Two years after its discovery, low energy signal transmission effect of the central nervous system was identified as its first physiological function.[4] Neurons found in the ventral tegmental area of midbrain in the hypothalamus express leptin receptors.[5] Energy homeostasis in the peripheral nervous system is regulated by highly complex interaction of neurons and leptin.[6] It can be maintained through interaction of leptin signaling pathways with neuropeptide Y neurons.[7] Leptin regulates the satiety, energy expenditure, inflammation, endothelial cells function, blood pressure, and insulin secretion.[8] It is proportional to the mass of adipose tissue.[9] Impairment of adipose tissue results in the release of effector adipokines, including leptin and resistin[10] (Figure 1). The signaling pathways of leptin can be impaired due to an increase in body mass.[11] Thus, fat storage and energy homeostasis in adipose tissue could

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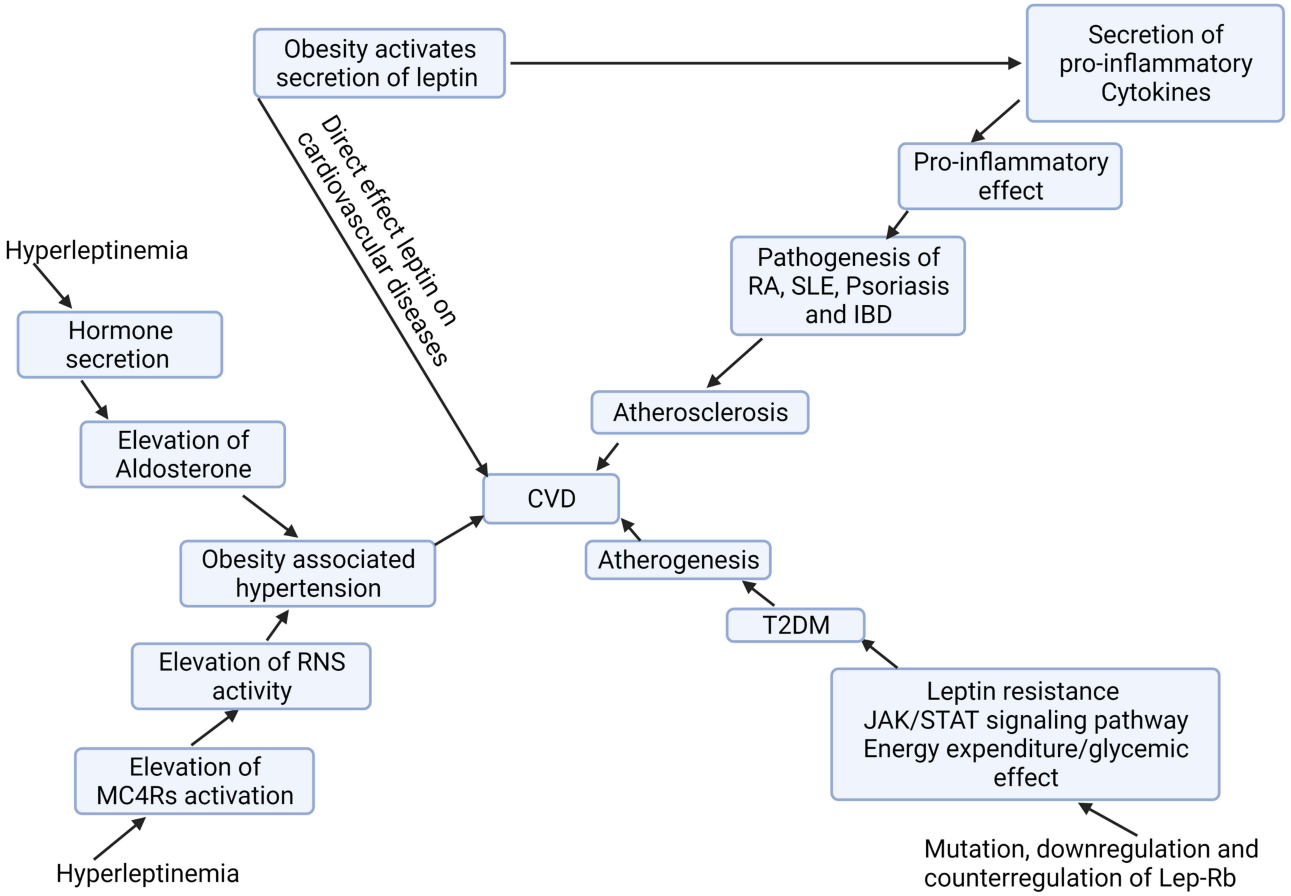

Figure 1 Leptin for progression of atherosclerosis in T2DM. The synthesis of leptin is associated with atherogenic effect because leptin receptors are found on endothelial cells. Thus, its elevation in obese individuals causes endothelial dysfunction. In this regard, obesity and secretion of leptin is a characteristic feature of T2DM. IL-6 secreted from endothelial cells activate Janus kinase/activators of transcription (JAKs) after it binds to the cytoplasmic domain of gp130 within macrophage, followed by the phosphorylation of transmembrane tyrosine receptor motifs, such as Tyr905, Tyr814, Tyr767, Tyr705 and Tyr915. This leads to increase expression of pro-inflammatory genes through *STAT3*, which aggravates inflammation and atherosclerosis in T2DM.

Abbreviations: CVD, cardiovascular disease; IL-6, Interleukin-6; JAK/STAT, Janus kinase/ activators of transcription; *STAT3*, activators of transcription-3; T2DM, type II diabetes mellitus.

be impaired due to the effect of obesity-associated inflammation.[10] Fatel et al[12] in 2018 mentioned leptin as a pro-inflammatory adipokine because it induces the activation and secretion of the pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), lipopolysaccharide, and interleukin (IL-1). In contrast, the inflammatory cytokines induce the generation and secretion of leptin to promote chronic inflammation.[12] The pro-inflammatory stimuli, IL-1, TNF-α, and lipopolysaccharide lead to upregulation of expression of leptin messenger RNA (mRNA) to aggravate inflammation.[13] Chronic inflammation may provoke leptin resistance through interruption of its receptor signaling cascade, which in turn leads to hyperleptinemia and obesity.[14]

Leptin is involved in the pathogenesis of various obesity-related inflammatory disorders, such as psoriasis, systemic sclerosis, diabetes, and hypertension.[15] Psoriasis is an inflammatory skin disease, which is mainly associated with pro-inflammatory cytokines, including IL-6, interleukin 17 (IL-17), interferon-gamma (IFN-γ), and TNF-α.[16] Obesity is an attributable risk factor for the complication of psoriasis.[17] The autoimmune inflammatory disorders, including systemic lupus erythematosus (SLE) induce the release of leptin to modulate the immune system[18] that in turn leads to chronic inflammation.[19] Although there are contradictory data, the majority of studies mentioned elevated level of leptin in SLE patients.[20] Rheumatoid arthritis (RA) is another chronic autoimmune inflammatory disorder, which leads to the synthesis both of leptin and cytokines.[21] Leptin also induces the activation of macrophage, regulatory T-cells and Th17 cells to release pro-inflammatory cytokines like interleukin 6 (IL-6), TNF-α, (IL-17), and other cytokines to promote inflammation.[22] The binding of leptin to its receptors induces an increase in arterial blood pressure[23] because obesity-related

inflammation causes an impairment in leptin sympathetic activity that control the renin–angiotensin system.[23] The sensitizing effect of leptin on upregulation of the renin–angiotensin system increases the risk of hypertension in obese individuals.[23] In addition to maintaining body weight, leptin is also involved in carbohydrate metabolism[24] and strengthening sensitivity of insulin in type I diabetes mellitus.[25] The expression of leptin receptor isoform, Lep-Rb in the peripheral tissue enhances the pathogenesis of various diseases, including immune dysregulation and type II diabetes.[26]

Recently, leptin has gained the insight of the scientific community due to its association with obesity, cardiovascular risk, and insulin resistance.[27] Evidence has suggested that obesity aggravates the development of chronic inflammation, which in turn leads to metabolic syndrome (MetS).[28] Characteristic features of MetS, such as hypertension, atherosclerosis, insulin resistance and obesity are correlated with elevated levels of leptin.[29] Studies revealed that obese individuals with hyperleptinemia are more likely to develop insulin resistance, type II diabetes mellitus, degenerative disease and cardiovascular complications.[13,30] Studies revealed that insulin sensitivity became decreased in pre-diabetes because of a higher level of leptin.[31] The development of these chronic diseases are associated with obesity-associated complications.[32] In contrast, hypertension is one of the obesity-associated MetS, which is caused by an abnormal secretion of leptin.[33] Increased levels of IL-6, TNF-α and leptin results in dysfunctional epithelial cells, proliferation of smooth muscle cells, and migration of macrophages toward the damaged endothelial cells, which also leads to the development of the cardiovascular risk factors, such as atherosclerosis and hypertension.[34] Even if contradictory data has been shown in vascular diseases,[35] hyperleptinemia is the adverse effect of cardiovascular complications such as stroke, heart failure, and acute myocardial infarction.[36] Although scientific evidence had argument on leptin effect in coronary artery disease, it has a correlation with intima-media thickness and calcification of coronary artery among type II diabetes mellitus patients.[37] Coronary artery disease (CAD) is associated with increased synthesis of the perivascular adipose tissue derived leptin and its atherogenic effect. Consequently, the therapeutic target of this active adipokine molecule is recommended to treat obesity-associated cardiovascular complications.[38] Hyperleptinemia is associated with the progress of atherosclerosis. Thus, the therapeutic target of leptin may decrease the complication of cardiovascular diseases.[39] Generally, hyperleptinemia acts as a major risk factor for the complication of cardiovascular disease (CVD) in addition to other traditional risk factors[40] (Figure 1). This review article evaluates the obesity-associated chronic inflammatory diseases and correlates the effect of these disorders with cardiovascular complications. It focuses on the pro-inflammatory effect of leptin in various chronic inflammatory disorders and obesity-associated MetS.

Effect of Leptin in the Pathogenesis of Rheumatoid Arthritis

According to a clinical and epidemiological global study in 2010, the prevalence of rheumatoid arthritis (RA) was estimated to be 0.24% and continues without change from 1990 to 2010.[41] It is characterized by a highly systemic inflammation, which leads to reduced life expectancy and increased mortality rate.[42] Obesity-associated inflammation increases the burden of RA.[43] Evidence argues about unknown plasma levels of leptin and its undefined effect in RA patients compared to healthy controls.[44] However, as early as 2006, a marked elevation of plasma leptin level was detected in RA patients.[45] Recently, in 2018, de Souza Fatel et al[46] tried to confirm the association of RA and leptin. Researchers have various insights about leptin and disease activity in RA.[47] Studies showed that higher disease activity of RA is associated with hyperleptinemia.[48] In patients with RA undergoing anti-TNF therapy due to disease severity, there was a strong positive correlation between body mass index of the patient and serum levels of leptin.[49] A recent 12-month multicenter study done in 2020 revealed that the ratio of leptin/fat was elevated in RA patients treated with tocilizumab.[50] However, the alteration of serum leptin level was not evaluated in their study. It was also the case for RA patients undergoing intravenous therapy with the anti-IL-6 receptortocilizumab.[51] Moreover, a significant reduction of leptin levels was observed following one single intravenous infusion of the anti-IL-6 receptor tocilizumab.[51] However, there was no a statistically significant differences in allele frequencies of leptin gene polymorphisms (LEP rs2167270) between RA patients and controls.[52] A brief report done in Mexico in 2015 suggested the presence of linear association of leptin with disease activity of RA. Skalska and Kontny,[53] in their 2016 study, clearly describe leptin as a risk factorfor the development of RA.

De Souza Fatel et al revealed that leptin has a pro-inflammatory effect in the development of RA by activating the secretion of effector cytokines.[46] Macrophages play a significant role in the development of RA.[54]

Leptin activated macrophage induces the release of IL-6 and TNF-α[55] (Figure 2). In vitro, the chemotactic activity of macrophage is associated with induction of leptin.[55] In autoimmune diseases, deregulated immune response of cells are affected by alteration of metabolic process within these cells[55] because leptin binds to its long isoform receptor (Ob-RB) to induce its biological and physiological effect through JAK/STAT signaling pathway. JAK/STAT signal transduction is caused by the involvement of Janus kinase 2 (*JAK2*), activators of transcription (STAT) and transducers found on longer receptor isoform (Ob-Rb).[13] In addition to leptin, this signaling pathway requires the interaction between complex molecules, including node-like receptor pyrin domain-containing protein 3 (*NLRP3*), micro RNA-98 (miR-98), caveolin-1 (CAV-1-NR2B) and IL-33.[56] JAKs are a group of tyrosine kinases, which bind to type I and II tyrosine receptor family,[57] whereas STATs are factors that are phosphorylated by cytokines activated tyrosine motifs.[58] Leptin-receptor interaction begins after leptin binds to Ob-Rb, extracellular domain, later Jak2 tyrosine kinase become activated.[59] This in turn causes auto-phosphorylation of Jak2 and intracellular Tyr1138, Tyr1077, and Tyr985 motifs.[13] Physically associated receptor-JAK complex activate phosphorylation of STATs, including *STAT1*, *STAT2*, *STAT3,* and other transcriptional signaling molecules.[60] In addition, phosphorylated Tyr1138 induces the phosphorylation of *STAT3*, which is exported to the nucleus for targeted gene transcriptional process.[59] This signaling cascade within macrophage induces synthesis of pro-inflammatory cytokines, including IL-6 and TNF-α[61] (Figure 2). Then, IL-6 and TNF-α are released from macrophage to promote inflammation and contribute to the pathogenesis of RA.[62] Although effective anti-arthritis therapies are designed from these first-class adipokines, drugs from leptin and other adipokines may also be formulated.[63] Chronic inflammation resulted from JAK/STAT signaling may be altered with a therapeutic drug (Jakinibs) in rheumatoid arthritis patients.[56] In addition, leptin induces macrophage chemotaxis, synthesis and

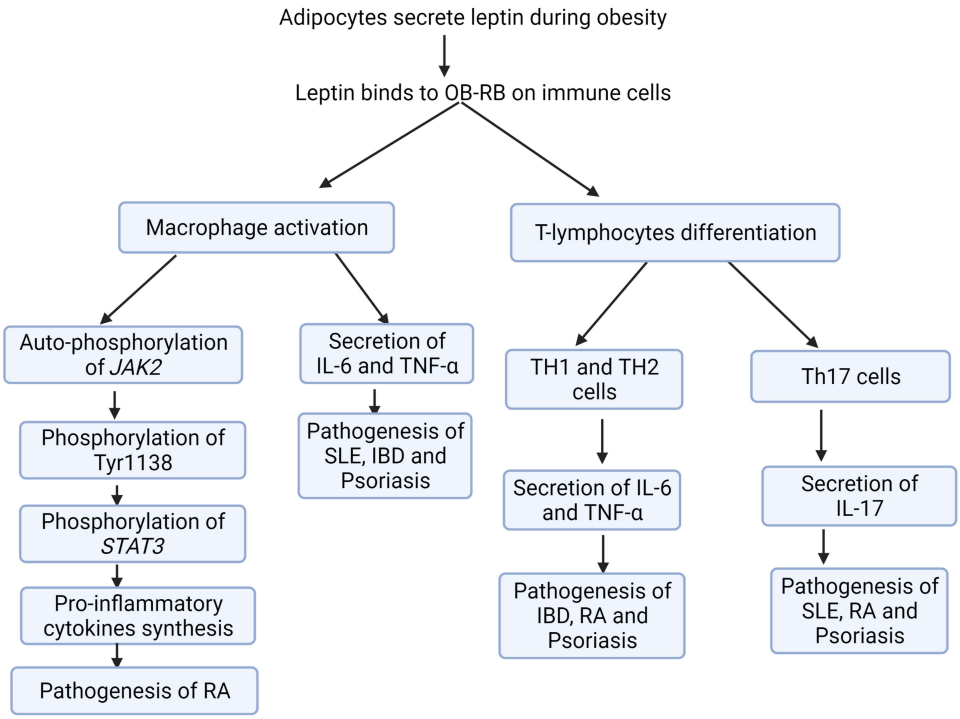

Figure 2 Cumulative effect of leptin on both chronic inflammatory disorders and further cardiovascular complication. The homeostatic role of adipose tissue impaired due to obesity-associated inflammation. The impairment of adipose tissue results in the release of effector adipokines, including leptin. The adipokines secreted by adipose tissue involve in obesity related inflammatory disorders, such as psoriasis, SLE and RA by activating of secretion of various cytokines. Conversely, obesity induced inflammation causes an impairment in sympathetic activity that controls the renin–angiotensin system through secretion of aldosterone, which results in elevation in water and salt retention and leads to obesity-associated hypertension. The reduced physiological activity of leptin on adipose tissue to oxidize stored fat leads to a phenomenon known as leptin resistance. In this regard, leptin resistance occurs in diabetic and obese subjects. Adiposity and obesity are risk factors for the occurrence of metabolic syndrome, such as T2DM and hypertension. In addition to this, RA, psoriasis and SLE are developed due to adiposity and obesity, which in turn leads to cardiovascular complications.
Abbreviations: CVD, cardiovascular disease; IBD, inflammatory bowel disease; JAK/STAT, Janus kinase/activators of transcription; Lep-Rb, leptin receptor isoform-b; RA, rheumatoid arthritis; MC4Rs, melanocortin-4 receptors; SLE, systemic lupus erythematosus; SNS, sympathetic nervous system; T2DM, type II diabetes mellitus.

release of pro-inflammatory cytokine, IL-12.[61] Similarly, leptin activated macrophage induces synthesis of IL-18 to mediate T-helper 1 immune response.[64] Secreted IL-18 and IL-12 enable differentiation of Th1 phenotype from T-helper cells and activate synthesis of interferon-γ (IFN-γ) and IL-2. Converely, Th1 cells synthesize leptin and induce the release of IL-18, IL-12, IL-6 and TNF-α by stimulating macrophage.[65] The expression of glycoprotein (CD38), adhesion molecules, CD25, and CD69 also increased within activated macrophage.[61]

In contrast, leptin contributes to the progression of RA by downregulating regulatory T-cell activity ($CD4^{+}CD25^{high}$) and upregulating the activity of T-helper 1 (T_H1) cells.[66] Diminished level of Treg cells seen in an opposite effect to the level of leptin and BMI in obese individuals.[55] The experiment done in leptin-deficient mice showed the anti-inflammatory potential of leptin by inhibiting inflammatory agents. However, it elevates systemic inflammation in RA through T_H1-mediated immune response.[67] T-helper 1(T_H1) cells promote inflammation in different autoimmune disorders, including RA.[68] The elevated ratio of both regulatory T-cell and Th17 cells (Th17/Treg) and Th1/Th2 promote the pathogenesis of RA[69] (Figure 2). Even if there is no well-defined association among adipokines and RA, leptin is one metabolic risk factor.[70] In addition, elevation in leptin/adiponectin ratio and positive association of leptin with homeostasis model assessment of insulin resistance (HOMA-IR) indicates magnitude of atherosclerosis development and plaque formation.[70] Therefore, leptin plays a significant role in the pathogenesis of RA and risk of cardiovascular complication.

Hyperleptinemia and Cardiovascular Risk in Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is chronic autoimmune inflammatory disease characterized by inflammation of connective tissue.[71] Versini et al[72] et al, in 2017, mentioned the availability of inadequate data regarding the association between obesity and SLE through their cross-sectional study. Although studies argue regarding the association of leptin with SLE, an increase in serum leptin concentration may elevate systemic inflammation in SLE.[73] Even though contradictory data are available, findings showed that the level of leptin increases in SLE.[27,66,73] In contrast to this, the other meta-analysis done on leptin and SLE revealed that diminished level of leptin is shown in SLE.[74] Alternatively, studies done in Egypt in 2018 confirmed the presence of higher level of serum leptin among SLE patients.[19] Elevated level of leptin is correlated with MetS and obesity, which act as an exposure risk factors for chronic autoimmune diseases, including SLE.[74] In the pathogenesis of SLE, the immune system is affected by leptin, which serves as a pro-inflammatory cytokine.[75] In this regard, macrophages synthesize TNF-α due to the stimulatory effect of leptin.[76] Therefore, SLE patients with CVD show an elevated level of IL-1 and TNF-α.[77] At the onset of inflammation, leptin increases the synthesis of inflammatory mediators, including IL-6 and TNF-α.[78]

Leptin contributes to the pathogenesis of SLE by activating the synthesis of auto-antibody production and dysregulation of the immune system.[79] Although the pathogenesis of SLE is still undefined, the circulating auto-antibodies activate secretion of inflammatory cytokines, which in turn contribute to the progress of SLE.[80] Beyond leptin's significant enrollment, both auto-antibodies and $CD4^{+}$ T-cells play another significant role in the pathogenesis of SLE.[18] The abnormal activation of $CD4^{+}$ T-cells and mediated inflammatory responses are seen in SLE patients.[80] Immune dysregulation associated with leptin is due to an increase in differentiation of Th17 cells,[18] which in turn lead to tissue damage in autoimmune disorders, including SLE.[79] The effector cell, Th17 induces inflammation by the activating secretion of IL-17 which also enhances tissue damage and inflammation in psoriasis, SLE, and RA[81] (Figure 2).

Role of Leptin in the Pathogenesis of Psoriasis

Psoriasis is a chronic inflammatory disease in joints, nails and skin due to immune modulation, environmental, and genetic variation.[82] The World Health Organization describes it as a global health burden, and the prevalence of disease is expected to be 2% in Western countries.[83] The complication of psoriasis is related to the effects both of MetS and obesity.[82] Profumo et al[84] in 2012 mentioned the development of obesity in psoriatic patients. Obesity has an association with inflammatory skin cells by modulating their activity.[85] It also induces chronic inflammation by activating the secretion of cytokines and leptin.[86] The release of adipokines contribute to a chronic cutaneous inflammation in psoriasis.[87] Leptin plays its own role in the promotion of psoriasis through secretion of pro-inflammatory mediators, which are recruited to cutaneous

lesions.[88] Although cutaneous psoriasis patients at moderate-to-severe stages of the disease treated with anti-TNF biologics, leptin correlated with MetS features and inflammation. In this regard, in these patients with moderate-to-severe psoriasis, leptin concentration is correlated with C-reactive protein and with systolic and diastolic blood pressure before the onset of the anti-TNF-adalimumab therapy.[89] A negative correlation with insulin sensitivity was also found.[89] Although clarification on anti-inflammatory and pro-inflammatory effect of psoriasis is challenging, the expression of anti-inflammatory cytokines resolve Th2 and Th1/Th17 unbalanced proportion in psoriasis.[16] However, studies done in mice showed that leptin induces and activates the differentiation of T-lymphocytes into T-helper-1 lymphocytes (Th1 lymphocytes) to release pro-inflammatory cytokines, including TNF-α, IL-6 and IL-8[90] (Figure 2). Researchers have confirmed that leptin increases the genetic expression of IL-6 both in humans and rats.[91]

Regard to psoriasis pathogenesis, Th1-cells are responsible for the synthesis of TNF-α, IFN-γ and IL–2.[16] Similarly, Th17 cell becomes differentiated due to stimulatory effect of IL-6 and this cell also induces the release of IL-17, IL-6, IL-22 and IL-21[16] (Figure 2). The systemic inflammation is due to a network of cytokines activation such as IL–2, TNF-α, IFN-γ, IL-6, IL-17, IL-21, IL-22 and others.[16] The secreted cytokines cascade promote the development of accelerated atherosclerosis in psoriasis patients.[89] The IL-17 deficient mice showed diminished level atherosclerotic plaque formation, hence IL-17 lymphocytes may be involved in atherosclerosis development.[83] From a common perspective, inflammation mediated atherosclerosis has a common process similar to CVD.[83] Similarly, leptin induces the secretion of pro-inflammatory cytokines like TNF-α and IL-6 from macrophages and inhibits secretion of Th2 cytokines.[92] In this context, the pro-inflammatory effect of TNF-α has been activated,[89] whereas the anti-inflammatory effect of Th2 cytokines will be downregulated.[92] Studies showed that Th2-produced IL-10 may assist psoriasis therapy because it diminishes synthesis of chemokines and pro-inflammatory cytokines from macrophage.[93] Inflammation enhances pathophysiology of psoriasis, which in turn leads to the risk of cardiovascular complications.[83]

Leptin and Intestinal Inflammation in Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic inflammation of the digestive tract that includes ulcerative colitis[88] and Crohn's disease.[76,94] The incidence of IBD is higher in developed countries, but its prevalence is lower in developing countries compared to the former one.[94] Intestinal microbiome difference, smoking habits, lifestyle modification, and a variation on dietary content are some of the factors, which contribute to variation in the prevalence of IBD. Genetic, environmental factor, abnormality in immune response, and intestinal microbiome contribute to the development of IBD.[94] Studies describe IBD as an inflammatory disorder, which is characterized by an increase in the level of pro-inflammatory cytokines, including, TNF-α, IL-6, and IL-1[94] (Figure 2). Researchers have revealed that the pathogenesis of IBD is associated with activation of nuclear factor-κB (NF-κB), which enhances the genetic expression of pro-inflammatory cytokines.[95] Binding of leptin to its receptors found on immune cells of lamina propria and small intestine enterocytes induce NF-κB activation,[96] which in turn leads to villi cell apoptosis phenomena within intestinal mucosa. Migration of macrophage toward dead cells enhance and release pro-inflammatory cytokines, including IL-6, IL-1, and IL-12.[97] Neutrophils migrate toward the inflamed intestine[98] and synthesize or secrete leptin, but its proportion is not comparable to adipose tissue.[99] The cytokines secreted from macrophage are due to the stimulatory effect of leptin, especially in patients with Crohn's disease (CD).[96] In contrast, pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1 induce an elevated activity of leptin in inflamed tissue.[100] Thus, neutrophils play a vital role in the pathogenesis of IBD by mediating intestinal inflammation.[98] During intestinal microbiome disturbance, adipocytes also involve in innate immune response through generation of leptin.[101] In addition, characteristic systemic inflammation shown in IBD is associated with elevated $CD4^+$ cells polarization to Th1 cells, which in turn lead to release of pro-inflammatory cytokines[97] (Figure 2).

Leptin Involved in the Progression of Atherosclerosis in Type II Diabetes Mellitus

In the US, 34% of the population are challenged with complication of type II diabetes mellitus (T2DM).[102] This is because both obesity and T2DM are highly associated with each other.[102] Obesity is the major risk factor for the pathogenesis of diabetes mellitus.[103] Type II diabetes mellitus is characterized by obesity and secretion of leptin.[104] The production of leptin is related with atherogenic effect,[104] because

its elevation in obese individuals causes endothelial dysfunction[103] (Figure 3). Leptin binds to its receptors on neutrophils[105] and activates the chemotaxis and phagocytosis process.[106] The effect of leptin on the generation of reactive oxygen species is still undefined,[105] but it causes the migration of leukocytes toward injured tissue.[106] At the onset of inflammation, leptin increases the synthesis of pro-inflammatory mediators like IL-6 and TNF-α.[78] IL-6 and TNF-α are synthesized from macrophage within endothelium and contribute to the atherogenic process.[107] In addition to macrophage, different types of cells are responsible for secretion of IL-6, including endothelial cells, adipocytes, and skeletal muscle cells.[108] In contrast to pro-inflammatory effect, leptin activates synthesis of anti-inflammatory cytokines, including IL-4 and IL-10 from different types of immune cells.[65] However, in T2DM, the vascular complication promoted by the active pro-inflammatory mediator, IL-6 through JAK/STAT signal transduction pathway.[109] The interaction of this cytokine with its receptor induce activation of JAK/STAT signaling pathway.[60] The transphosphorylation of JAK and STATs is related with stimulation of receptors.[57] Janus kinase/activators of transcription (JAK) activation is caused by the binding of IL-6 to the cytoplasmic domain of gp130 followed by auto-phosphorylation of JAK and phosphorylation of transmembrane tyrosine receptor motifs, including Tyr905, Tyr814, Tyr767 and Tyr915.[99,110] In addition, phosphorylation of both ser727 and Tyr705 residues of Ob-RB also occurred within macrophage.[111] Mitogen activated protein kinases (MAPKs) are responsible for serine 727-phosphorylation of *STAT3* and *STAT1*, which act as linkage sites for MAPK and STATs.[112] Activators of transcription-3 (*STAT3*) are the major activation transcription factor for leptin signaling cascade, which requires phosphorylation of Tyr705.[109] In addition to Tyr705, extracellular regulated kinase (ERK)-activated phosphorylated ser727 also mediates *STAT3* stimulation during leptin signaling cascade.[111] Then, *STAT3* dimerizes, phosphorylates and translocates to the nucleus to activate pro-inflammatory gene expression.[109] The translocated STAT binds to gamma-activated sites[113] and interferon-stimulated response elements (ISREs) which

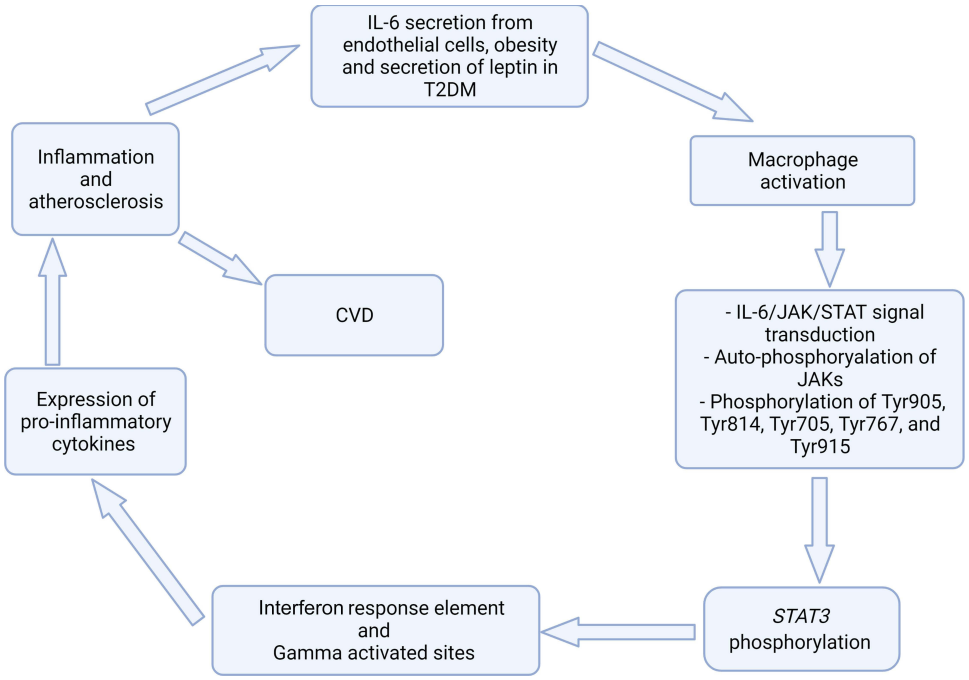

Figure 3 The impact of leptin on the pathogenesis of chronic autoimmune inflammatory disorders. Leptin binds to its long isoform receptor (Ob-RB) on macrophage to induce its biological and physiological effect through a JAK/STAT signaling pathway. This signaling cascade within macrophage induces the synthesis of pro-inflammatory cytokines, including IL-6 and TNF-α. The synthesis and release of IL-6 and TNF-α also involves the pathogenesis of RA. Similarly, IBD is one of inflammatory disorders which is characterized by elevation in the level of pro-inflammatory cytokines, including TNF-α, IL-6 and IL-1 that leads to the development of diseases. In contrast, the immune dysregulation related to leptin is due to elevated differentiation of Th17 cell, which in turn leads to tissue damage in autoimmune inflammatory disorders, including, SLE, psoriasis, and RA. The effector cell, Th17 induces inflammation by the activating secretion of IL-17 which also enhance tissue damage and inflammation in SLE. In the pathogenesis of psoriasis, studies done in mice showed that leptin induces and activates the differentiation of T-lymphocytes to T-helper-1 lymphocytes (Th1 lymphocytes) to release pro-inflammatory mediators, including TNF-α, IL-6 and IL-8.

Abbreviations: IBD, inflammatory bowel disease; IL-6, interleukin-6; IL-17, interleukin-17; JAK/STAT, Janus kinase/activators of transcription; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; Th1 and 2 cells, T-helper-1 and 2- lymphocytes; Th17 cells, T-helper-17 cells; TNF-α, tumor necrosis factor-alpha.

are involved in the signaling cascade of IFN and acute phase response[109] (Figure 3).

In contrast, the lower level of leptin seen both in rodents and humans indicates the presence of normal metabolic activity of cells.[114] The higher insulin concentration in the circulation leads to the deposition of fat in adipose tissue in the form of triglyceride.[115,116] In response to accumulated fat, leptin will be secreted by adipose tissue to oxidize it. But, the physiological activity of leptin does not act on adipose tissue to oxidize stored fat, which leads to a phenomenon called leptin resistance.[114] The demonstration done on rats showed that leptin resistance may be caused by downregulation of genetic expression of Lep-Rb in the hypothalamus. In addition to this, its signal transduction pathway can be inhibited through suppressor of cytokine signaling-3 (*SOCS3*) having counter regulatory effect.[117] Studies done on mice confirm that obesity was inhibited by avoiding *SOCS3* and protein tyrosine phosphatase 1B in the pro-opiomelanocortin (POMC) neurons.[118] Elevation of counter regulatory signaling pathways and overexpression of leptin receptor cause inhibition of leptin signaling cascade, which in turn leads to leptin resistance. Therefore, hypothalamus promotes the sensitivity of leptin through upregulation of *STAT3*, *JAK2* and diminished genetic expression of *SOCS3*.[119] In addition to its receptor aberration, a defect in transportation of leptin also contributes to leptin resistance.[120] The expression of leptin receptor isoform (Lep-Rb) in the brain activates transportation of leptin to undergo its biological and physiological effect on hypothalamus. However, the blood–brain barrier inhibits transportation of leptin.[121]

Diminished response to biological and physiological action of leptin commonly occurs in obese individuals.[122] The observational study done by Kennedy et al[123] in 2016 explained that elevated level of leptin was seen in hyperglycemia condition. In the hypothalamus, the JAK–STAT signaling pathway is induced through interaction of Lep-Rb and leptin, which leads to the biological effect of leptin action.[124] The glycolipid metabolism is regulated by leptin binding to its long isoform receptor, Lep-Rb which is found in the liver and hypothalamus.[125] Lep-Rb/*STAT3* signaling controls glycemic index, hence leptin regulates *STAT3* and phosphatidyl inositol-3 kinase (PI3K) activity.[126] Glucose reduction activity of leptin through energy expenditure enhances insulin sensitivity effect.[127] However, in animal models, the mutated leptin receptor gene may be associated with leptin action, T2DM pathogenesis, and obesity[124] (Figure 1). Leptin resistance occurs both in diabetes and obese subjects.[128] An investigation done on an animal model showed that leptin replacement therapy decreased hepatic gluconeogenesis and hyperglycemia condition.[129] Leptin therapy is not an adequate alternative method due to unresponsiveness to its physiological action. Therefore, additional desensitizing molecules should be combined with leptin to strengthen its anti-obesity activity.[122] If the anti-obesity activity of leptin therapy is enhanced, the stored fat will be oxidized, as well as insulin sensitivity elevated. Hence, the pathogenesis of diabetes might be decreased.

Leptin in the Pathogenesis of Obesity-associated Hypertension

Globally, the obesity-associated hypertension increases at a higher rate.[130] Several researchers confirmed that leptin leads to obesity related to hypertension.[131] A recent investigation tried to evaluate blood pressure in lipodystrophy patients through administration of leptin. Although they identified elevated level of leptin, patients did not show a significant variation as their blood pressure is measured.[132] However, mutation of leptin and its receptor may cause severe obesity in human beings, but normal or lower arterial pressure and sympathetic tone may be detected.[133–135] Obesity is a well-known risk factor for the development of hypertension.[136] In premenopausal women, obesity induces three-fold elevation for the progression of hypertension.[131] The abnormal secretion of biologically active peptide, leptin leads to aberration of the appetite regulation, insulin sensitivity, inflammation, and elevation of blood pressure (BP).[137] A recent investigation revealed that hypertension developed through elevation of the sympathetic nervous activity.[138] Blood pressure is maintained through interconnected activity of the hormonal factors, such as TNF-α, angiotensin, melanocortin, and leptin.[130] High fat diet intake causes the secretion of effector molecules, such as leptin and TNF-α to induce their sympathetic activity on hypothalamus.[130] Independent of food consumption, leptin regulates sympathetic activity and BP.[139] It affects BP by elevating sympathetic nervous system and aldosterone levels.[139] Protein tyrosine phosphatase 1B (PTP1B) and *SOCS3* have negative feedback on the effect of leptin by induction of leptin resistance. As leptin resistance occurred, the biological effect of leptin on sympathetic nervous system (SNS) becomes disrupted, which contributes to arterial hypertension pathogenesis.[140] Investigations done on rodents and humans revealed that BP becomes elevated as leptin infusion occurred at hypothalamic arcuate nucleus (ARC). On

contrast, BP and heart rate decreased due to downregulation of leptin receptor in the proopiomelanocortinergic (POMC) neurons.[141]

Leptin activates SNS to induce obesity related to hypertension[23] because it affects autonomic nervous system in Lep-Rb containing neurons.[142] In contrast to this, the activity of SNS and BP can be impaired during intravenous administration of leptin in humans.[143] Sympathetic nervous system and BP are regulated through the activation of melanocortin-4 receptors (MC4Rs) in brain stem nuclei, hence the renal SNS is altered.[144] The lysis of POMC protein induces the synthesis of α-melanocyte-stimulating hormone (α-MSH), which in turn activates MC4Rs.[144] The sensitization of hypothalamus MC4Rs induces an increase in renal system activity, including elevated sodium retention and secretion of renin, further leading to an increase in BP.[144] In addition to this, receptors of leptin are mainly expressed in the hypothalamus and are responsible for elevated secretion of aldosterone, which also depends on the level of Ca2+.[145] Xie and Bollag et al[146] in their focused review elaborate that leptin stimulates overproduction of aldosterone. The elevated level of aldosterone also leads to elevate retention of salt and water by the kidney, which results in an increase in BP[146] (Figure 1). Consequently, elevated level of leptin among obese individual leads to hypertension through increased production and secretion of aldosterone.

Hyperleptinemia Aggravates Further Cardiovascular Risk Complication

Globally, cardiovascular diseases (CVD) are a major health burden, which accounts for up to 12.3 and 17.6 million deaths in 1990 and 2016, respectively.[147] Different types of diseases are categorized under CVD, including coronary artery diseases,[148] myocardial infarction, heart failure, rheumatic heart diseases, stroke, and congenital heart diseases.[149] Stroke and coronary artery disease (CAD) are the major factors for the global death burden both in high and low-income countries.[150] In the USA, 15.4 million people were diagnosed with CAD from 2007 to 2010 whose age was greater than 20 years old.[40] Researchers are in contention whether leptin has a positive or negative impact on the heart and vascular system.[151] Perivascular fat has a characteristic of atheroprotective vascular homeostasis and give a mechanical strength for vasculature through release of leptin. However, it loses its biological function during obesity.[152,153] The expression of leptin has been elevated because of obesity-associated perivascular adipose tissue.[154] In contrast, investigations done on hypertensive rats showed the expression of perivascular adipose tissue (PVAT)-derived leptin was decreased.[155] Perivascular-derived leptin leads to vessel stiffness during obesity.[153] In addition, SNS activity become elevated due to the release of leptin.[156] In addition to leptin, PVAT activates the release of monocyte chemoattractant protein-1 (MCP-1), IL-8, IL-6, and TNF-α to promote the development of atherosclerosis through activation of smooth muscle cell migration.[157] Perivascular-derived leptin activates macrophage migration, expression of adhesion molecule, synthesis of free radicals, secretion of IL-6, and TNF-α.[158] Obesity-associated perivascular adipose tissue activates p38 mitogen-activated protein kinases signaling pathways to induce phenotypic change on vascular smooth muscle cells.

Published scientific conclusions on the effect of leptin on vascular diseases differ.[35] Several animal studies revealed that the pathogenesis of cardiac hypertrophy is associated with obesity.[159] Although leptin causes increased ventricular thickness and cardiac mass, its effect on cardiac hypertrophy is still undefined. It may lead to cardiac remodeling through triggering its biological and physiological effect using PI3K, mitogen-activated protein kinase (MAPK) and JAK/*STAT3* signaling cascade mechanism.[160] However, cardiac hypertrophy may develop because of activation of SNS and renin–angiotensin-aldosterone system.[161] Stangl et al[162] in 2000 carried out a demonstration on mice, and they confirmed that infusion of leptin leads to an increase in sympathetic activity of certain organs. Binding of leptin to its receptors induce the activation of SNS.[163] Receptors of leptin found on vascular cells indicate the potential role of leptin in the function of the vascular system.[164] Therefore, it has autocrine and paracrine effects on the vascular modulation process.[36] Investigations done on animal models showed that leptin leads to the development of atherosclerosis and thrombosis, which act as risk factors for CAD.[27] Even though animal investigations revealed that it contributes to atherosclerosis development,[115] findings from clinical investigations as well as experimental animal studies showed leptin's protective effect against atherosclerosis.[165,166] With regard to this, the synthesis of reactive oxygen species (ROS) increased rapidly after the treatment of leptin.[167] In addition to CAD, evidence revealed that heart failure is caused by increased genetic expression of leptin and its receptors.[168] In contrast,

congestive heart failure causes an elevation in leptin plasma level.[167] The induction of leptin signal transduction pathway through PI3K, MAPK, *JAK2/STAT3* results in biological and physiological response in different tissues, including left ventricular, which is related to left ventricular hypertrophy (LVH).[160] Moreover, angiotensin II-associated myocardial remodeling may be due to the biological effect of leptin through its signal transduction.[160] In vitro investigation showed that rodent and human cardiomyocyte hyperplasia were activated by the effect of leptin.[169]

Adiposity and obesity are the major risk factors for the pathogenesis of MetS, such as T2DM and hypertension, which in turn leads to cardiovascular complications,[170] because abnormality in adipose tissue and obesity induce a chronic inflammation.[55] Adiponectin/leptin ratio will be diminished during systemic inflammation to induce pathogenesis of various MetS.[10] In this regard, researchers agree with influence of dysfunctional adipokines on the pathogenesis of MetS.[171] This is due to a positive correlation between the level of leptin and development of atherosclerosis[172] (Figure 1). Elevated mass of adipose tissue is characterized by increased secretion of adipokines, which contribute to the pathogenesis of atherosclerosis.[35] Furthermore, the association between leptin and atherosclerosis is mainly associated with leptin resistance instead of hyperleptinemia.[173] Leptin resistance occurs in diabetes and obese subjects.[128] On behalf of the obesity-associated hypertension, elevated level of leptin leads to an increase in the production of aldosterone. Elevated aldosterone level also leads to increased retention of salt and water by the kidney, which results in an increase in blood pressure.[146]

Although it is difficult to clarify the mechanism of development of atherosclerosis, SLE patients may develop atherosclerosis.[174] This is because of development of atherosclerosis, which may be associated with the deposition of cholesterol ester (CE) in foam cells during endothelial dysfunction.[175] Concerning the atherosclerosis, a huge cohort study was done in Systemic Lupus International Collaborative Clinics (SLICC) on 1249 patients and 31 of them developed atherosclerosis.[174] In addition to this cohort study, the population-based research done in Sweden confirmed that higher incidence of CVD was seen in SLE patients.[176] According to this study, SLE patient's within the age range of 20–39 years have 16 times higher cardiovascular mortality risk than the general population. Similarly, Lewandowski and Kaplan[177] in 2016 also describe that one third of deaths of SLE patients are due to cardiovascular complications. Therefore, the risk of developing CVD is higher in SLE patients due to the development of atherosclerosis[174] (Figure 1). In contrast, numerous investigations confirmed that IBD leads to the risk of cardiovascular complication,[178] which is associated with involvement of leptin in the development of atherosclerosis[178] (Figure 1). Regarding psoriasis, inflammation promotes pathophysiology of disease, which in turn leads to the risk of cardiovascular complication.[83] Thus, CVD is one of the comorbidity effects of psoriasis.[83] Similarly, patients with RA are 1.5 times more likely to develop CVD as compared to the general population.[179] Adipokines modify the immune system and metabolic activity of cartilage, and bone which results in the occurrence of MetS.[170]

Conclusion

Leptin induces the activation and release of pro-inflammatory cytokines, including IL-6, TNF-α, IL-17 and other cytokines to promote systemic inflammation in RA, SLE and psoriasis. Leptin-activated pro-inflammatory mediators contribute to complication of atherosclerosis in T2DM. Conversely, it induces obesity-associated hypertension through activation of sympathetic nervous system in Lep-Rb containing neurons. It increases the secretion of aldosterone, which in turn causes an increase in arterial blood pressure. Consequently, the development of both MetS and chronic inflammatory disorders leads to the pathogenesis of CVD such as coronary artery disease and stroke. This review strongly suggests that the adverse individual effect of leptin on chronic inflammatory diseases in turn increases the risk of developing CVD. Therapeutic target of leptin regarding its pro-inflammatory effect and dysregulated sympathetic nervous system activity may prevent further cardiovascular complication. Therefore, we recommend that treating an elevated level of leptin has broad therapeutic potential to inhibit the pathogenesis of chronic inflammatory disorders and associated further cardiovascular complications. Early therapeutic management of hyperleptinemia in obesity-associated inflammatory disorders has a cumulative therapeutic potential to manage complications of CVD.

Abbreviations

CVD, cardiovascular disease; IBD, inflammatory bowel disease; IL, interleukin; JAK2/STAT3, Janus kinase/activators of transcription-3; MetS, metabolic syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TNF-α, tumor necrosis factor-alpha.

Data Sharing Statement

Data sharing is not applicable to this article because no data sets were generated or analyzed during the review.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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