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

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Autores:

Jonathan Francisco Gavidia Pazmiño

CI: 1722012505

Correo electrónico: j_gavidia3001@hotmail.com

María Isabel Bravo Guapisaca

CI: 0105357131

Correo electrónico: mibravoguapisaca@gmail.com

Directora:

Ruth Viviana Intriago Morales.

CI: 0301406484

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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.

Keywords: Adipokines. Dental pulp disease. Inflammation mediators. Regenerative endodontics. Leptin.

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C.I: 1722012505

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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.

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].
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 l, T helper 1 cell; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule

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].

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.

Ethical Statement

Ethical approval was not required for this review study.

Conflict of Interest

The authors declare no conflicts of interest.

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.

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