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Review

Adipokines in dental pulp: Physiological, pathological, and potential therapeutic roles

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ABSTRACT

Background: Hundreds of adipokines have been identified, and their extensive range of endocrine functions—regulating distant organs such as oral tissues—and local autocrine/paracrine roles have been studied. In dentistry, however, adipokines are poorly known proteins in the dental pulp; few of them have been studied despite their large number. This study reviews recent advances in the investigation of dental-pulp adipokines, with an emphasis on their roles in inflammatory processes and their potential therapeutic applications.

Highlights: The most recently identified adipokines in dental pulp include leptin, adiponectin, resistin, ghrelin, oncostatin, chemerin, and visfatin. They have numerous physiological and pathological functions in the pulp tissue: they are closely related to pulp inflammatory mechanisms and actively participate in cell differentiation, mineralization, angiogenesis, and immune-system modulation.

Conclusion: Adipokines have potential clinical applications in regenerative endodontics and as biomarkers or targets for the pharmacological management of inflammatory and degenerative processes in dental pulp. A promising direction for the development of new therapies may be the use of agonists/antagonists to modulate the expression of the most studied adipokines.

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Contents

Abbreviations: AR, adiponectin receptor; DMP, dentin matrix protein; DPSC, dental pulp stem cell; DSPP, dentin sialophosphoprotein; EDM, enamel matrix-derived proteins; GHSR, growth hormone secretagogue receptor; I, inhibition; ICAM, intercellular adhesion molecule; IL, interleukin; LPS, lipopolysaccharides; MMP, matrix metalloproteinase; NAMPT, nicotinamide phosphoribosyltransferase; NK, natural killer; NO, nitric oxide; OSM, oncostatin M; OSMR, receptor for oncostatin M; PDL, periodontal ligament; PDLSC, periodontal ligament stem cell; ROS, reactive oxygen species; S, stimulation; SASP, senescence-associated secretory phenotype; TH-1 cell, T helper-1 cell; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

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1. Introduction

For years, adipose tissue was underestimated as just an energy reservoir [1–7]; however, it is now acknowledged as an endocrine organ producing numerous multifunctional bioactive proteinaceous molecules, known as adipokines [2,3,8–11]. Recent studies have identified >700 types, with diverse chemical structures, in the secretome of adipose tissue [12–15]. Hence, they have even been catalogued in other molecular families, such as cytokines, growth factors, hormones, and complement proteins [1,2,16,17].

Adipokines are predominantly produced by adipocytes [16], which form part of white and brown adipose tissue [4,9,18], constituting a key station as a multilevel network regulating human physiology [2,4]. Cells such as fibroblasts, osteoblasts, neutrophils, monocytes, macrophages, T lymphocytes, and natural killer (NK) lymphocytes also secrete adipokines [8,16]. However, the location, origin, and function of many of them remain unknown. Adipokines were considered exclusively associated with pathological processes, as they are linked to obesity, diabetes, cardiovascular diseases, and inflammation, among other pathologies [1,2,4,8,16,17,19]. However, adipokines also orchestrate a multitude of physiological processes [4,20], such as regulation of metabolic homeostasis, food intake, sleep functions, and anti-inflammatory activity [1,8,18,21–23].

Ubiquitous in nature, they are located throughout the body, and the oral tissues are no exception. Several studies have demonstrated the role of visfatin, chemerin, leptin, and omentin in temporomandibular joint disorders [24–29]. Adiponectin, leptin, resistin, chemerin, omentin, vaspin, and visfatin play active roles in bone remodeling [30]. Leptin and adiponectin promote osteogenesis through differentiation of mesenchymal stem cells into preosteoblasts and the proliferation and maturation of osteoblasts. Contrarily, omentin-1 is a proposed biomarker of metabolic disorders, including bone pathologies [31].

Adipokine quantity in periodontal tissues correlates with certain systemic conditions [30,32]. In obese patients, leptin and adiponectin levels are increased and decreased in the periodontal ligament (PDL) and gingival crevicular fluid, respectively [33,34]. Conversely, higher levels of vaspin and visfatin were identified in the crevicular fluid of patients with periodontal disease, than in healthy individuals [35,36]. Furthermore, adiponectin [37] and leptin [30] protect the periodontium by neutralizing the effects of lipopolysaccharides (LPS) of the periodontal pathogenic bacteria, inhibiting cell apoptosis, inducing antimicrobial peptide expression, and increasing growth factors that promote the proliferation of PDL cells, improving healing *in vitro* [30,34,37–39].

Although these biomolecules are crucial for multiple organic functions, information on the influence of adipokines on the dental pulp is limited. Most studies were performed in animals [8,28,40–44]. Therefore, although their results should be extrapolated to humans with caution, these studies open a window for research in humans. In the pulp tissue, few adipokines have been isolated with a pro-or anti-inflammatory effect [45–47]. Adipokines mediate pulp tissue mineralization and repair [30,41,48–53], making them a suitable target for new regenerative therapies combined with the currently available bioactive materials [41,52]. Nevertheless, to date, no studies have integrated information on the role of adipokines in physiological and pathological processes in dental pulp and their potential clinical application in pulp therapy. Therefore, this review aimed to explore the physiological, pathological, and potential therapeutic roles of adipokines in the dental pulp.

2. Materials and methods

Available literature was searched in PubMed and Scopus databases to identify relevant articles published until February 28, 2021, using the keywords dental pulp, odontoblasts, pulp fibroblasts, adipokines, leptin, adiponectin, visfatin, resistin, ghrelin, and chemerin. Articles focusing on adipokines in the dental pulp were selected. Additionally, to ensure that the information obtained was comprehensive, a manual search was performed on the reference lists of the articles initially selected.

3. Adipokines in dental pulp

The most recently identified adipokines in dental pulp include leptin, adiponectin, resistin, ghrelin, oncostatin, chemerin, and visfatin. Table 1 summarizes these aspects. This article reviews their origins, receptors, synthesis, physiologic and pathologic functions, and potential therapeutic roles in the dental pulp tissue.

3.1. Leptin

Discovered in 1994, Leptin is a 16 kDa protein [5,130] encoded by the Ob gene [1,5]. Its Ob-R receptor has six isoforms, Ob-Rb being the main isoform [18,59–61]. It is distributed in almost all tissues, explaining the pleiotropic function of leptin [51,131–133]. Although predominantly produced by adipocytes [30,134,135], it is produced on a smaller scale by skeletal muscle [136], placenta [137], gastric epithelium [138], liver, brain, and pituitary gland [139–141]; it is also synthesized and secreted by ameloblasts, pulp odontoblasts, and fibroblasts [54,61]. Dental pulp and periodontal tissues are important sources of leptin, both locally and systemically, because the expression of leptin in these tissues is equivalent or higher than that in the bone marrow [30,42].

Leptin and its receptors are expressed in human dental pulp cells and are involved in various pathophysiological processes. *In vitro,* odontoblasts have shown higher expression of leptin and its receptors than that by cells of the pulp core; even some cytoplasmic processes of odontoblasts extending into the dentinal tubules have shown leptin immunoreactivity [30]. The involvement of leptin in the differentiation of odontoblast-like cells from PDL stem cells (PDLSCs) and dental pulp stem cells (DPSCs) has been shown [49], indicating its role in the regeneration and repair of impaired dental structures [142] through formation of dentinal bridges protecting pulp tissue [30,41,45,49,62]. Furthermore, leptin reduces adipogenesis in DPSCs and PDLSCs, preventing their differentiation into adipocytes, thereby acting as an important modulator of dental stem cell differentiation [49].

Table 1
Summary of data available on adipokines in the dental pulp.

Adipokine	Origin	Stimulation (S) or inhibition (I)	Receptor	Receptor expression	Functions	Influences on inflammation
Leptin	Pulp fibroblasts, odontoblasts [42,51,54,55].	Neuropeptides (S) [54]. IL-1B, IL-6, TNF-α, and LPS (S) [56,57]. Heat exposure (S), Cold exposure (I) [58].	Ob-Rb [18,59–61].	High expression in the dental pulp [30]. Odontoblasts [30].	Stimulates the differentiation of DPSC into odontoblast-like cells [49]. Inhibits adipogenic differentiation of PDLSC and DPSC [49]. Stimulates the secretion of DSPP and DMP-1 [41,52,55], promotes the formation of dentin bridges [30,41,45,49,62]. Induces angiogenesis [41,52,63,64]. Induces maturation of tooth germ during odontogenesis [42].	Regulates innate and adaptive immune response [9,65], Proinflammatory [9,65], promotes the differentiation of TH1 cells, stimulates the oxidative burst of monocytes and macrophages [66,67]. Production of proinflammatory cytokines, such as TNF-α, IL-1, IL-2, IL-6, IL-8 and CC chemokine ligands [9,49,51,65,68–70]. Dose-dependent anti-inflammatory effect [30,41].
Adiponectin	Lymphocytes, neutrophils, and endothelial cells [71,72].	Heat exposure (I), Cold exposure (S) [58].	AR1 and AR2 [72–74].	AR1 and AR2 receptors are expressed in dental pulp [43].	Facilitates osteoblast proliferation and differentiation [75,76]. Promotes reparative dentin formation by increasing DSPP and DPP expression and stimulating hydroxyapatite crystals formation [43,77]. Induces angiogenesis [78].	Anti-inflammatory effect by regulating immune cells such as macrophages and inducing secretion of anti-inflammatory ILs [79]. Inhibits TLR-4 expression [80].
Resistin	Monocytes and macrophages [81].	IL-1, IL-6 and TNF-α (S) [81]. EDM (S) [82].	Not identified [83], although potential candidates have been ascribed [84–86].	N/A	Functions not clarified [82,87].	Proinflammatory; induces the production of cytokines such as IL-6, IL-1, IL-12, and TNF-α [88,89]. Counteracts the anti-inflammatory effects of adiponectin by promoting the expression of VCAM, ICAM, and pentraxin 3 [87,90]. Inflammaging [83]
Chemerin	Dental pulp cells such as odontoblasts [91].	Obesity, diabetes and cardiovascular disease (S) [92–94] IL-1B (S) [93,95]	CMKLR1, also known as ChemR23 or DEZ [96].	Odontoblasts [91], immune cells such as immature plasmacytoid dendritic cells, myeloid dendritic cells, macrophages, and NK cells [44,97].	Differentiation of odontoblasts and ameloblasts [91,98]. Induces calcium mobilization, during odontogenesis [91]. Induces angiogenesis [99].	Proinflammatory, it incites the release of proinflammatory cytokines such as TNF-α, IL6 and IL-1 [100,101]. Anti-inflammatory, mediated by the release of NO and inhibition of VCAM-1 expression [16,102].
Ghrelin	Preodontoblasts, odontoblasts and blood vessels [40,50].	Obesity (I) [103].	GHSR [104].	Suspected to be found in odontoblasts [105,106].	Stimulation of GHSR expression [104]. Stimulates proliferation, differentiation, bone metabolism and regulates osteoblast apoptosis [107–109]. Regulates development and formation of hard tissues, such as bones and teeth [40]. Influences dentinogenesis [40,110].	Anti-inflammatory, inhibits the production of proinflammatory cytokines [111].

(*continued on next page*)

Table 1 (*continued*)

Adipokine	Origin	Stimulation (S) or inhibition (I)	Receptor	Receptor expression	Functions	Influences on inflammation
Oncostatin	Odontoblasts, fibroblasts, endothelial and inflammatory cells [46], neutrophils [112,113], dendritic cells [114].	IL-1a, TNF-α and IL-6 (S) [115,116] and bacterial LPS (S) [114].	OSMR [117].	Pulp stem cells [118].	Increases chondrogenic, adipogenic and osteogenic differentiation of dental pulp stem cells [118]. Regulates growth, differentiation, gene expression, immune response and tissue remodeling processes [118,119].	Proinflammatory, through induction of cytokines and MMP [116,120–123].
Visfatin	Neutrophils [124,125].	FK866: visfatin inhibitor (I) [126].	Not identified [16,127,128].	N/A	Inhibits neutrophil apoptosis and increases neutrophil inflammatory response [124]. Pulpal aging, through cellular senescence [47]. It creates chronic proinflammatory microenvironments that favor pulp pathology [47].	Production of proinflammatory cytokines, such as IL-1β, TNF-α, IL-6, and co-stimulatory molecules, by CD14+ monocytes [124]. Increases the expression of ICAM-1 and VCAM-1 [129].

AR, adiponectin receptor; DMP, dentin matrix protein; DPP, dentin phosphoprotein; DPSC, dental pulp stem cell; DSPP, dentin sialophosphoprotein; ICAM, intercellular adhesion molecule; IL: interleukin; LPS, lipopolysaccharides; N/A: no information available; MMP, matrix metalloproteinase; NK, natural killer; NO, nitric oxide; OSM, oncostatin M; OSMR, receptor for oncostatin M; Ob-Rb, leptin receptor (b isoform); PDLSC, periodontal ligament stem cell; TLR-4, toll-like receptor-4; TH1, T helper 1 cell; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.

Leptin stimulates odontoblasts by increasing the secretion and expression of dentin sialophosphoprotein (DSPP) and dentin matrix protein 1 (DMP-1) [41,52,55], which are important for odontogenic differentiation and dentin mineralization [143]. Additionally, if we consider odontoblasts the first line defense against microorganisms and their by-products, leptin may inevitably contribute to autocrine/paracrine signaling pathways for repair, mineralization, and tertiary dentin formation.

Leptin has proangiogenic effects [63,64] and increases the expression of vascular endothelial growth factor (VEGF) and fibroblast growth factor, positively influencing proliferation, differentiation, mineralization, neovascularization, and reparative dentin formation in pulp tissue, as demonstrated both *in vitro* and *in vivo* [30,42,52,144]. These growth factors are synergistic with leptin for the stimulation of angiogenesis [145], crucial for the recruitment and mobilization of stem cells to the site of pulp injury [41] and for tooth development [146].

During odontogenesis, intense expression of leptin and VEGF in ameloblasts, cells of the stratum intermedium, odontoblasts, and some cells of the dental papilla, induce angiogenesis in the tooth germ and support its maturation [42]; similar expression was found in human and rat dental germs [42,147,148]. Additionally, leptin expressed by these cells promotes tooth development by facilitating endothelial cell recruitment and blood vessel branching [42], leading to the release of leptin from specialized cells of the gingival epithelium [30].

However, similar to its systemic effect, leptin is proinflammatory in dental pulp and regulates both innate and adaptive immune responses under normal and pathological conditions [9,65,149]. Leptin expression is increased in inflammatory conditions [68,149], additionally promoting the secretion of other acute phase reactant cytokines, such as interleukin IL-1, IL-2, IL-6, IL-8, tumor necrosis factor alpha (TNF-α), and CC chemokine ligands (CCL3, CCL4, and CCL5) [9,49,51,68–70]. Like other proinflammatory cytokines, leptin promotes T helper 1 (TH1) cell differentiation, stimulates the oxidative burst in macrophages [66,67], influences the proliferation, differentiation, activation, and cytotoxicity of NK cells [150], and modulates the initiation and progression of autoimmune responses [134,151]. This shows that high local leptin levels stimulate the immune system [152], modulating its development, proliferation, maturation, and activation [65,68]. Further, leptin is associated with increased expression of CCL20 [153], allowing the recruitment of memory T cells and immature dendritic cells [154,155] and lymphocyte trafficking, magnifying pulpal inflammatory response [68].

Further, physiologically, neuropeptides induce leptin release, whereas in a pathological state, IL-1β, IL-6, TNF-α, infectious and inflammatory stimuli, such as LPS, do so [56,57], triggering greater production of neuropeptides that increase the release of leptin and cytokines, thereby increasing inflammatory process. Despite the proinflammatory nature of leptin [68,149], it likely induces a dose-dependent, anti-inflammatory effect [41,51]. Though this has not been well elucidated, it may be assumed that leptin increases the recruitment of lymphocytes and macrophages to the dental pulp and, together with its angiogenic, mineralizing, and differentiating effects, it promotes the repair and regeneration of the pulp–dentin complex, thus protecting it from infection and inflammation [30,41,55].

3.2. Adiponectin

Isolated in 1995, adiponectin is a 30 kDa protein [2], encoded by the ADIPOQ gene [156], and mainly produced by adipocytes. However, it was recently reported to be synthesized also by lymphocytes, neutrophils [71,72], myocytes, endothelial cells, and cardiomyocytes [157]. Two distinct isoforms have been identified: a full-length, low-molecular-weight adiponectin that functions primarily in the brain, and a globular form that functions in the liver,

which act as ligands for the receptors, adipoR1 and adipoR2 [72–74]. The first is expressed ubiquitously, but predominantly in skeletal muscle, while the second is expressed mainly in the liver [74,158]. Both types of receptors have been isolated within pulp tissue, with a higher affinity for the full-length isoform [43].

Although known primarily as an anti-inflammatory adipokine, recent studies have indicated that their biological functions differ according to the isoform. Full-length adiponectin blocks endotoxin-induced IL-6 secretion and induces anti-inflammatory interleukins secretion [79]. However, the globular form triggers cytokine production, making it proinflammatory [159]. This is evidenced in skeletal joints, where adiponectin plays a proinflammatory role by inducing release of IL-6 and metalloproteinase 1 from synovial fibroblasts involved in matrix degradation; higher amount of adiponectin was found in the synovial fluid of rheumatoid arthritis and osteoarthritis patients [160,161]. Further studies may clarify this dual biological effect.

Adiponectin plays a major role in two important hard tissues. In bone, adiponectin promotes osteoblast proliferation and differentiation [75,76] and protects against bone resorption [162,163]. However, an *in vitro* study performed on rat pulp cells determined that the application of 10 μg/ml adiponectin for 12 days significantly improved pulp tissue mineralization, which is assumed to occur because adiponectin increases the expression of DSPP and dentin phosphoprotein, forming complexes with type I collagen and promoting the formation of hydroxyapatite crystals, resulting in reparative dentin formation. However, no significant differences were observed on previous days and at different concentrations, indicating the importance of concentration and time in tissue mineralization [43,77].

Adiponectin induces the synthesis of anti-inflammatory mediators in immune cells, primarily targeting macrophages [80]. Adiponectin inhibits the activation of M1 macrophages (proinflammatory), promotes the proliferation of M2 macrophages (anti-inflammatory) [164–166] and its production of interleukin 10 (IL-10) [167], and inhibits the expression of Toll-like receptor 4, preventing the activation of NF-κB [80]. These anti-inflammatory mechanisms may also occur in the dental pulp; however, clinical application of adiponectin requires further research.

3.3. Resistin

Resistin is a 12.5 kDa dimeric protein, first identified in 2001 [88,168]. In humans, it is predominantly produced by macrophages and monocytes, induced by proinflammatory cytokines, such as IL-1, IL-6, and TNF-α [81]. It circulates throughout the bloodstream in the organism because of its affinity for vascular endothelial cells [87], though concentrating in inflamed areas [37,88]. The resistin receptor remains unknown [83], although potential candidates have been ascribed [84–86].

The biological function of resistin remains ambiguous [87]; nevertheless, it has a predominantly proinflammatory function, due to increased concentration in inflamed areas [169]. It induces the release of proinflammatory cytokines, such as IL-6, IL-1, IL-12, and TNF-α [88,89], and directly counteracts the anti-inflammatory effects of adiponectin in vascular endothelial cells by promoting the expression of vascular adhesion molecule (VCAM), intercellular adhesion molecule (ICAM), and pentraxin 3 [87,90]. Moreover, resistin was recently shown to severely influence aging due to its proinflammatory function as it always increases during inflammaging [83].

In cells of mesenchymal origin, including human dental pulp cells, enamel matrix-derived proteins (EDM) dramatically increase the expression of resistin, indicating that part of the biological effects of EDM on tissue regeneration may involve resistin [82]. Although EDM has been successfully used in periodontal regeneration and root surgery for its antimicrobial and mineralization capabilities [170,171], its role in dental pulp remains unclear because of its ability to increase resistin levels, which are proinflammatory at high concentrations [82]. Therefore, further exploration is necessary before the clinical application of resistin.

3.4. Chemerin

Chemerin, a chemotactic protein whose weight varies according to its state of activity (16 kDa) or inactivity (18 kDa), was discovered in 2007 [96,172]. It acts as a ligand for the G protein-coupled receptor CMKLR1 (ChemR23 or DEZ) [96]. The presence of chemerin and its receptor is established in odontoblasts and ameloblasts [91]; the chemerin receptor is also expressed in several immune cells, such as immature dendritic cells, myeloid dendritic cells, macrophages, and NK cells [44,97].

Chemerin plays a dual role, in both proinflammatory and anti-inflammatory activities, in the body. It triggers chemotaxis of immature dendritic cells and macrophages and promotes the release of proinflammatory cytokines such as TNF, IL-6, and IL-1 [100,101,173,174]. Its anti-inflammatory action on vascular endothelial cells could be due to nitric oxide (NO) release via activation of endothelial NO synthase, and inhibition of TNF-α-induced VCAM-1 expression in endothelial cells [16,102].

Though the biological function of chemerin within dental pulp is not yet known, it has been suggested to participate in angiogenesis [99]; during odontogenesis, it is assumed to promote the differentiation of ameloblasts and odontoblasts through the Chem23 signaling pathway [91,98]. This was corroborated *in vitro* in mice, where chemerin and its receptor were found to be expressed during odontogenesis, allowing the differentiation of mesenchymal and epithelial cells. Chemerin is the first receptor expressed at a later stage of tissue differentiation, leading to the assumption that in early stages, chemerin binds to other receptors (GPR1 and CCRL2) to induce calcium mobilization for hard tissue formation [91].

3.5. Ghrelin

Ghrelin is a 3.3 kDa peptide hormone with two major forms (acylated and deacylated [biologically inactive]) [104,175,176]. First identified in 1999 as an endogenous ligand for the growth hormone secretagogue receptor (GHSR) [104], ghrelin is an anti-inflammatory adipokine that inhibits proinflammatory cytokines [111]. Though produced predominantly by the stomach, it is also expressed in tissues such as the placenta, pancreas, hematopoietic cells, liver, kidneys, lungs [104,177,178], mammary tissue, and pulp cells [50,179,180]. The presence of ghrelin has been reported in many biological fluids, such as blood [104,177], cerebrospinal fluid [181], breast milk [179,182], and saliva [183–186].

Several studies demonstrated the presence of ghrelin mRNA in human osteoblasts, stimulating autocrine and/or paracrine proliferation, differentiation mechanisms, and bone metabolism [107–109]. As dental tissue shares several functional, developmental, and anatomical similarities with bone, ghrelin activity might be similar in them [187]. Its presence in human dental pulp, especially in the odontoblast layer, where it is speculated to influence dentinogenesis, healing, regeneration [105,106], and mineralization [50], was identified *in vitro*. Another study in rats demonstrated decreased ghrelin tissue levels in obesity, in organs including the tongue and teeth, corroborating the presence of ghrelin in the dental pulp [103]. However, the presence of ghrelin receptors in teeth has not yet been established [50].

Although ghrelin can reach dental pulp via the bloodstream, it was proposed to be produced *in situ* by odontoblasts or blood vessels [50]. An analysis on extracted teeth showed ghrelin levels of 26.4 fmol/mg and 28.2 fmol/mg in the pulp of canines and molars, respectively. This represents low ghrelin levels compared with those in the gastric mucosa [104], but higher than that in many other tissues, as detected by RT-PCR [180]. It could be speculated that teeth constitute an important source of ghrelin, locally and systemically.

The presence of ghrelin during odontogenesis was determined in embryonic and postnatal mice by detecting the acylated form in ameloblasts and odontoblasts. In the initial stages of tooth formation, ghrelin was evidently expressed in the enamel organ epithelium and mildly in the underlying mesenchyme. In advanced and postnatal stages, ghrelin is expressed preferentially in preameloblasts, preodontoblasts, ameloblasts, and odontoblasts, related to the synthesis of dentin and enamel matrices [40], indicating the importance of this adipokine in tooth development.

The function of ghrelin-induced GH needs to be determined, as it can reportedly promote bone and tooth development through the GH/insulin-like growth factor-1 axis [110,188]. Furthermore, as ghrelin functions through GHSR, the presence of GHSR in ameloblasts and odontoblasts should be determined.

3.6. Oncostatin

Oncostatin M (OSM) is a 28 kDa pleiotropic cytokine related to the interleukin-6 family [189,190]. Its receptor (OSMR) is a signal transduction receptor for IL-6-type cytokines [117]. OSM contributes to inflammation and tissue remodeling and is involved in regulating growth, differentiation, gene expression, and immune response [117,191,192]. Detected in several inflammatory processes in the oral cavity, such as chronic periodontitis [193,194] and epithelialized apical periodontitis lesions [123], OSM is part of their cytokine network [112].

OSM mRNA presence in dental pulp tissue was demonstrated *in vitro*, showing an increased expression (2.36 times) during inflammatory processes, compared to clinically healthy pulp. This adipokine was identified in the cytoplasm of odontoblasts, fibroblasts, inflammatory cells, and endothelial cells; therefore, the cytosol of these cells is a reservoir of OSM, which might be released during certain stages of inflammation [46]. Moreover, neutrophils are potent cellular sources of OSM biosynthesis and release under inflammatory conditions [113,114], and bacterial LPS induces its expression in dendritic cells [115]. OSM alone can stimulate IL-6 production, or act synergistically to increase the production of matrix metalloproteinases (MMP-1, MMP-8, MMP-13) and IL-6 [116,120,121], playing an important role in pulpal pathogenesis [122,123,195–197]. Therefore, the expression of OSM in inflamed pulp is induced directly by bacteria or indirectly by inflammatory cytokines from resident cells [46].

OSM was shown to act on dental pulp stem cells (DPSCs) in extracted supernumerary teeth, showing the potential to differentiate into chondrogenic, adipogenic, and especially osteogenic lineages, by increasing the production of bone morphogenetic proteins BMP2, BMP4, BMP6, osteopontin, transcription factor RUNX2, and alkaline phosphatase [118]. This demonstrates the potential of this adipokine for stimulation of DPSC differentiation.

3.7. Visfatin

Visfatin, also known as nicotinamide phosphoribosyltransferase (Nampt), or as pre-B cell colony enhancing factor, is a 52 kDa adipokine identified in 2005 [2] secreted predominantly by adipose tissue and in low levels by neutrophils in response to endotoxins via TLR4. It plays a crucial role in regulating the production of proinflammatory cytokines, contributing to various inflammatory disorders [124,125]. Though the specific receptor for visfatin is not yet identified [16], some of its actions have been ascribed to its intrinsic Nampt enzymatic activity [127,128]. It is believed to show proinflammatory activity through the production of IL-1β, TNF-α, IL-6, and co-stimulatory molecules in CD14+ monocytes [124].

Visfatin, strongly proinflammatory by promoting the expression of cell adhesion molecules such as ICAM-1 and VCAM-1 [129], increases neutrophil inflammatory response. It inhibits the apoptosis of these cells in a dose-dependent manner by decreasing the activity of caspase-3 and 8 [124], enhancing oxidative burst activity, and reactive oxygen species (ROS) generation [16].

Visfatin may be involved in cellular senescence in several tissues, including the dental pulp [47,126]. However, it protects the retina from senescence, suggesting that its effect is tissue-dependent. Cellular senescence is characterized by reduced alkaline phosphatase activity, indicating impaired regeneration of injured pulp tissue [47,198], telomere damage in vascular endothelial cells [47], irreversible growth arrest, and acquisition of the senescence-associated secretory phenotype (SASP) [126,199].

Upon acquiring the SASP phenotype, the cells secrete inflammatory cytokines, chemokines, growth factors, MMPs (MMP-1, MMP-3, MMP-10) [200], and enzymes with autocrine/paracrine activity [198,201], which causes tissue remodelling and local inflammation [47,201]. Hence, at the pulp level, DNA damage induced by oxidative stress through SASP creates a chronic inflammatory microenvironment, causing visible inflammatory pathologies such as pulpitis and fibrosis, and pulpal aging. A visfatin inhibitor (FK866) diminished this response in the dental pulp [126], not only by annulling its effect, but also by other independent mechanisms, such as the inhibition of oxidative stress produced by ROS and decreased expression of SASP-producing genes. Thus, FK866 interrupts the aging process through anti-inflammatory, anti-tumorigenic, and antioxidant mechanisms [126,202]. Studies should be continued on visfatin as a possible therapeutic target, and on its inhibitor, that can decrease the aging of dental pulp tissues and maintain its viability [47].

4. Therapeutic potential

It is evident that adipokines are closely related to pulp inflammatory mechanisms and thereby useful in regenerative procedures and vital pulp therapy, as they actively participate in cell differentiation, mineralization, angiogenesis, and modulation of the immune system [30,41].

Although many adipokines promote inflammation, leptin was demonstrated *in vivo* to promote pulp regeneration [41] depending on the type of tissue [47]. Leptin, applied directly to exposed rat pulp tissue *in vivo*, induces mineralization and dentin bridging, protecting the dentin-pulp complex [41]. This could be dose-dependent, since leptin, when applied through a collagen scaffold, showed a favorable inflammatory response and a greater capacity to induce angiogenesis, odontogenic differentiation, and mineralization at concentrations of 10 mmol/L, than at concentrations of 1 mmol/L [41].

In rats, leptin improved the gene expression of collagen types I and III when applied topically on wounds, stimulating collagen synthesis [203]. Additionally, it has been determined that the exogenous application of leptin by intraperitoneal injections in rats provides a therapeutic effect by decreasing burn-induced inflammation. This inhibits the passage of neutrophils, which are responsible for the release of substances that destroy normal cells and dissolve the connective tissue [204], indicating the possible use of leptin in pulp regeneration.

Adiponectin also has high potential for the regeneration of dental tissues, despite the limited information available. In dental pulp, its increase promotes dentin mineralization by inducing the expression of DSPP [43] and generating a suitable environment for the formation of dentin bridges, thereby providing protection against pulp exposure [77]. This mineralization could be complemented with that of leptin and both adipokines could be used together for clinical application, while considering their proangiogenic effects [63,64,78,145].

A benefit of adiponectin, in PDL cells, is the ability to accelerate wound closure. This was demonstrated *in vitro*, by removing the first layers of PDL cells and directly applying adiponectin (3 μg/ml). This resulted in accelerated healing as adiponectin increased cell proliferation and the expression of certain growth factors and extracellular matrix, which underscores its favorable role in periodontal homeostasis and soft and hard tissue healing [34]. Although not yet clinically applied in pulp therapy, these data suggest that if adiponectin was placed on exposed pulp, it could have a similar favorable action, especially considering the results of a previously mentioned study [43] that demonstrated mineralization of pulp tissue.

Contrarily, evidence indicates that ghrelin promotes the synthesis and secretion of dentin and enamel matrices, as it is present in odontoblasts and ameloblasts during tooth development and after eruption [40,50]. Hence, it influences hard tissue mineralization in the tooth, and could be used when mineralized tissue formation is required in the form of dentin bridges, as in direct pulp protection. However, GH and ghrelin promote the proliferation and differentiation of primary osteoblasts and inhibit their apoptosis [108,109,205], suggesting that they could help form bone tissue in large periapical lesions.

OSM functions as an inflammatory mediator [112] and acts with other cytokines and MMPs to amplify the inflammatory cycle [46]. However, the capacity of OSM to induce differentiation of DPSCs towards chondrogenic, adipogenic, and osteogenic lineages (in conjunction with BMP2, BMP4, BMP6) have been demonstrated *in vitro*, showing its potential in developing craniofacial regenerative therapies and alveolar bone regeneration [118,119]. Therefore, it is important to clarify the conditions necessary to clinically apply this adipokine in regenerative endodontics [118].

The therapeutic potential of chemerin is not yet clear, due to its dual effect (proinflammatory and anti-inflammatory). However, since it has been found within the odontogenic process, it could be assumed to be of great importance for dental tissue engineering [91]. Contrarily, it has been shown that in pulp fibroblasts, its receptor ChemR23 has affinity for resolvin E1 as a ligand, which allows an anti-inflammatory effect in the early stages of pulpitis [44,98]. The mechanism by which this effect is achieved is the suppression of the proinflammatory activity of pulp fibroblasts [44]. It must be considered that this latter cell can remove the survival signals, normalize the chemokine gradients, and facilitate the apoptosis of the infiltrating leukocytes or their elimination through the lymphatics; by inhibiting these functions of the fibroblast, the regeneration of the pulp tissue would be favored [206]. Additionally, chemerin exhibits potent angiogenic effects and can induce the production of MMP-2 and MMP-9 and key cell survival and angiogenic cascades in endothelial cells [99].

5. Future perspectives

The use of different adipokines as biomarkers to determine the health status of patients has been proposed. A study focused on the potential of visfatin to predict mortality in critically ill patients and found it to be strongly associated with disease severity and organ failure. Hence, it could also be used as a biomarker to determine the presence of pulp degradation in future research [207].

A main concern while applying adipokine-based pulp regeneration techniques is obtaining them. Fat auto-transplantation techniques are widely used in aesthetic procedures and have shown potential for wound healing [208]. Recently, it was demonstrated that adipose tissue obtained from lipoaspirates, using the Coleman or Shippert technique, employing centrifugation and sedimentation processes, contains significant amounts of adipokines, such as leptin and adiponectin, and growth factors relevant to wound healing [208,209]. Therefore, lipoaspirates could be extracted and cryopreserved for potential endodontic therapeutic uses without significant loss of their biological activity [208].

The biological mechanisms of regulation and adaptation of adipokines can be systematically exploited for pulp therapy. Leptin secretion increases during the day [210,211], while that of adiponectin, resistin, and visfatin, during the night [212,213]. Moreover, modifications in the sleep schedule [214] and diet [215] can desynchronize the circadian rhythm, which increases leptin production when it is usually low [216]. Thus, by combining treatment with an adequate diet, sleep rhythm, and application period, it would be possible to stimulate/inhibit adipokine secretion at defined times to enhance the desired therapeutic effect.

Conversely, many cells can adapt to extreme conditions [217], and adipocytes exposed to heat shock modify the production of adipokines as an adaptive response [218]. It has been shown that when the temperature is raised to 41 °C, production of leptin increases and that of adiponectin decreases as a compensatory measure. An increase in leptin can protect the tissue against aggression by increasing energy, tissue metabolism, and induction of apoptosis. Meanwhile, the decrease in adiponectin is derived from protein synthesis reduction, favoring the induction of the response to heat shock [58]. Contrarily, low temperatures decrease leptin expression and increase adiponectin expression [58]. Hence, the response of dental pulp cells to heat shock could be similar to that of adipocytes, since the pulp tissue is exposed to multiple thermal stimuli during mastication [219,220] and dental procedures [221–223]. To date, no studies have determined these possible changes in the expression of adipokines in the dental pulp that could clarify their functions in physiological and pathological states.

Finally, although proteomic profiling studies have identified hundreds of adipokines in the secretome of adipose tissue [12–15] and, recently, have even identified new adipokines [224], the human adipokinome has not yet been fully characterized [12]. Secretomics could unveil new biological, pathological, and homeostasis mechanisms of adipokines in pulp tissue. Furthermore, the precise mechanisms leading to the secretion of many adipokines requires investigation.

6. Conclusion

Adipokines carry out several physiological and pathological functions in the pulp tissue. Though scarcely studied with limited understanding of their actions, they are potential therapeutic agents to be researched in the management of inflammatory disorders of the dentin-pulp complex and regenerative endodontics. The use of agonists/antagonists modulating the expression of the most studied adipokines may be promising in developing new therapeutic agents; taking into consideration the available evidence on their use and their unique characteristics and functions, such as angiogenesis and reparative dentin formation, leptin and adiponectin seem to be the best candidates for use as therapeutics.

Author statement

Because this is a review study, informed consent is not required. Ethical approval was not required for this review study.

Ethical statement

Ethical approval was not required for this review study.

CRediT authorship contribution statement

José Luis Álvarez-Vásquez: Conceptualization, Methodology, Formal analysis, Literature search, Writing - review & editing, Project administration. **María Isabel Bravo-Guapisaca:** Literature search, Writing - review & editing. **Jonathan Francisco Gavidia-Pazmiño:** Literature search, Writing - review & editing. **Ruth Viviana Intriago-Morales:** Literature search, Writing - review & editing.

Conflicts of interest

The authors declare no conflicts of interest.

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References

[1] Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol 2011;11:85–97. https://doi.org/10.1038/nri2921.
[2] Kyrou I, Mattu HS, Chatha K, Randeva HS. Fat hormones, Adipokines. Elsevier; 2017. https://doi.org/10.1016/B978-0-12-803111-7.00007-5.
[3] Choi CHJ, Cohen P. Adipose crosstalk with other cell types in health and disease. Exp Cell Res 2017;360:6–11. https://doi.org/10.1016/j.yexcr.2017.04.022.
[4] Raucci R, Rusolo F, Sharma A, Colonna G, Castello G, Costantini S. Functional and structural features of adipokine family. Cytokine 2013;61:1–14. https://doi.org/10.1016/j.cyto.2012.08.036.
[5] Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;372:425–32. https://doi.org/10.1038/372425a0.
[6] Siiteri PK. Adipose tissue as a source of hormones. Am J Clin Nutr 1987;45:277–82. https://doi.org/10.1093/ajcn/45.1.277.
[7] Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. Am J Clin Nutr 2006;83:461S–5S. https://doi.org/10.1093/ajcn/83.2.461S.
[8] Blüher M, Mantzoros CS. From leptin to other adipokines in health and disease: facts and expectations at the beginning of the 21st century. Metabolism 2015;64:131–45. https://doi.org/10.1016/j.metabol.2014.10.016.
[9] Fernández-Riejos P, Sánchez-Margalet V, Najib S, Santos-Alvarez J, Martín-Romero C, Pérez-Pérez A, et al. Role of leptin in the activation of immune cells. Mediat Inflamm 2010;1–8. https://doi.org/10.1155/2010/568343.
[10] Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K. Obesity, adiponectin and vascular inflammatory disease. Curr Opin Lipidol 2003;14:561–6. https://doi.org/10.1097/00041433-200312000-00003.
[11] Berg AH, Scherer PE. Adipose tissue, inflammation, and cardiovascular disease. Circ Res 2005;96:939–49. https://doi.org/10.1161/01.RES.0000163635.62927.34.
[12] Lehr S, Hartwig S, Lamers D, Famulla S, Müller S, Hanisch FG, et al. Identification and validation of novel adipokines released from primary human adipocytes. Mol Cell Proteomics 2012;11. https://doi.org/10.1074/mcp.M111.010504.
[13] Dahlman I, Elsen M, Tennagels N, Korn M, Brockmann B, Sell H, et al. Functional annotation of the human fat cell secretome. Arch Physiol Biochem 2012;118:84–91. https://doi.org/10.3109/13813455.2012.685745.
[14] Rosenow A, Arrey TN, Bouwman FG, Noben JP, Wabitsch M, Mariman ECM, et al. Identification of novel human adipocyte secreted proteins by using SGBS cells. J Proteome Res 2010;9:5389–401. https://doi.org/10.1021/pr100621g.
[15] Alvarez-Llamas G, Szalowska E, de Vries MP, Weening D, Landman K, Hoek A, et al. Characterization of the human visceral adipose tissue secretome. Mol Cell Proteomics 2007;6:589–600. https://doi.org/10.1074/mcp.M600265-MCP200.
[16] Żelechowska P, Kozłowska E, Pastwińska J, Agier J, Brzezińska-Błaszczyk E. Adipocytokine involvement in innate immune mechanisms. J Interferon Cytokine Res 2018;38:527–38. https://doi.org/10.1089/jir.2018.0102.
[17] Maximus PS, Al Achkar Z, Hamid PF, Hasnain SS, Peralta CA. Adipocytokines: are they the theory of everything? Cytokine 2020;133. https://doi.org/10.1016/j.cyto.2020.155144.
[18] Lago F, Dieguez C, Gómez-Reino J, Gualillo O. The emerging role of adipokines as mediators of inflammation and immune responses. Cytokine Growth Factor Rev 2007;18:313–25. https://doi.org/10.1016/j.cytogfr.2007.04.007.
[19] Falcão-Pires I, Castro-Chaves P, Miranda-Silva D, Lourenço AP, Leite-Moreira AF. Physiological, pathological and potential therapeutic roles of adipokines. Drug Discov Today 2012;17:880–9. https://doi.org/10.1016/j.drudis.2012.04.007.
[20] Scotece M, Conde J, López V, Lago F, Pino J, Gómez-Reino JJ, et al. Adiponectin and leptin: new targets in inflammation. Basic Clin Pharmacol Toxicol 2014;114:97–102. https://doi.org/10.1111/bcpt.12109.
[21] Lago F, Dieguez C, Gómez-Reino J, Gualillo O. Adipokines as emerging mediators of immune response and inflammation. Nat Clin Pract Rheumatol 2007;3:716–24. https://doi.org/10.1038/ncprheum0674.
[22] Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol 2006;6:772–83. https://doi.org/10.1038/nri1937.
[23] Shea SA, Hilton MF, Orlova C, Ayers RT, Mantzoros CS. Independent circadian and sleep/wake regulation of adipokines and glucose in humans. J Clin Endocrinol Metab 2005;90:2537–44. https://doi.org/10.1210/jc.2004-2232.
[24] Yapıcı Yavuz G, Şimşek Kaya G, Kızıltunç A. Analysis of synovial fluid visfatin level in temporomandibular joint disorders. Cranio - J Craniomandib Pract 2019;37:296–303. https://doi.org/10.1080/08869634.2018.1429367.
[25] Yaman D, Alpaslan C, Akca G, Avcı E. Correlation of molecular biomarker concentrations between synovial fluid and saliva of the patients with temporomandibular disorders. Clin Oral Invest 2020;24:4455–61. https://doi.org/10.1007/s00784-020-03310-8.
[26] Xiong H, Li W, Li J, Fang W, Ke J, Li B, et al. Elevated leptin levels in temporomandibular joint osteoarthritis promote proinflammatory cytokine IL-6 expression in synovial fibroblasts. J Oral Pathol Med 2019;48:251–9. https://doi.org/10.1111/jop.12819.
[27] Şimşek Kaya G, Yapıcı Yavuz G, Kızıltunç A. Expression of chemerin in the synovial fluid of patients with temporomandibular joint disorders. J Oral Rehabil 2018;45:289–94. https://doi.org/10.1111/joor.12608.
[28] Xiong H, Li W, Ke J, Fang W, Li B, Wei L. Leptin levels in the synovial fluid of patients with temporomandibular disorders. J Oral Maxillofac Surg 2019;77:493–8. https://doi.org/10.1016/j.joms.2018.09.012.
[29] Obada DN. Circulating Omentin-1- A new adipokine with diagnostic and therapeutic role in TMJ disorders: advanced endeavor to dental field. Oral Health Dent Manag 2018;17:4172. https://doi.org/10.4172/2247-2452-c6-081.
[30] Li W, Zhu W, Hou J, Huang B, Liu K, Meng H. Leptin and its receptor expression in dental and periodontal tissues of primates. Cell Tissue Res 2014;355:181–8. https://doi.org/10.1007/s00441-013-1729-0.
[31] Liu Y, Song CY, Wu SS, Liang QH, Yuan LQ, Liao EY. Novel adipokines and bone metabolism. Int J Endocrinol 2013;2013. https://doi.org/10.1155/2013/895045.
[32] Liu YY, Shi D, Li W, Zhang X, Sun XJ, Xu L, et al. Association between plasma leptin level and systemic inflammatory markers in patients with aggressive periodontitis. Chin Med J (Engl) 2015;128:528–32. https://doi.org/10.4103/0366-6999.151110.
[33] Zohaib A, Abduljabbar T, Abu Hassan MI, Javed F, Vohra F. Cytokine profile in chronic periodontitis patients with and without obesity: a systematic review and meta-analysis. Dis Markers 2016;1–12. https://doi.org/10.1155/2016/4801418.
[34] Nokhbehsaim M, Keser S, Nogueira AVB, Cirelli JA, Jepsen S, Jäger A, et al. Beneficial effects of adiponectin on periodontal ligament cells under normal and regenerative conditions. J Diabetes Res 2014;2014. https://doi.org/10.1155/2014/796565.
[35] Pradeep AR, Raghavendra NM, Prasad MVR, Kathariya R, Patel SP, Sharma A. Gingival crevicular fluid and serum visfatin concentration: their relationship in periodontal health and disease. J Periodontol 2011;82:1314–9. https://doi.org/10.1902/jop.2011.100690.
[36] Pradeep AR, Karvekar S, Nagpal K, Patnaik K. Vaspin: a new adipokine correlating the levels of crevicular fluid and tear fluid in periodontitis and obesity. J Investig Clin Dent 2016;7:232–8. https://doi.org/10.1111/jicd.12149.
[37] Furugen R, Hayashida H, Yamaguchi N, Yoshihara A, Ogawa H, Miyazaki H, et al. The relationship between periodontal condition and serum levels of resistin and adiponectin in elderly Japanese. J Periodontal Res 2008;43:556–62. https://doi.org/10.1111/j.1600-0765.2008.01085.x.
[38] Borilova Linhartova P, Janos J, Poskerova H, Kavrikova D, Fassmann A, Dusek L, et al. Adipokine gene variability and plasma levels in patients with chronic periodontitis-a case-control study. Braz Oral Res 2019;33. https://doi.org/10.1590/1807-3107BOR-2019.VOL33.0034.
[39] Nokhbehsaim M, Keser S, Nogueira AVB, Jäger A, Jepsen S, Cirelli JA, et al. Leptin effects on the regenerative capacity of human periodontal cells. Int J Endocrinol 2014;2014. https://doi.org/10.1155/2014/180304.
[40] Liu B, Han X, Feng W, Cui J, Hasegawa T, Amizuka N, et al. Altered distribution of Ghrelin protein in mice molar development. Arch Oral Biol 2016;65:82–6. https://doi.org/10.1016/j.archoralbio.2016.01.019.
[41] Choi SH, Jang JH, Koh JT, Chang HS, Hwang YC, Hwang IN, et al. Effect of leptin on odontoblastic differentiation and angiogenesis: an in vivo study. J Endod 2019;45:1332–41. https://doi.org/10.1016/j.joen.2019.08.003.

[42] Ide S, Tokuyama R, Davaadorj P, Shimozuma M, Kumasaka S, Tatehara S, et al. Leptin and vascular endothelial growth factor regulate angiogenesis in tooth germs. Histochem Cell Biol 2011;135:281–92. https://doi.org/10.1007/s00418-011-0789-z.
[43] Yasuda Y, Koike T, Kawamorita T, Saito T. Adiponectin induces dentin sialophosphoprotein in rat dental pulp cells: an in vitro study. J Endod 2008;34:679–83. https://doi.org/10.1016/j.joen.2008.02.038.
[44] Xu H, Chen J, Ge J, Xia K, Tao S, Su Y, et al. Resolvin E1 ameliorates pulpitis by suppressing dental pulp fibroblast activation in a chemerin receptor 23-dependent manner. J Endod 2019;45:1126–1134.e1. https://doi.org/10.1016/j.joen.2019.05.005.
[45] Martín-González J, Pérez-Pérez A, Sánchez-Jiménez F, Díaz-Parrado EM, De Miguel M, Sánchez-Margalet V, et al. Leptin promotes dentin sialophosphoprotein expression in human dental pulp. J Endod 2015;41:487–92. https://doi.org/10.1016/j.joen.2014.11.026.
[46] Huang F-M, Tsai C-H, Yang S-F, Chang Y-C. The upregulation of oncostatin M in inflamed human dental pulps. Int Endod J 2009;42:627–31. https://doi.org/10.1111/j.1365-2591.2009.01567.x.
[47] Ok CY, Park S, Jang H-O, Takata T, Bae M-K, Kim Y-D, et al. Visfatin induces senescence of human dental pulp cells. Cells 2020;9:193. https://doi.org/10.3390/cells9010193.
[48] Turner R, Kalra S, Wong C, Philbrick K, Lindenmaier L, Boghossian S, et al. Peripheral leptin regulates bone formation. J Bone Miner Res 2013;28:22–34. https://doi.org/10.1002/jbmr.1734.
[49] Um S, Choi JR, Lee JH, Zhang Q, Seo BM. Effect of leptin on differentiation of human dental stem cells. Oral Dis 2011;17:662–9. https://doi.org/10.1111/j.1601-0825.2011.01820.x.
[50] Aydin S, Ozercan IH, Geckil H, Dagli F, Aydin S, Kumru S, et al. Ghrelin is present in teeth. J Biochem Mol Biol 2007;40:368–72. https://doi.org/10.5483/bmbrep.2007.40.3.368.
[51] Wei L, Chen Y, Zhang C, Liu M, Xiong H. Leptin induces IL-6 and IL-8 expression through leptin receptor Ob-Rb in human dental pulp fibroblasts. Acta Odontol Scand 2019;77:205–12. https://doi.org/10.1080/00016357.2018.1536280.
[52] Ngo VA, Jung JY, Koh JT, Oh WM, Hwang YC, Lee BN. Leptin induces odontogenic differentiation and angiogenesis in human dental pulp cells via activation of the mitogen-activated protein kinase signaling pathway. J Endod 2018;44:585–91. https://doi.org/10.1016/j.joen.2017.11.018.
[53] Martín-González J, Carmona-Fernández A, Pérez-Pérez A, Sánchez-Jiménez F, Sánchez-Margalet V, Segura-Egea JJ. Expression and immunohistochemical localization of leptin in human periapical granulomas. Med Oral Patol Oral Cir Bucal 2015;20:e334–9. https://doi.org/10.4317/medoral.20385.
[54] El karim IA, Linden GJ, Irwin CR, Lundy FT. Neuropeptides regulate expression of angiogenic growth factors in human dental pulp fibroblasts. J Endod 2009;35:829–33. https://doi.org/10.1016/j.joen.2009.03.005.
[55] Martín-González J, Pérez-Pérez A, Cabanillas-Balsera D, Vilariño-García T, Sánchez-Margalet V, Segura-Egea JJ. Leptin stimulates DMP-1 and DSPP expression in human dental pulp via MAPK 1/3 and PI3K signaling pathways. Arch Oral Biol 2019;98:126–31. https://doi.org/10.1016/j.archoralbio.2018.11.019.
[56] Bernotiene E, Palmer G, Gabay C. The role of leptin in innate and adaptive immune responses. Arthritis Res Ther 2006;8. https://doi.org/10.1186/ar2004.
[57] Sarraf P, Frederich RC, Turner EM, Ma G, Jaskowiak NT, Rivet DJ, et al. Multiple cytokines and acute inflammation raise mouse leptin levels: potential role in inflammatory anorexia. J Exp Med 1997;185:171–5. https://doi.org/10.1084/jem.185.1.171.
[58] Preedy V, Hunter R. Adipokines. 1st ed., vol. 1. CRC Press; 2011.
[59] Bjørbæk C, Uotani S, Da Silva B, Flier JS. Divergent signaling capacities of the long and short isoforms of the leptin receptor. J Biol Chem 1997;272:32686–95. https://doi.org/10.1074/jbc.272.51.32686.
[60] Murakami T, Yamashita T, Iida M, Kuwajima M, Shima K. A short form of leptin receptor performs signal transduction. Biochem Biophys Res Commun 1997;231:26–9. https://doi.org/10.1006/bbrc.1996.6030.
[61] Lõpez-Lõpez J, Jané-Salas E, Estrugo-Devesa A, Castellanos-Cosano L, Martín-González J, Velasco-Ortega E, et al. Frequency and distribution of root-filled teeth and apical periodontitis in an adult population of Barcelona, Spain. Int Dent J 2012;62:40–6. https://doi.org/10.1111/j.1875-595X.2011.00087.x.
[62] Sueyama Y, Kaneko T, Ito T, Kaneko R, Okiji T. Implantation of endothelial cells with mesenchymal stem cells accelerates dental pulp tissue regeneration/healing in pulpotomized rat molars. J Endod 2017;43:943–8. https://doi.org/10.1016/j.joen.2017.01.035.
[63] Bouloumié A, Drexler HCA, Lafontan M, Busse R. Leptin, the product of Ob gene, promotes angiogenesis. Circ Res 1998;83:1059–66. https://doi.org/10.1161/01.RES.83.10.1059.
[64] Sierra-Honigmann MR, Nath AK, Murakami C, García-Cardeña G, Papapetropoulos A, Sessa WC, et al. Biological action of leptin as an angiogenic factor. Science (80-) 1998;281:1683–6. https://doi.org/10.1126/science.281.5383.1683.
[65] Stofkova A. Leptin and adiponectin: from energy and metabolic dysbalance to inflammation and autoimmunity. Endocr Regul 2009;43:157–68.
[66] Maingrette F, Renier G. Leptin increases lipoprotein lipase secretion by macrophages: involvement of oxidative stress and protein kinase C. Diabetes 2003;52:2121–8. https://doi.org/10.2337/diabetes.52.8.2121.
[67] Sánchez-Pozo C, Rodriguez-Baño J, Domínguez-Castellano A, Muniain MA, Goberna R, Sánchez-Margalet V. Leptin stimulates the oxidative burst in control monocytes but attenuates the oxidative burst in monocytes from HIV-infected patients. Clin Exp Immunol 2003;134:464–9. https://doi.org/10.1111/j.1365-2249.2003.02321.x.
[68] Martín-González J, Sánchez-Jiménez F, Pérez-Pérez A, Carmona-Fernández A, Sánchez-Margalet V, Segura-Egea JJ. Leptin expression in healthy and inflamed human dental pulp. Int Endod J 2013;46:442–8. https://doi.org/10.1111/iej.12009.
[69] Santos-Alvarez J, Goberna R, Sánchez-Margalet V. Human leptin stimulates proliferation and activation of human circulating monocytes. Cell Immunol 1999;194:6–11. https://doi.org/10.1006/cimm.1999.1490.
[70] Kiguchi N, Maeda T, Kobayashi Y, Fukazawa Y, Kishioka S. Leptin enhances CC-chemokine ligand expression in cultured murine macrophage. Biochem Biophys Res Commun 2009;384:311–5. https://doi.org/10.1016/j.bbrc.2009.04.121.
[71] Pang TTL, Narendran P. The distribution of adiponectin receptors on human peripheral blood mononuclear cells. Ann N Y Acad Sci 2008;1150:143–5. https://doi.org/10.1196/annals.1447.021. Blackwell Publishing Inc.
[72] Chinetti G, Zawadski C, Fruchart J, Staels B. Expression of adiponectin receptors in human macrophages and regulation by agonists of the nuclear receptors PPARα, PPARγ, and LXR. Biochem Biophys Res Commun 2004;314:151–8. https://doi.org/10.1016/j.bbrc.2003.12.058.
[73] Kadowaki T, Yamauchi T. Adiponectin and adiponectin receptors. Endocr Rev 2005;26:439–51. https://doi.org/10.1210/er.2005-0005.
[74] Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature 2003;423:762–9. https://doi.org/10.1038/nature01705.
[75] Luo XH, Guo LJ, Yuan LQ, Xie H, De Zhou H, Wu XP, et al. Adiponectin stimulates human osteoblasts proliferation and differentiation via the MAPK signaling pathway. Exp Cell Res 2005;309:99–109. https://doi.org/10.1016/j.yexcr.2005.05.021.
[76] Berner HS, Lyngstadaas SP, Spahr A, Monjo M, Thommesen L, Drevon CA, et al. Adiponectin and its receptors are expressed in bone-forming cells. Bone 2004;35:842–9. https://doi.org/10.1016/j.bone.2004.06.008.
[77] Tamura I, Ueda K, Matsuda Y, Kamada A, Yoshikawa Y, Domae E, et al. Influence of adiponectin and leptin on the kinetics of human pulp cells. Open J Stomatol 2020;10:360–71. https://doi.org/10.4236/ojst.2020.1012033.
[78] Shibata R, Ouchi N, Kihara S, Sato K, Funahashi T, Walsh K. Adiponectin stimulates angiogenesis in response to tissue ischemia through stimulation of AMP-activated protein kinase signaling. J Biol Chem 2004;279:28670–4. https://doi.org/10.1074/jbc.M402558200.
[79] Krysiak R, Handzlik-Orlik G, Okopien B. The role of adipokines in connective tissue diseases. Eur J Nutr 2012;51:513–28. https://doi.org/10.1007/s00394-012-0370-0.
[80] Fang H, Judd RL. Adiponectin regulation and function. Comp Physiol 2018;8:1031–63. https://doi.org/10.1002/cphy.c170046.
[81] Kaser S, Kaser A, Sandhofer A, Ebenbichler CF, Tilg H, Patsch JR. Resistin messenger-RNA expression is increased by proinflammatory cytokines in vitro. Biochem Biophys Res Commun 2003;309:286–90. https://doi.org/10.1016/j.bbrc.2003.07.003.
[82] Obregon-Whittle MV, Stunes AK, Almqvist S, Brookes SJ, Lee JD, Syversen U, et al. Enamel matrix derivative stimulates expression and secretion of resistin in mesenchymal cells. Eur J Oral Sci 2011;119:366–72. https://doi.org/10.1111/j.1600-0722.2011.00902.x.
[83] Acquarone E, Monacelli F, Borghi R, Nencioni A, Odetti P. Resistin – A reappraisal. Mech Ageing Dev 2019;178:46–63. https://doi.org/10.1016/j.mad.2019.01.004.
[84] Tarkowski A, Bjersing J, Shestakov A, Bokarewa MI. Resistin competes with lipopolysaccharide for binding to toll-like receptor 4. J Cell Mol Med 2010;14:1419. https://doi.org/10.1111/j.1582-4934.2009.00899.x.
[85] Daquinag A, Zhang Y, Amaya-Manzanares F, Simmons P, Kolonin M. An isoform of decorin is a resistin receptor on the surface of adipose progenitor cells. Cell Stem Cell 2011;9:74–86. https://doi.org/10.1016/J.STEM.2011.05.017.
[86] Boström E, Svensson M, Andersson S, Jonsson I, Ekwall A, Eisler T, et al. Resistin and insulin/insulin-like growth factor signaling in rheumatoid arthritis. Arthritis Rheum 2011;63:2894–904. https://doi.org/10.1002/art.30527.
[87] Verma S, Li SH, Wang CH, Fedak PWM, Li RK, Weisel RD, et al. Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction. Circulation 2003;108:736–40. https://doi.org/10.1161/01.CIR.0000084503.91330.49.
[88] Bokarewa M, Nagaev I, Dahlberg L, Smith U, Tarkowski A. Resistin, an adipokine with potent proinflammatory properties. J Immunol 2005;174:5789–95. https://doi.org/10.4049/jimmunol.174.9.5789.
[89] Silswal N, Singh AK, Aruna B, Mukhopadhyay S, Ghosh S, Ehtesham NZ. Human resistin stimulates the pro-inflammatory cytokines TNF-α and IL-12 in macrophages by NF-κB-dependent pathway. Biochem Biophys Res Commun 2005;334:1092–101. https://doi.org/10.1016/j.bbrc.2005.06.202.
[90] Kawanami D, Maemura K, Takeda N, Harada T, Nojiri T, Imai Y, et al. Direct reciprocal effects of resistin and adiponectin on vascular endothelial cells: a new insight into adipocytokine-endothelial cell interactions. Biochem Biophys Res Commun 2004;314:415–9. https://doi.org/10.1016/j.bbrc.2003.12.104.

[91] Ohira T, Spear D, Azimi N, Andreeva V, Yelick PC. Chemerin-ChemR23 signaling in tooth development. J Dent Res 2012;91:1147–53. https://doi.org/10.1177/0022034512464777.
[92] Perumalsamy P, Aqilah Mohd Zin N, Widodo R, Wan Ahmad W, Vethakkan S, Huri H. Chemokine like receptor-1 (CMKLR-1) receptor: a potential therapeutic target in management of chemerin induced type 2 diabetes mellitus and cancer. Curr Pharm Des 2017;23. https://doi.org/10.2174/1381612823666170616081256.
[93] Ernst M, Sinal C. Chemerin: at the crossroads of inflammation and obesity. Trends Endocrinol Metab 2010;21:660–7. https://doi.org/10.1016/J.TEM.2010.08.001.
[94] Sell H, Divoux A, Poitou C, Basdevant A, Bouillot J, Tordjman A, et al. Chemerin correlates with markers for fatty liver in morbidly obese patients and strongly decreases after weight loss induced by bariatric surgery. J Clin Endocrinol Metab 2010;95:2892–6. https://doi.org/10.1210/JC.2009-2374.
[95] Kralisch S, Weise S, Sommer G, Lipfert J, Lossner U, Bluher M, et al. Interleukin-1beta induces the novel adipokine chemerin in adipocytes in vitro. Regul Pept 2009;154:102–6. https://doi.org/10.1016/J.REGPEP.2009.02.010.
[96] Goralski KB, McCarthy TC, Hanniman EA, Zabel BA, Butcher EC, Parlee SD, et al. Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism. J Biol Chem 2007;282:28175–88. https://doi.org/10.1074/jbc.M700793200.
[97] Wittamer V, Grégoire F, Robberecht P, Vassart G, Communi D, Parmentier M. The C-terminal nonapeptide of mature chemerin activates the chemerin receptor with low nanomolar potency. J Biol Chem 2004;279:9956–62. https://doi.org/10.1074/jbc.M313016200.
[98] Chen J, Xu H, Xia K, Cheng S, Zhang Q. Resolvin E1 accelerates pulp repair by regulating inflammation and stimulating dentin regeneration in dental pulp stem cells. Stem Cell Res Ther 2021;12:75. https://doi.org/10.1186/s13287-021-02141-y.
[99] Kaur J, Adya R, Tan BK, Chen J, Randeva HS. Identification of chemerin receptor (ChemR23) in human endothelial cells: chemerin-induced endothelial angiogenesis. Biochem Biophys Res Commun 2010;391:1762–8. https://doi.org/10.1016/j.bbrc.2009.12.150.
[100] Meder W, Wendland M, Busmann A, Kutzleb C, Spodsberg N, John H, et al. Characterization of human circulating TIG2 as a ligand for the orphan receptor ChemR23. FEBS Lett 2003;555:495–9. https://doi.org/10.1016/S0014-5793(03)01312-7.
[101] Zabel BA, Allen SJ, Kulig P, Allen JA, Cichy J, Handel TM, et al. Chemerin activation by serine proteases of the coagulation, fibrinolytic, and inflammatory cascades. J Biol Chem 2005;280:34661–6. https://doi.org/10.1074/jbc.M504868200.
[102] Yamawaki H, Kameshima S, Usui T, Okada M, Hara Y. A novel adipocytokine, chemerin exerts anti-inflammatory roles in human vascular endothelial cells. Biochem Biophys Res Commun 2012;423:152–7. https://doi.org/10.1016/j.bbrc.2012.05.103.
[103] Aydin S, Sahin I, Ozkan Y, Dag E, Gunay A, Guzel SP, et al. Examination of the tissue ghrelin expression of rats with diet-induced obesity using radioimmunoassay and immunohistochemical methods. Mol Cell Biochem 2012;365:165–73. https://doi.org/10.1007/s11010-012-1256-4.
[104] Kojima M, Kangawa K. Ghrelin: structure and function. Physiol Rev 2005;85:495–522. https://doi.org/10.1152/physrev.00012.2004.
[105] Balasubramaniam A, Wood S, Joshi R, Su C, Friend LA, Sheriff S, et al. Ghrelin stimulates food intake and growth hormone release in rats with thermal injury: synthesis of ghrelin. Peptides 2006;27:1624–31. https://doi.org/10.1016/j.peptides.2006.02.005.
[106] Konturek PC, Brzozowski T, Walter B, Burnat G, Hess T, Hahn EG, et al. Ghrelin-induced gastroprotection against ischemia-reperfusion injury involves an activation of sensory afferent nerves and hyperemia mediated by nitric oxide. Eur J Pharmacol 2006;536:171–81. https://doi.org/10.1016/j.ejphar.2006.02.032.
[107] Delhanty PJD, van der Eerden BCJ, van der Velde M, Gauna C, Pols HAP, Jahr H, et al. Ghrelin and unacylated ghrelin stimulate human osteoblast growth via mitogen-activated protein kinase (MAPK)/phosphoinositide 3-kinase (PI3K) pathways in the absence of GHS-R1a. J Endocrinol 2006;188:37–47. https://doi.org/10.1677/joe.1.06404.
[108] Maccarinelli G, Sibilia V, Torsello A, Raimondo F, Pitto M, Giustina A, et al. Ghrelin regulates proliferation and differentiation of osteoblastic cells. J Endocrinol 2005;184:249–56. https://doi.org/10.1677/joe.1.05837.
[109] Kim SW, Her SJ, Park SJ, Kim D, Park KS, Lee HK, et al. Ghrelin stimulates proliferation and differentiation and inhibits apoptosis in osteoblastic MC3T3-E1 cells. Bone 2005;37:359–69. https://doi.org/10.1016/j.bone.2005.04.020.
[110] Ohlsson C, Bengtsson B, Isaksson O, Andreassen T, Slootweg M. Growth hormone and bone. J Pediatr Endocrinol 1992;5:91–3. https://doi.org/10.1210/edrv.19.1.0324.
[111] Pereira JADS, Da Silva FC, De Moraes-Vieira PMM. The impact of ghrelin in metabolic diseases: an immune perspective. J Diabetes Res 2017;2017. https://doi.org/10.1155/2017/4527980.
[112] Modur V, Feldhaus MJ, Weyrich AS, Jicha DL, Prescott SM, Zimmerman GA, et al. Oncostatin M is a proinflammatory mediator: in vivo effects correlate with endothelial cell expression of inflammatory cytokines and adhesion molecules. J Clin Invest 1997;100:158–68. https://doi.org/10.1172/JCI119508.
[113] Grenier A, Dehoux M, Boutten A, Arce-Vicioso M, Durand G, Gougerot M, et al. Oncostatin M production and regulation by human polymorphonuclear neutrophils. Blood 1999;93:1413–21.
[114] Hurst SM, McLoughlin RM, Monslow J, Owens S, Morgan L, Fuller GM, et al. Secretion of oncostatin M by infiltrating neutrophils: regulation of IL-6 and chemokine expression in human mesothelial cells. J Immunol 2002;169:5244–51. https://doi.org/10.4049/jimmunol.169.9.5244.
[115] Suda T, Chida K, Todate A, Ide K, Asada K, Nakamura Y, et al. Oncostatin M production by human dendritic cells in response to bacterial products. Cytokine 2002;17:335–40. https://doi.org/10.1006/cyto.2002.1023.
[116] Brown T, Rowe M, Liu J, Shoyan M. Regulation of IL-6 expression by oncostatin M. J Immunol 1991;147:2175–80.
[117] Heinrich PC, Behrmann I, Haan S, Hermanns HM, Müller-Newen G, Schaper F. Principles of interleukin (IL)-6-type cytokine signalling and its regulation. Biochem J 2003;374:1–20. https://doi.org/10.1042/BJ20030407.
[118] Kim YH, Lee JS, Seo EJ, Park JK, Yea K, Shin J, et al. Oncostatin M enhances osteogenic differentiation of dental pulp stem cells derived from supernumerary teeth. Biochem Biophys Res Commun 2020;529:169–74. https://doi.org/10.1016/j.bbrc.2020.06.013.
[119] Feng X, Shen S, Cao P, Zhu L, Zhang Y, Zheng K, et al. The role of oncostatin M regulates osteoblastic differentiation of dental pulp stem cells through STAT3 pathway. Cytotechnology 2016;68:2699–709. https://doi.org/10.1007/s10616-016-9995-9.
[120] Manicourt DH, Poilvache P, Van Egeren A, Devogelaer JP, Lenz ME, Thonar EJMA. Synovial fluid levels of tumor necrosis factor α and oncostatin M correlate with levels of markers of the degradation of crosslinked collagen and cartilage aggrecan in rheumatoid arthritis but not in osteoarthritis. Arthritis Rheum 2000;43:281–8. https://doi.org/10.1002/1529-0131(200002)43:2<281::AID-ANR7>3.0.CO;2-7.
[121] Cawston TE, Ellis AJ, Humm G, Lean E, Ward D, Curry V. Interleukin-1 and oncostatin M in combination promote the release of collagen fragments from bovine nasal cartilage in culture. Biochem Biophys Res Commun 1995;215:377–85. https://doi.org/10.1006/bbrc.1995.2476.
[122] Chang YC, Yang SF, Hsieh YS. Regulation of matrix metalloproteinase-2 production by cytokines and pharmacological agents in human pulp cell cultures. J Endod 2001;27:679–82. https://doi.org/10.1097/00004770-200111000-00007.
[123] Tsai CH, Huang FM, Chang YC. Immunohistochemical localization of oncostatin M in epithelialized apical periodontitis lesions. Int Endod J 2008;41:772–6. https://doi.org/10.1111/j.1365-2591.2008.01430.x.
[124] Jia SH, Li Y, Parodo J, Kapus A, Fan L, Holstein OD, et al. Pre-B cell colony-enhancing factor inhibits neutrophil apoptosis in experimental inflammation and clinical sepsis. J Clin Invest 2004;113:1318–27. https://doi.org/10.1172/JCI19930.
[125] Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, et al. Visfatin: a protein secreted by visceral fat that Mimics the effects of insulin. Science (80-) 2005;307:426–30. https://doi.org/10.1126/science.1097243.
[126] Ok CY, Park S, Jang H-O, Takata T, Lee O-H, Bae M-K, et al. FK866 protects human dental pulp cells against oxidative stress-induced cellular senescence. Antioxidants 2021;10:271. https://doi.org/10.3390/antiox10020271.
[127] Busso N, Karababa M, Nobile M, Rolaz A, Van Gool F, Galli M, et al. Pharmacological inhibition of nicotinamide phosphoribosyltransferase/visfatin enzymatic activity identifies a new inflammatory pathway linked to NAD. PLoS One 2008;3. https://doi.org/10.1371/JOURNAL.PONE.0002267.
[128] Romacho T, Azcutia V, Vázquez-Bella M, Matesanz N, Cercas E, Nevado J, et al. Extracellular PBEF/NAMPT/visfatin activates pro-inflammatory signalling in human vascular smooth muscle cells through nicotinamide phosphoribosyltransferase activity. Diabetologia 2009;52:2455–63. https://doi.org/10.1007/s00125-009-1509-2.
[129] Kim SR, Bae YH, Bae SK, Choi KS, Yoon KH, Koo TH, et al. Visfatin enhances ICAM-1 and VCAM-1 expression through ROS-dependent NF-κB activation in endothelial cells. Biochim Biophys Acta Mol Cell Res 2008;1783:886–95. https://doi.org/10.1016/j.bbamcr.2008.01.004.
[130] Rosenbaum M, Leibel RL, Hirsch J. Obesity. N Engl J Med 1997;337:396–407. https://doi.org/10.1056/NEJM199708073370606.
[131] Abella V, Scotece M, Conde J, Pino J, Gonzalez-Gay MA, Gómez-Reino JJ, et al. Leptin in the interplay of inflammation, metabolism and immune system disorders. Nat Rev Rheumatol 2017;13:100–9. https://doi.org/10.1038/nrrheum.2016.209.
[132] Lam QLK, Lu L. Role of leptin in immunity. Cell Mol Immunol 2007;1:1–13.
[133] Mantzoros CS, Magkos F, Brinkoetter M, Sienkiewicz E, Dardeno TA, Kim SY, et al. Leptin in human physiology and pathophysiology. Am J Physiol Endocrinol Metab 2011;301. https://doi.org/10.1152/ajpendo.00315.2011.
[134] La Cava A, Matarese G. The weight of leptin in immunity. Nat Rev Immunol 2004;4:371–9. https://doi.org/10.1038/nri1350.
[135] Ahima RS, Flier JS. Leptin. Annu Rev Physiol 2000;62:413–37. https://doi.org/10.1146/annurev.physiol.62.1.413.
[136] Wang J, Liu R, Hawkins M, Barzilial N, Rossetti L. A nutrient-sensing pathway regulates leptin gene expression in muscle and fat. Nature 1998;393:684–8. https://doi.org/10.1038/31474.
[137] Masuzaki H, Ogawa Y, Sagawa N, Hosoda K, Matsumoto T, Mise H, et al. Nonadipose tissue production of leptin: leptin as a novel placenta- derived hormone in humans. Nat Med 1997;3:1029–33. https://doi.org/10.1038/nm0997-1029.

[138] Bado A, Levasseur S, Attoub S, Kermorgant S, Laigneau JP, Bortoluzzi MN, et al. The stomach is a source of leptin. Nature 1998;394:790–3. https://doi.org/10.1038/29547.
[139] Jin L, Burguera BG, Couce ME, Scheithauer BW, Lamsan J, Eberhardt NL, et al. Leptin and leptin receptor expression in normal and neoplastic human pituitary: evidence of a regulatory role for leptin on pituitary cell proliferation. J Clin Endocrinol Metab 1999;84:2903–11. https://doi.org/10.1210/jcem.84.8.5908.
[140] Morash B, Li A, Murphy PR, Wilkinson M, Ur E. Leptin gene expression in the brain and pituitary gland. Endocrinology 1999;140:5995–8. https://doi.org/10.1210/endo.140.12.7288.
[141] Margetic S, Gazzola C, Pegg GG, Hill RA. Leptin: a review of its peripheral actions and interactions. Int J Obes 2002;26:1407–33. https://doi.org/10.1038/sj.ijo.0802142.
[142] Gay IC, Chen S, MacDougall M. Isolation and characterization of multipotent human periodontal ligament stem cells. Orthod Craniofac Res 2007;10:149–60. https://doi.org/10.1111/j.1601-6343.2007.00399.x.
[143] Suzuki S, Haruyama N, Nishimura F, Kulkarni AB. Dentin sialophosphoprotein and dentin matrix protein-1: two highly phosphorylated proteins in mineralized tissues. Arch Oral Biol 2012;57:1165–75. https://doi.org/10.1016/j.archoralbio.2012.03.005.
[144] Cross MJ, Claesson-Welsh L. FGF and VEGF function in angiogenesis: signalling pathways, biological responses and therapeutic inhibition. Trends Pharmacol Sci 2001;22:201–7. https://doi.org/10.1016/S0165-6147(00)01676-X.
[145] Cao R, Brakenhielm E, Wahlestedt C, Thyberg J, Cao Y. Leptin induces vascular permeability and synergistically stimulates angiogenesis with FGF-2 and VEGF. Proc Natl Acad Sci U S A 2001;98:6390–5. https://doi.org/10.1073/pnas.101564798.
[146] Nait Lechguer A, Kuchler-Bopp S, Hu B, Haïkel Y, Lesot H. Vascularization of engineered teeth. J Dent Res 2008;87:1138–43. https://doi.org/10.1177/154405910808701216.
[147] Spector JA, Mehrara BJ, Greenwald JA, Saadeh PB, Steinbrech DS, Bouletreau PJ, et al. Osteoblast expression of vascular endothelial growth factor is modulated by the extracellular microenvironment. Am J Physiol Cell Physiol 2001;280. https://doi.org/10.1152/ajpcell.2001.280.1.c72.
[148] Reseland JE, Syversen U, Bakke I, Qvigstad G, Eide LG, Hjertner, et al. Leptin is expressed in and secreted from primary cultures of human osteoblasts and promotes bone mineralization. J Bone Miner Res 2001;16:1426–33. https://doi.org/10.1359/jbmr.2001.16.8.1426.
[149] Martín-González J, Pérez-Pérez A, Sánchez-Jiménez F, Carmona-Fernández A, Torres-Lagares D, Sánchez-Margalet V, et al. Leptin receptor is up-regulated in inflamed human dental pulp. J Endod 2013;39:1567–71. https://doi.org/10.1016/j.joen.2013.08.014.
[150] Tian Z, Sun R, Wei H, Gao B. Impaired natural killer (NK) cell activity in leptin receptor deficient mice: leptin as a critical regulator in NK cell development and activation. Biochem Biophys Res Commun 2002;298:297–302. https://doi.org/10.1016/S0006-291X(02)02462-2.
[151] Matarese G, Moschos S, Mantzoros CS. Leptin in immunology. J Immunol 2005;174:3137–42. https://doi.org/10.4049/jimmunol.174.6.3137.
[152] Gainsford T, Willson TA, Metcalf D, Handman E, Mcfarlane C, Ng A, et al. Leptin can induce proliferation, differentiation, and functional activation of hemopoietic cells. Proc Natl Acad Sci U S A 1996;93:14564–8. https://doi.org/10.1073/pnas.93.25.14564.
[153] Farquharson AJ, Steele RJ, Carey FA, Drew JE. Novel multiplex method to assess insulin, leptin and adiponectin regulation of inflammatory cytokines associated with colon cancer. Mol Biol Rep 2012;39:5727–36. https://doi.org/10.1007/s11033-011-1382-1.
[154] Shimizu Y, Murata H, Kashii Y, Hirano K, Kunitani H, Higuchi K, et al. CC-chemokine receptor 6 and its ligand macrophage inflammatory protein 3α might be involved in the amplification of local necroinflammatory response in the liver. Hepatology 2001;34:311–9. https://doi.org/10.1053/jhep.2001.26631.
[155] Dieu MC, Vanbervliet B, Vicari A, Bridon JM, Oldham E, Aït-Yahia S, et al. Selective recruitment of immature and mature dendritic cells by distinct chemokines expressed in different anatomic sites. J Exp Med 1998;188:373–86. https://doi.org/10.1084/jem.188.2.373.
[156] Crawford LJA, Peake R, Price S, Morris TCM, Irvine AE. Adiponectin is produced by lymphocytes and is a negative regulator of granulopoiesis. J Leukoc Biol 2010;88:807–11. https://doi.org/10.1189/jlb.1109723.
[157] Ahima RS. Metabolic actions of adipocyte hormones: focus on adiponectin. Obesity (Silver Spring) 2006;14(Suppl 1). https://doi.org/10.1038/oby.2006.276.
[158] Yamauchi T, Nio Y, Maki T, Kobayashi M, Takazawa T, Iwabu M, et al. Targeted disruption of AdipoR1 and AdipoR2 causes abrogation of adiponectin binding and metabolic actions. Nat Med 2007;13:332–9. https://doi.org/10.1038/nm1557.
[159] Kyriazi E, Tsiotra PC, Boutati E, Ikonomidis I, Fountoulaki K, Maratou E, et al. Effects of adiponectin in TNF-α, IL-6, and IL-10 cytokine production from coronary artery disease macrophages. Horm Metab Res 2011;43:537–44. https://doi.org/10.1055/s-0031-1277227.
[160] Otero M, Logo R, Gomez R, Logo F, Dieguez C, Gómez-Reino JJ, et al. Changes in plasma levels of fat-derived hormones adiponectin, leptin, resistin and visfatin in patients with rheumatoid arthritis. Ann Rheum Dis 2006;65:1198–201. https://doi.org/10.1136/ard.2005.046540.
[161] Ehling A, Schäffler A, Herfarth H, Tarner IH, Anders S, Distler O, et al. The potential of adiponectin in driving arthritis. J Immunol 2006;176:4468–78. https://doi.org/10.4049/jimmunol.176.7.4468.
[162] Yamaguchi N, Kukita T, Li YJ, Kamio N, Fukumoto S, Nonaka K, et al. Adiponectin inhibits induction of TNF-α/RANKL-stimulated NFATc1 via the AMPK signaling. FEBS Lett 2008;582:451–6. https://doi.org/10.1016/j.febslet.2007.12.037.
[163] Tu Q, Zhang J, Dong LQ, Saunders E, Luo E, Tang J, et al. Adiponectin inhibits osteoclastogenesis and bone resorption via APPL1-mediated suppression of Akt1. J Biol Chem 2011;286:12542–53. https://doi.org/10.1074/jbc.M110.152405.
[164] Luo Y, Liu M. Adiponectin: a versatile player of innate immunity. J Mol Cell Biol 2016;8:120–8. https://doi.org/10.1093/jmcb/mjw012.
[165] Ohashi K, Parker JL, Ouchi N, Higuchi A, Vita JA, Gokce N, et al. Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype. J Biol Chem 2010;285:6153–60. https://doi.org/10.1074/jbc.M109.088708.
[166] Yokota T, Oritani K, Takahashi I, Ishikawa J, Matsuyama A, Ouchi N, et al. Adiponectin, a new member of the family of soluble defense collagens, negatively regulates the growth of myelomonocytic progenitors and the functions of macrophages. Blood 2000;5:1723–32.
[167] Kumada M, Kihara S, Ouchi N, Kobayashi H, Okamoto Y, Ohashi K, et al. Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. Circulation 2004;109:2046–9. https://doi.org/10.1161/01.CIR.0000127953.98131.
[168] Steppan CM, Brown EJ, Wright CM, Bhat S, Banerjee RR, Dai CY, et al. A family of tissue-specific resistin-like molecules. Proc Natl Acad Sci U S A 2001;98:502–6. https://doi.org/10.1073/pnas.98.2.502.
[169] Zhang J, Lei T, Chen X, Peng Y, Long H, Zhou L, et al. Resistin up-regulates COX-2 expression via TAK1-IKK-NF-κB signaling pathway. Inflammation 2010;33:25–33. https://doi.org/10.1007/s10753-009-9155-x.
[170] Newman SA, Coscia SA, Jotwani R, Iacono VJ, Cutler CW. Effects of enamel matrix derivative on porphyromonas gingivalis. J Periodontol 2003;74:1191–5. https://doi.org/10.1902/jop.2003.74.8.1191.
[171] Sculean A, Windisch P, Dori F, Keglevich T, Molnár B, Gera I. Emdogain in regenerative periodontal therapy. A review of the literature. Fogorv Sz 2007;100:211–9.
[172] Bozaoglu K, Bolton K, McMillan J, Zimmet P, Jowett J, Collier G, et al. Chemerin is a novel adipokine associated with obesity and metabolic syndrome. Endocrinology 2007;148:4687–94. https://doi.org/10.1210/en.2007-0175.
[173] Wittamer V, Franssen JD, Vulcano M, Mirjolet JF, Le Poul E, Migeotte I, et al. Specific recruitment of antigen-presenting cells by chemerin, a novel processed ligand from human inflammatory fluids. J Exp Med 2003;198:977–85. https://doi.org/10.1084/jem.20030382.
[174] Zabel BA, Ohyama T, Zuniga L, Kim JY, Johnston B, Allen SJ, et al. Chemokine-like receptor 1 expression by macrophages in vivo: regulation by TGF-β and TLR ligands. Exp Hematol 2006;34:1106–14. https://doi.org/10.1016/j.exphem.2006.03.011.
[175] Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 1999;402:656–60. https://doi.org/10.1038/45230.
[176] Delhanty PJD, Neggers SJ, Van Der Lely AJ. Ghrelin: the differences between acyl- and des-acyl ghrelin. Eur J Endocrinol 2012;167:601–8. https://doi.org/10.1530/EJE-12-0456.
[177] Aydin S, Caylak E. Ghrelin and its biochemical functions: Review. Turkiye Klinikleri J Med Sci 2006;26:272–83.
[178] Ghelardoni S, Carnicelli V, Frascarelli S, Ronca-Testoni S, Zucchi R. Ghrelin tissue distribution: comparison between gene and protein expression. J Endocrinol Invest 2006;29:115–21. https://doi.org/10.1007/BF03344083.
[179] Kierson J, Dimatteo D, Locke R, MacKley A, Spear M. Ghrelin and cholecystokinin in term and preterm human breast milk. Acta Paediatr Int J Paediatr 2006;95:991–5. https://doi.org/10.1080/08035250600669769.
[180] Gnanapavan S, Kola B, Bustin SA, Morris DG, McGee P, Fairclough P, et al. The tissue distribution of the mRNA of ghrelin and subtypes of its receptor, GHS-R, in humans. J Clin Endocrinol Metab 2002;87:2988–91. https://doi.org/10.1210/jcem.87.6.8739.
[181] Tritos NA, Kokkinos A, Lampadariou E, Alexiou E, Katsilambros N, Maratos-Flier E. Cerebrospinal fluid ghrelin is negatively associated with body mass index. J Clin Endocrinol Metab 2003;88:2943–6. https://doi.org/10.1210/jc.2003-030300.
[182] Aydin S, Aydin S, Ozkan Y, Kumru S. Ghrelin is present in human colostrum, transitional and mature milk. Peptides 2006;27:878–82. https://doi.org/10.1016/j.peptides.2005.08.006.
[183] Aydin S, Halifeoglu I, Ozercan IH, Erman F, Kilic N, Aydin S, et al. A comparison of leptin and ghrelin levels in plasma and saliva of young healthy subjects. Peptides 2005;26:647–52. https://doi.org/10.1016/j.peptides.2004.11.008.
[184] Aydin S, Ozercan HI, Aydın S, Ozkan Y, Dagli F, Geckil H. Biological rhythm of saliva ghrelin in humans. Biol Rhythm Res 2006;37:169–77. https://doi.org/10.1080/09291010600576860.
[185] Gröschl M, Topf HG, Bohlender J, Zenk J, Klussmann S, Dötsch J, et al. Identification of ghrelin in human saliva: production by the salivary glands and potential role in proliferation of oral keratinocytes. Clin Chem 2005;51:997–1006. https://doi.org/10.1373/clinchem.2004.040667.

[186] Gröschl M, Topf HG, Rauh M, Kurzai M, Rascher W, Köhler H. Postprandial response of salivary ghrelin and leptin to carbohydrate uptake [2]. Gut 2006;55:433–4. https://doi.org/10.1136/gut.2005.082255.
[187] Rani CSS, MacDougall M. Dental cells express factors that regulate bone resorption. Mol Cell Biol Res Commun 2000;3:145–52. https://doi.org/10.1006/mcbr.2000.0205.
[188] Olney RC. Regulation of bone mass by growth hormone. Med Pediatr Oncol 2003;41:228–34. https://doi.org/10.1002/mpo.10342.
[189] Stawski L, Trojanowska M. Oncostatin M and its role in fibrosis. Connect Tissue Res 2019;60:40–9. https://doi.org/10.1080/03008207.2018.1500558.
[190] Zarling JM, Shoyab M, Marquardt H, Hanson MB, Lioubin MN, Todaro GJ, et al. A growth regulator produced by differentiated histiocytic lymphoma cells. Proc Natl Acad Sci U S A 1986;83:9739–43. https://doi.org/10.1073/pnas.83.24.9739.
[191] Tanaka M, Miyajima A. Oncostatin M, a multifunctional cytokine. Rev Physiol Biochem Pharmacol 2003;149:39–52. https://doi.org/10.1007/s10254-003-0013-1.
[192] Richards CD. The enigmatic cytokine oncostatin M and roles in disease. ISRN Inflamm 2013;2013:1–23. https://doi.org/10.1155/2013/512103.
[193] Lu HK, Chen YL, Chang HC, Li CL, Kuo MYP. Identification of the osteoprotegerin/receptor activator of nuclear factor-kappa B ligand system in gingival crevicular fluid and tissue of patients with chronic periodontitis. J Periodontal Res 2006;41:354–60. https://doi.org/10.1111/j.1600-0765.2006.00883.x.
[194] Lin SJ, Chen YL, Bin Kuo M, Li CL, Lu HK. Measurement of gp130 cytokines - oncostatin M and IL-6 in gingival crevicular fluid of patients with chronic periodontitis. Cytokine 2005;30:160–7. https://doi.org/10.1016/j.cyto.2004.12.018.
[195] Chang YC, Lai CC, Yang SF, Chan Y, Hsieh YS. Stimulation of matrix metalloproteinases by black- pigmented bacteroides in human pulp and periodontal ligament cell cultures. J Endod 2002;28:90–3. https://doi.org/10.1097/00004770-200202000-00010.
[196] Huang FM, Yang SF, Hsieh YS, Liu CM, Yang LC, Chang YC. Examination of the signal transduction pathways involved in matrix metalloproteinases-2 in human pulp cells. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004;97:398–403. https://doi.org/10.1016/j.tripleo.2003.10.007.
[197] Shin SJ, Lee JI, Baek SH, Lim SS. Tissue levels of matrix metalloproteinases in pulps and periapical lesions. J Endod 2002;28:313–5. https://doi.org/10.1097/00004770-200204000-00013.
[198] Maeda H. Aging and senescence of dental pulp and hard tissues of the tooth. Front Cell Dev Biol 2020;8:1–9. https://doi.org/10.3389/fcell.2020.605996.
[199] Byun HO, Lee YK, Kim JM, Yoon G. From cell senescence to age-related diseases: differential mechanisms of action of senescence-associated secretory phenotypes. BMB Rep 2015;48:549–58. https://doi.org/10.5483/BMBRep.2015.48.10.122.
[200] Borodkina A, Deryabin P, Giukova A, Nikolsky N. "Social life" of senescent cells: what is SASP and why study it? Acta Naturae 2018;10:4–14.
[201] Lopes-Paciencia S, Saint-Germain E, Rowell MC, Ruiz AF, Kalegari P, Ferbeyre G. The senescence-associated secretory phenotype and its regulation. Cytokine 2019;117:15–22. https://doi.org/10.1016/j.cyto.2019.01.013.
[202] Hasmann M, Schemainda I. FK866, a highly specific noncompetitive inhibitor of nicotinamide phosphoribosyltransferase, represents a novel mechanism for induction of tumor cell apoptosis. Am Assoc Cancer Res 2003:436–42.
[203] Li PB, Jin H, Liu DX, Wang HW, Nan WK. Study on leptin enhancing collagen synthesis in wounded rats. Chin J Appl Physiol 2011;27:72–4.
[204] Çakir B, Çevik H, Contuk G, Ercan F, Ekşioğlu-Demiralp E, Yeğen BÇ. Leptin ameliorates burn-induced multiple organ damage and modulates postburn immune response in rats. Regul Pept 2005;125:135–44. https://doi.org/10.1016/j.regpep.2004.08.032.
[205] Fukushima N, Hanada R, Teranishi H, Fukue Y, Tachibana T, Ishikawa H, et al. Ghrelin directly regulates bone formation. J Bone Miner Res 2005;20:790–8. https://doi.org/10.1359/JBMR.041237.
[206] Patel R, Filer A, Barone F, Buckley CD. Stroma: fertile soil for inflammation. Best Pract Res Clin Rheumatol 2014;28:565–76. https://doi.org/10.1016/j.berh.2014.10.022.
[207] Bienertova-Vasku J, Vinciguerra M, Buzga M, Villaroya F. Adipokines as biomarkers in health and disease. Dis Markers 2018;2018. https://doi.org/10.1155/2018/5696815.
[208] Herold C, Engeli S, Beckmann B, Vogt PM, Rennekampff HO. Adipokine concentrations in lipoaspirates may have a role in wound healing. Indian J Plast Surg 2017;50:56–63. https://doi.org/10.4103/ijps.IJPS.
[209] Pallua N, Pulsfort AK, Suschek C, Wolter TP. Content of the growth factors bFGF, IGF-1, VEGF, and PDGF-BB in freshly harvested lipoaspirate after centrifugation and incubation. Plast Reconstr Surg 2009;123:826–33. https://doi.org/10.1097/PRS.0b013e318199ef31.
[210] Cuesta M, Clesse D, Pévet P, Challet E. From daily behavior to hormonal and neurotransmitters rhythms: comparison between diurnal and nocturnal rat species. Horm Behav 2009;55:338–47. https://doi.org/10.1016/j.yhbeh.2008.10.015.
[211] Chakir I, Dumont S, Pévet P, Ouarour A, Challet E, Vuillez P. The circadian gene Clock oscillates in the suprachiasmatic nuclei of the diurnal rodent Barbary striped grass mouse, Lemniscomys barbarus: a general feature of diurnality? Brain Res 2015;1594:165–72. https://doi.org/10.1016/j.brainres.2014.10.063.
[212] Rudic RD, McNamara P, Curtis A-M, Boston RC, Panda S, Hogenesch JB, et al. BMAL1 and CLOCK, two essential components of the circadian clock, are involved in glucose homeostasis. PLoS Biol 2004;2:e377. https://doi.org/10.1371/journal.pbio.0020377.
[213] Oliver P, Ribot J, Rodríguez AM, Sánchez J, Picó C, Palou A. Resistin as a putative modulator of insulin action in the daily feeding/fasting rhythm. Pflugers Arch Eur J Physiol 2006;452:260–7. https://doi.org/10.1007/s00424-005-0034-5.
[214] Husse J, Hintze SC, Eichele G, Lehnert H, Oster H. Circadian clock genes Per1 and Per2 regulate the response of metabolism-associated transcripts to sleep disruption. PLoS One 2012;7:e52983. https://doi.org/10.1371/journal.pone.0052983.
[215] Ahima RS, Prabakaran D, Flier JS. Postnatal leptin surge and regulation of circadian rhythm of leptin by feeding. Implications for energy homeostasis and neuroendocrine function. J Clin Invest 1998;101:1020–7. https://doi.org/10.1172/JCI1176.
[216] Challet E. Circadian aspects of adipokine regulation in rodents. Best Pract Res Clin Endocrinol Metab 2017;31:573–82. https://doi.org/10.1016/j.beem.2017.09.003.
[217] De Maio A. The heat-shock response. N Horizons Sci Pract Acute Med 1986;3:1151–91. https://doi.org/10.1146/annurev.bi.55.070186.005443.
[218] Bernabucci U, Basiricò L, Morera P, Lacetera N, Ronchi B, Nardone A. Heat shock modulates adipokines expression in 3T3-L1 adipocytes. J Mol Endocrinol 2009;42:139–47. https://doi.org/10.1677/JME-08-0068.
[219] Çelik Köycü B, İmirzalıoğlu P. Heat transfer and thermal stress analysis of a mandibular molar tooth restored by different indirect restorations using a three-dimensional finite element method. J Prosthodont 2017;26:460–73. https://doi.org/10.1111/jopr.12397.
[220] Palmer DS, Barco MT, Billy EJ. Temperature extremes produced orally by hot and cold liquids. J Prosthet Dent 1992;67:325–7. https://doi.org/10.1016/0022-3913(92)90239-7.
[221] Attrill DC, Davies RM, King TA, Dickinson MR, Blinkhorn AS. Thermal effects of the Er:YAG laser on a simulated dental pulp: a quantitative evaluation of the effects of a water spray. J Dent 2004;32:35–40. https://doi.org/10.1016/S0300-5712(03)00137-4.
[222] Hamze F, Ganjalikhan Nasab SA, Eskandarizadeh A, Shahravan A, Akhavan Fard F, Sinaee N. Thermal scanning of dental pulp chamber by thermocouple system and infrared camera during photo curing of resin composites. Iran Endod J 2018;13:195–9. https://doi.org/10.22037/iej.v13i2.18756.
[223] Hussey DL, Biagioni PA, Lamey PJ. Thermographic measurement of temperature change during resin composite polymerization in vivo. J Dent 1995;23:267–71. https://doi.org/10.1016/0300-5712(95)91149-H.
[224] Zhang Y, Yu M, Dong J, Wu Y, Tian W. Identification of novel adipokines through proteomic profiling of small extracellular vesicles derived from adipose tissue. J Proteome Res 2020;19:3130–42. https://doi.org/10.1021/acs.jproteome.0c00131.