LETÍCIA FERNANDA DUFFLES RODRIGUES

ASSOCIAÇÃO ENTRE OBESIDADE E ADIPOCINAS NA SALIVA E FLUIDO GENGIVAL CREVICULAR: *UMA REVISÃO SISTEMÁTICA E META-ANÁLISE*.

Faculdade de Odontologia
Universidade Federal de Minas Gerais
Belo Horizonte
2018

Letícia Fernanda Duffles Rodrigues

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Dissertação apresentada ao Colegiado de Pós-Graduação em Odontologia da Faculdade de Odontologia da Universidade Federal de Minas Gerais, como requisito parcial à obtenção do grau de Mestre em Odontologia – área de concentração em Odontopediatria.

Orientadora: Profa.: Isabela Almeida Pordeus
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FOLHA DE APROVAÇÃO

Associação entre obesidade e adipocinas na saliva e fluido gengival crevicular: uma revisão sistemática.

LETICIA FERNANDA DUFFLES RODRIGUES

Dissertação submetida à Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em Odontologia, como requisito para obtenção do grau de Mestre, área de concentração Odontopediatria.

Aprovada em 25 de junho de 2018, pela banca constituída pelos membros:

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Belo Horizonte, 25 de junho de 2018.

O mundo encontra-se em meio a guerras, destruição, egoísmo, desigualdades, desafeto e falta de compaixão, epidemias, completo descaso com os recursos naturais... indago-me se tudo encontra-se perdido, mas atraco-me ao pensamento de que o conhecimento, a educação, uma melhor compreensão desses problemas possa nos levar a um estado de evolução. Dessa forma, dedico esse trabalho ao bem e à evolução da ciência, fornecendo minha simples e humilde contribuição, sendo uma pequena gota no oceano.

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“All our dreams can come true if we have the courage to pursue them”

Walt Disney

RESUMO

A obesidade vem aumentando sua prevalência na população mundial e brasileira nos últimos anos, atingindo todas as faixas etárias. As adipocinas são um grupo de citocinas inflamatórias produzidas ou expressas no tecido adiposo, que desempenham diversas funções no organismo. Classicamente essas moléculas são avaliadas no soro ou tecido adiposo. Estudos recentes, entretanto, têm avaliado a presença destas moléculas na saliva e no fluido gengival crevicular (FGC) e sua associação com a obesidade. Dessa forma, o objetivo desse trabalho foi avaliar a associação entre obesidade e a concentração de adipocinas na saliva e FGC. A busca eletrônica foi realizada em quatro bases de dados. Buscas manuais e no Google Acadêmico também foram realizadas. Dois autores calibrados (Kappa=0.82) realizaram a seleção dos artigos, a extração de dados e avaliaram o risco de viés por meio da análise de qualidade metodológica dos artigos incluídos. Trinta e quatro artigos foram incluídos. As meta-análises demonstraram que a concentração aumentada de TNF-α na saliva de indivíduos com obesidade quando comparado aos não obesos. Em contrapartida, concentrações de resistina, adiponectina, leptina, grelina e IL-6 na saliva e de resistina, adiponectina, leptina, IL-6, IL-8, TNF-α e PAI-1 no FGC foram estatisticamente similares em indivíduos com e sem obesidade. Em geral, a evidência científica a respeito de níveis alterados de adipocinas específicas na saliva e/ou no FGC em quadros de obesidade é fraca, exceto para o TNF-α na saliva. A disponibilidade limitada e a heterogeneidade dos dados não permitem afirmar se as alterações nos níveis de adipocinas na saliva e no FGC estão associadas à obesidade ou a outras causas.

Palavras-chave: Obesidade. Adipocinas. Saliva.

ABSTRACT

Association between obesity and adipokines´ levels in saliva and gingival crevicular fluid: a systematic review.

Obesity is an increasing disease characterized by accumulation of fat in different organs and tissues. Currently, adipose tissue has been described as an endocrine organ, once it secrets a lot of metabolic active molecules, inflammatory cytokines and adipokines. Several molecules are classified as adipokines and they are classically evaluated in blood or adipose tissue. Recent studies have been evaluating adipokines in gingival crevicular fluid (GCF) and saliva and its relation to obesity. The objective of this systematic review was to evaluate the association between obesity and the concentration of adipokines in gingival crevicular fluid (GCF) and saliva. The search was conducted in four databases. Manual and Google Scholar searches were also conducted. Two calibrated authors performed study selection, data extraction and quality assessment of included articles. Thirty four articles were included. Meta-analysis demonstrated that TNF-α concentration in saliva was statistically increased in individuals with obesity compared with individuals without obesity. In contrast, concentrations of resistin, adiponectin, leptin, ghrelin and IL-6 in saliva and of resistin, adiponectin, leptin, IL-6, IL-8, TNF-α, lL-8 and PAI-1 in GCF, were statistically similar in individuals with and without obesity. Overall, the scientific evidence regarding altered levels of specific adipokines in saliva and or GCF among persons with obesity is weak, except for salivary TNF-α. The limited availability and heterogeneity of data do not allow us to state whether changes of adipokines in GCF and saliva are associated with obesity or otherwise.

Keywords: Obesity. Adipokines. Saliva. Gingival crevicular fluid

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LISTA DE ABREVIATURAS E SIGLAS

BMI	Body Mass Index
CCL2	Quimiocina CC do Ligante 2 / CC Chemokine Ligand 2
CI	Confidence Interval
ELISA	Enzyme-Linked Immunosorbent Assay
FGC	Fluido Gengival Crevicular
GCF	Gingival Crevicular Fluid
IL-1	Interleucina 1 / Interleukin 1
IL-6	Interleucina 6 / Interleukin 6
IL-8	Interleucina 8 / Interleukin 8
IL-10	Interleucina 10 / Interleukin 10
IMC	Índice de Massa Corporal
MCP-1	Proteína Quimioatrativa de Monócito 1 / Monocyte Chemoattractant Protein-1
OMS	Organização Mundial da Saúde
PAI-1	Inibidor do Ativador de Plasminogênio do Tipo 1 / Plasminogen activator inhibitor-1
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROSPERO	International Prospective Register of Systematic Reviews
TGF-β	Fator Transformador do Crescimento-beta
TNF-α	Fator de Necrose Tumoral alfa / Tumor Necrosis Factor Alpha
VASPIN	Visceral Adipose Tissue-derived Serpin
VASPINA	Serpina Derivada do Tecido Adiposo Visceral

SUMÁRIO

1 CONSIDERAÇÕES INICIAIS

1.1 Obesidade

A obesidade é caracterizada pelo acúmulo alterado e excessivo de gordura corporal (WHO, 2017). Segundo a Organização Mundial da Saúde (OMS) (2017), apesar de incompleto, pelo fato de não corresponder ao mesmo grau de gordura em diferentes indivíduos, o método mais utilizado para identificar a obesidade é o Índice de Massa Corporal (IMC). Geralmente são considerados obesos, os indivíduos cujo IMC é maior ou igual a 30 Kg/m^2. Um valor de IMC entre 25 e 29,9 Kg/m^2, comumente, classifica a pessoa em um estado de sobrepeso, e um valor entre 18,5 e 24,9 Kg/m^2 é considerado autrófico (WHO, 2017).

Muito tem-se discutido sobre a frequência do excesso de peso e obesidade na população mundial. Em 2016, 40% das mulheres e 39% dos homens adultos apresentavam sobrepeso, o que significa aproximadamente 2 bilhões de adultos no mundo. Destaca-se que 15% das mulheres e 11% dos homens adultos foram classificados como obesos, o que significa mais de 650 milhões de adultos com essa desordem no mundo (WHO, 2017). Também em 2016, 41 milhões de crianças abaixo dos 5 anos de idade e 340 milhões de crianças e adolescentes (5 a 19 anos de idade) foram classificadas como obesos ou acima do peso (WHO, 2017).

A população brasileira também tem sido cada vez mais acometida pela obesidade. Em 1989, 3,3% e 13,5% das crianças com idades entre 5 a 9 anos apresentavam obesidade e excesso de peso, respectivamente. Já em 2009, esses números passaram para 14,3% e 33,5% (BRASIL, 2010). Para a faixa etária de 10 a 19 anos, a prevalência de obesidade e sobrepeso, respectivamente, foi de 5,9% e 21,7% para o sexo masculino, e de 4% e 19,4% para o sexo feminino no ano de 2009 (BRASIL, 2010). Na população adulta a prevalência de sobrepeso no sexo masculino, passou de 29,9% em 1989 para 50,1% em 2009. No sexo feminino essa mudança foi de 41,4% para 48%. No mesmo período, a prevalência de obesidade aumentou de 5,4% para 12,4% nos homens e de 13,2% para 16,9% nas mulheres (BRASIL, 2010).

O aumento na prevalência de obesidade torna-se ainda mais alarmante uma vez que pode estar elencado a outras desordens sistêmicas incluindo as cardiovasculares, diabetes tipo 2 e a síndrome metabólica (KOPELMAN, 2000). Essa relação pode ser explicada pelo fato de a obesidade estar associada a uma resposta inflamatória crônica no organismo com produção de citocinas inflamatórias e repercussões em diferentes órgãos e tecidos (KIRWAN *et al*., 2017).

A resposta inflamatória gerada pelo acúmulo de tecido adiposo recebe o nome de metainflamação ou inflamação metabólica, com o intuito de diferenciar esse processo da resposta inflamatória clássica desencadeada, por exemplo, pela resposta a um agente patogênico (ESSER *et al*., 2014; KREDEL; SIEGMUND, 2014).

1.2 Tecido adiposo

O tecido adiposo é um órgão dinâmico que pode ser dividido, classicamente, em tecido adiposo branco (mais presente no organismo) cuja principal função é o armazenamento energético e tecido adiposo marrom, responsável pela termogênese, principalmente em neonatos (FANTUZZI, 2005).

Recentemente, o tecido adiposo deixou seu papel “estático” de armazenamento de gordura e proteção mecânica e passou a ser considerado um órgão endócrino, o qual secreta uma infinidade de moléculas metabolicamente ativas como os hormônios derivados do tecido adiposo, citocinas inflamatórias e adipocinas (PRINS, 2002; RAUCCI *et al*., 2013).

1.3 Adipocinas

As adipocinas são um grupo de citocinas inflamatórias, produzidas ou expressas pelo tecido adiposo branco, que desempenham diversas funções no organismo, participando do controle energético, sensibilidade à insulina e resposta imune-inflamatória (FANTUZZI, 2005; PRINS, 2002). Estas moléculas são altamente

diversificadas em termos de estrutura proteica e função fisiológica. Diversas moléculas são classificadas como adipocinas, podendo citar como exemplos: adiponectina, resistina, leptina, omentina, lipocalina-2, serpina derivada do tecido adiposo visceral (vaspina) e quemerina (CAO, 2014; FASSHAUER; BLÜHER, 2015; GORALSKI *et al*., 2007; MANCUSO, 2016).

Algumas dessas adipocinas apresentam níveis reduzidos no sangue de indivíduos obesos, como a adiponectina (MENEZES *et al*., 2018; YIN *et al*., 2016). Em contrapartida, diante de um quadro de obesidade, essas moléculas podem ser identificadas em níveis aumentados no sangue, como no caso da resistina (KO *et al*., 2013; MANTOVANI *et al*., 2016).

Além dessas adipocinas, no contexto da obesidade alguns mediadores inflamatórios clássicos também são identificados como adipocinas como o fator de necrose tumoral (TNF-α) (DAS, 2001), a interleucina 6 (IL-6) (DEROSA *et al*., 2013) e a quimiocina CC do ligante 2 (CCL2), também chamada de proteína quimioatrativa de monócito 1 (MCP-1) (DUARTE *et al*., 2015). Dessa maneira, a obesidade está relacionada a uma resposta inflamatória sistêmica, que pode refletir-se em diferentes órgãos e tecidos do corpo (KIRWAN *et al*., 2017).

Durante o desenvolvimento do presente trabalho, foram identificados estudos que avaliaram a expressão das principais adipocinas, bem como marcadores inflamatórios que atuam como adipocinas, na cavidade bucal (por meio da análise do FGC e saliva). Essas moléculas serão descritas a seguir, de forma a oferecer um panorama de cada uma delas, bem como da literatura acerca de sua expressão sistêmica em quadros de obesidade.

1.3.1 Adiponectina

A adiponectina é produzida, predominantemente, por adipócitos e essa produção depende do estado nutricional do indivíduo (CARBONE; LA ROCCA; MATARESE, 2012). Essa adipocina encontra-se em níveis reduzidos na obesidade e seu papel está relacionado à regulação da sensibilidade à insulina, pontencializando sua ação. Além disso, possui função anti-aterogênica, regula a homeostase dos lipídeos, induz a oxidação de gorduras e possui ação anti-

inflamatória, uma vez que reduz a produção de TNF-α, bem como inibe sua ação (FANTUZZI, 2005). As atividades anti-inflamatórias da adiponectina estendem-se à inibição da produção de IL-6, acompanhada de indução das citocinas anti-inflamatórias interleucina 10 (IL-10) e antagonista do receptor de interleucina 1 (IL-1) (FANTUZZI, 2005).

1.3.2 Leptina

A leptina é considerada a principal adipocina, apesar de ser produzida por outras células e tecidos (placenta, estômago), sua síntese é realizada, principalmente, por adipócitos. Sua função está diretamente relacionada ao consumo alimentar e ao gasto energético e seus níveis encontram-se associados à massa de gordura corporal, peso corpóreo e funções neuroendócrinas (FANTUZZI, 2005). Essa adipocina é conhecida por sua função na saciedade, apresentando decréscimo de seu nível logo após o início do jejum (RAUCCI *et al*., 2013). Além das funções relacionadas ao tecido adiposo, a leptina atua no sistema imune, regulando a proliferação e ativação de células T (FAROOQI *et al*., 2002).

Apesar da leptina exercer um papel na supressão da saciedade, pacientes com sobrepeso e obesos apresentam níveis aumentados de leptina no sangue, podendo ser explicado pelo fato desses pacientes desenvolverem resistência à leptina (CONSIDINE *et al*., 1995), que ocorre devido ao comprometimento no transporte dessa molécula ou uma disfunção da sinalização de seu receptor (ZHOU; RUI, 2013).

1.3.3 Resistina

A resistina recebeu seu nome a partir do primeiro estudo que observou sua capacidade de induzir resistência à insulina em camundongos (STEPPAN *et al*., 2001). É uma adipocina produzida por adipócitos, mas também por células do epitélio intestinal, da glândula supra-renal e do músculo esquelético, sendo as células mononucleares periféricas do sangue as principais responsáveis por sua produção (HUANG; YANG, 2016).

Um estudo *in vitro* demonstrou que a expressão de resistina por células mononucleares periféricas do sangue é altamente regulada e induzida por citocinas pró-inflamatórias, tais como o TNF-α e a lL-6 (KASER *et al*., 2003). Além disso, os níveis de resistina no sangue estão associados a marcadores inflamatórios: receptor 2 de TNF-α, lL-6, proteína C reativa e a lipoproteína associada à fosfolipase A2 (SHETTY *et al*., 2004).

Os estudos em humanos são inconclusivos no que diz respeito à relação entre os níveis de resistina circulante e a obesidade ou a resistência à insulina (HUANG; YANG, 2016).

1.3.4 Quemerina

Quemerina é uma adipocina recentemente descrita, secretada por adipócitos (GORALSKI *et al*., 2007). Seu receptor foi primeiramente descrito como um peptídeo quimiotático, estando envolvido tanto na imunidade inata quanto adaptativa (WITTAMER *et al*., 2003). A quemerina é regulada positivamente em células do tecido adiposo branco a partir da estimulação de IL-1, acreditando-se dessa forma, que ela possa ser um elo funcional entre a inflamação crônica e a obesidade (ERNST; SINAL, 2010). Uma meta-análise demonstrou que as concentrações de quemerina no sangue estão aumentadas em indivíduos obesos (LI; SHI; LI, 2014).

1.3.5 Grelina

É um hormônio produzido, principalmente, pelo estômago, está presente também no cérebro e em vários tecidos periféricos (ZOLOTUKHIN, 2013) e é produzida por glândulas salivares (GRÖSCHL *et al*., 2001). As funções da grelina são variadas e englobam secreções hormonais neuroendócrinas, regulação da ingestão de alimentos e metabolismo energético, adipogênese, regulação da motilidade gastrointestinal, homeostase da glicose, papel na função pancreática e

cardiovascular e no metabolismo ósseo, além de participar da regulação de funções centrais como memória, sono e humor (RAUCCI *et al*., 2013).

Os níveis de grelina no sangue, durante processos patológicos, encontram-se alterados, estando reduzidos durante a obesidade (MIHALACHE *et al*., 2016).

1.3.6 Adipsina

A adipsina, também conhecida como fator de complemento D, é uma adipocina relacionada tanto com o metabolismo energético quanto com as respostas imunológicas (ROSEN *et al*., 1989). Essa adipocina é sintetizada durante a lipólise e estimula o centro da fome (LO *et al*., 2014), sendo o metabolismo do tecido adiposo normalmente regulado pela secreção alternada de adipsina, durante o período de fome, e leptina na fase de saturação (LO *et al*., 2014).

Em quadros de obesidade, os níveis de adipsina no sangue humano encontram-se sem alteração ou em níveis reduzidos (CIANFLONE; XIA; CHEN, 2003).

1.3.7 Omentina-1

A omentina-1 é uma adipocina com característica anti-inflamatória produzida, principalmente, pelo tecido adiposo visceral (GUERRERO-GARCÍA *et al*., 2016). Pode ser conhecida por outra denominação: intelectina (RAUCCI *et al*., 2013). Sua expressão, no sangue, mostra-se reduzida em quadros de obesidade (GUERRERO-GARCÍA *et al*., 2016).

1.3.8 Vaspina

A vaspina é uma proteína produzida pelo tecido adiposo, músculo esquelético, pâncreas, pele e, principalmente, pelo fígado (GOKTAS *et al*., 2013; KÖRNER *et al*., 2011). Alguns estudos observaram uma redução na concentração de vaspina no soro após a alimentação, mediada pela insulina e independente da ingestão de nutrientes ou concentração de glicose (JEONG *et al*., 2010; KOVACS *et al*., 2013). Em contrapartida, uma meta-análise demonstrou níveis significativamente elevados de vaspina no sangue de indivíduos obesos (FENG *et al*., 2014).

1.3.9 Visfatina

A visfatina é uma adipocina produzida por leucócitos, macrófagos do tecido adiposo, hepatócitos e células do músculo esquelético (STASTNY; BIENERTOVA-VASKU; VASKU, 2012). Possui atividades imunológicas, induzindo a produção de IL-6, TNF-α, IL-1β e monócitos (MOSCHEN *et al*., 2007).

Essa adipocina é regulada positivamente por hipóxia, inflamação e hiperglicemia e regulada negativamente pela insulina, somatostatina e estatinas (ADEGHATE, 2008). A visfatina tem a capacidade de se ligar ao receptor de insulina e agir de forma mimética à insulina. No entanto, essa ação causa hipoglicemia, uma vez que aumenta a captação e o metabolismo de glicose nos adipócitos, enquanto bloqueia tanto a formação, quanto a liberação de glicose no fígado (SETHI; VIDAL-PUIG, 2005).

Diversos estudos demonstraram níveis elevados de visfatina no sangue em crianças e adultos obesos, entretanto existem estudos que não demonstraram esta associação (JAMURTAS *et al*., 2015; RAUCCI *et al*., 2013).

1.3.10 Irisina

A irisina é classificada como uma miocina, isto é, um hormônio produzido e secretado pelo músculo esquelético, cujo padrão de secreção pode ser alterado pelo tipo e intensidade de uma atividade física (POLYZOS *et al*., 2013). A irisina é

secretada e sintetizada, também, pelo fígado e pelo tecido adiposo, sendo esse a segunda fonte mais importante dessa miocina (ROCA-RIVADA *et al*., 2013). Sua principal função é a indução de “escurecimento” do tecido adiposo branco, caracterizado pela ocorrência de adipócitos marrons nesse tecido, aumentando, assim, o gasto energético (BOSTRÖM *et al*., 2012; VILLARROYA, 2012). Em humanos, a redução nas concentrações de irisina leva ao aumento do consumo de energia e, consequentemente, ao efeito metabólico de sobrenutrição.

A maioria dos estudos que avaliam os níveis de irisina no sangue em associação com a obesidade demonstram que indivíduos obesos apresentam níveis aumentados, bem como uma associação positiva entre esses níveis e IMC, circunferência abdominal, gordura corporal, peso (POLYZOS *et al*., 2013).

1.3.11 Progranulina

A progranulina é uma proteína glicosilada expressa em diversos tecidos e órgãos, mas particularmente proeminente em células epiteliais e hematopoiéticas, e tende a ser expressa em maiores quantidades nos tecidos que apresentam um alto *turnover*, como a mucosa gástrica, tecidos linfoides e linhagens de células tumorais (BHANDARI; GIAID; BATEMAN, 1993; DANIEL *et al*., 2000). Essa proteína exerce funções diversas, atuando por exemplo, como fator de crescimento tanto autócrino quanto atípico (BATEMAN; BENNETT, 2009), possui habilidade de reparo tecidual e propriedades anti-inflamatórias. Entretanto, dependendo do receptor ao qual essa molécula se liga e suas vias de sinalização, a progranulina pode desempenhar funções pró-inflamatórias (NGUYEN *et al*., 2013).

No contexto da obesidade induzida por dieta, a progranulina atua, aparentemente, como uma molécula pró-inflamatória (NGUYEN *et al*., 2013). Apesar de ainda desconhecido o sistema de atuação, estudos mostram que há uma maior expressão de progranulina circulante em indivíduos obesos (QU; DENG; HU, 2013; YOUN *et al*., 2009).

1.3.12 Lipocalina-2

A lipocalina-2 é membro da família das lipocalinas (MOSCHEN *et al*., 2017). É considerada uma glicoproteína secretora e é expressa no sangue (MOSCHEN *et al*., 2017), tecido adiposo (RAUCCI *et al*., 2013). No tecido adiposo sua atividade é induzida por estímulos inflamatórios, principalmente, através da ativação do fator nuclear-κβ (RAUCCI *et al*., 2013), sugerindo seu envolvimento na metainflamação e em desordens relacionadas à obesidade. Estudos têm observado um aumento dos níveis de lipocalina-2 no sangue de indivíduos obesos (AUGUET *et al*., 2011; WANG *et al*., 2006).

1.3.13 IL-10

A IL-10 é uma citocina anti-inflamatória clássica produzida principalmente por monócitos, células T e células B (MOORE *et al*., 2001). Essa citocina pode desempenhar um papel protetor na desregulação metabólica induzida pela obesidade e resistência à insulina (VAN EXEL *et al*., 2002). A perda de peso aumenta a expressão de IL-10 no tecido adiposo branco, coincidindo com a redução da expressão de genes pró-inflamatórios (CANCELLO *et al*., 2005).

Em quadros de obesidade são observadas menores proporções de macrófagos M2 ativados (FUJISAKA *et al*., 2009; LUMENG; BODZIN; SALTIEL, 2007), esse tipo celular é responsável pela secreção de citocinas anti-inflamatórias, como a IL-10 (LUMENG; BODZIN; SALTIEL, 2007).

1.3.14 IL-6

A IL-6 é uma citocina inflamatória produzida por diferentes tipos celulares, dentre eles os adipócitos maduros (RAUCCI *et al*., 2013). É expressa no tecido adiposo branco, músculos esqueléticos e fígado (FASSHAUER *et al*., 2003; WEISBERG *et al*., 2003; WIECKOWSKA *et al*., 2008). O tecido adiposo visceral é

um importante produtor de IL-6, o que indica potenciais ligações entre gordura visceral, resistência à insulina e inflamação (RAUCCI *et al*., 2013). Além do seu potencial de homeostase de insulina, a IL-6 tem papel na homeostase lipídica (CURAT *et al*., 2004).

Estudos *in vitro* demonstraram a capacidade da IL-6 de impedir a adipogênese, bem como o acúmulo de lipídeos em pré-adipócitos (GUSTAFSON; SMITH, 2006; MCGILLICUDDY *et al*., 2009). Em quadros de obesidade em humanos existe maior proporção de macrófagos M1 ativados (FUJISAKA *et al*., 2009; LUMENG; BODZIN; SALTIEL, 2007). Esse tipo celular é responsável pela secreção de citocinas pró-inflamatórias, como a IL-6 (LUMENG; BODZIN; SALTIEL, 2007). Sendo assim, os níveis de IL-6 apresentam-se elevados no plasma e no tecido adiposo branco de indivíduos obesos (VOZAROVA *et al*., 2001).

1.3.15 IL-8

A interleucina 8 (IL-8) é uma citocina pró-inflamatória produzida principalmente por macrófagos e monócitos (BAGGIOLINI; LOETSCHER; MOSER, 1995), mas também é produzida por adipócitos (BRUUN; PEDERSEN; RICHELSEN, 2000; 2001). Essa citocina atua no recrutamento e ativação de neutrófilos, promovendo a proliferação e migração de células vasculares da musculatura lisa (YUE *et al*., 1994), bem como a quimiotaxia e adesão de monócitos às células endoteliais (GERSZTEN *et al*., 1999). Estudos têm demonstrado níveis aumentados de IL-8 em indivíduos obesos (ROSA *et al*., 2011; STRACZKOWSKI *et al*., 2002).

1.3.16 TNF-α

O TNF-α é uma citocina pró-inflamatória secretada por macrófagos, monócitos, adipócitos (MCARDLE *et al*., 2013). No entanto, os adipócitos não são a principal fonte de TNF-α na obesidade, mas sim os macrófagos. O aumento na produção dessa citocina no tecido adiposo correlaciona-se positivamente com o grau

de obesidade, os níveis de insulina e a resistência à insulina (KERN *et al*., 2001). Isso se deve ao mecanismo de ação do TNF-α no tecido adiposo que é um processo autócrino via cascata de sinalização da insulina, impedindo a interação da insulina com seu receptor (PAZ *et al*., 1997).

A expressão de TNF-α encontra-se aumentada no sangue de indivíduos obesos (ZAHORSKA-MARKIEWICZ *et al*., 2000), podendo ser explicada, em parte, pela infltração aumentada de macrófagos M1 no tecido adiposo (WEISBERG *et al*., 2003).

1.3.17 PAI-1

O inibidor do ativador de plasminogênio do tipo 1 (PAI-1) é uma proteína produzida por diversos tecidos, incluindo fígado, células endoteliais e tecido adiposo branco (BASTELICA *et al*., 2002). Tem sido descrito que os níveis de PAI-1 circulante e no tecido adiposo se encontram aumentados em indivíduos obesos (ALESSI; POGGI; JUHAN-VAGUE, 2007). Essa expressão aumentada de PAI-1 durante a obesidade pode ser regulada por fatores tais como: TNF-α, trombospondina 1, fator transformador do crescimento-beta (TGF-β) e o estresse oxidativo (ALESSI; POGGI; JUHAN-VAGUE, 2007), além de proteínas relacionadas ao ciclo circadiano (OISHI *et al*., 2006).

1.3.18 MCP-1 / CCL2

MCP-1 é uma quimiocina CC, atualmente conhecida como CCL2. É expressa em vários tipos de células e regulada por diversos estímulos, além disso, os adipócitos têm sido reconhecidos como uma importante fonte de CCL2 (PANEE, 2012).

A obesidade provoca uma hipertrofia dos adipócitos, os quais aumentam a secreção de CCL2, a qual promove o recrutamento de monócitos para o tecido adiposo (XU *et al*., 2015). Esses monócitos se diferenciam em macrófagos, desencadeando a secreção de citocinas pró-inflamatórias e estabelecendo um

quadro de inflamação (XU *et al*., 2015). Entretanto, é importante salientar que nem todo recrutamento de macrófagos para o tecido adiposo ocorre via interação da CCL2 com seu receptor (XU *et al*., 2015).

Estudos têm demonstrado um aumento generalizado nos níveis plasmáticos de CCL2 tanto em adultos (CATALÁN *et al*., 2007) quanto em crianças obesas (BRESLIN *et al*., 2012).

2 JUSTIFICATIVA

As adipocinas são produzidas pelo tecido adiposo, níveis alterados dessas moléculas podem estar associados à obesidade, bem como a uma inflamação local ou sistêmica. Apesar de a associação entre a obesidade e alterações bucais ter sido previamente descrita, os níveis de adipocinas nos fluidos bucais foram pouco estudados. A literatura anseia por essa avaliação como um parâmetro auxiliar em se determinar a relação entre alterações bucais e sistêmicas.

3 OBJETIVOS

3.1 Objetivo Geral

Avaliar a associação entre obesidade e as adipocinas presentes na saliva e fluido gengival crevicular.

3.2 Objetivos Específicos

a) Avaliar se os níveis de adipocinas identificados na saliva de pacientes obesos difere dos níveis encontrados na saliva de pacientes não obesos;
b) Avaliar se os níveis de adipocinas identificados no FGC de pacientes obesos difere dos níveis encontrados no FGC de pacientes não obesos;
c) Avaliar quais adipocinas têm sido identificadas na saliva e/ou no FGC, e o valor das mesmas como instrumento auxiliar na identificação da obesidade.

4 METODOLOGIA

4.1 Desenho do estudo

Este trabalho consistiu de uma revisão sistemática, cujo objetivo foi avaliar a evidência científica a respeito da associação da obesidade com os níveis de adipocinas específicas na saliva e no FGC.

4.2 Protocolo e Registro

Esta revisão sistemática foi realizada seguindo as diretrizes propostas pelo PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*) (MOHER *et al*., 2009).

Um protocolo foi registrado na base internacional de registros de revisões sistemáticas PROSPERO (*International Prospective Register of Ongoing Systematic Reviews*), obtendo-se o número de registro CRD42017078518. Esse registro tem como objetivo favorecer a transparência da pesquisa, reduzir a chance de duplicidade de estudos e minimizar o viés nas revisões.

4.3 Formulação da pergunta e preparação das estratégias de busca

A questão a ser respondida (PECO *question*) para as revisões sistemáticas baseia-se nos seguintes elementos metodológicos:

População: correspondendo aos indivíduos investigados; *Exposição:* correspondente ao fator de exposição ao qual um grupo de pessoas que faz parte da população dos estudos incluídos foi submetido; *Grupo controle:* referente ao grupo de pessoas, dentro da população de estudo, que não foi submetido ao fator de

exposição; *Desfecho:* corresponde à doença, condição avaliada ou à variável dependente do estudo.

Essa revisão sistemática teve o objetivo de responder à seguinte PECO: “A obesidade está associada a alterações nos níveis de adipocinas na saliva e no FGC?”

P= *População* (indivíduos)

E= *Exposição* (obesidade)

C= *Grupo controle ou sem exposição* (sem obesidade)

O= *Desfecho* (níveis de adipocinas na saliva e no FGC)

4.4 Critérios de elegibilidade

Os critérios de elegibilidade para inclusão de artigos originais que respondessem à pergunta PECO foram pré-definidos pelos autores. Como critérios de inclusão foram considerados todos os estudos epidemiológicos (estudos coorte prospectivos e retrospectivos, estudos transversais, estudos caso-controle, ensaios clínicos randomizados e não randomizados), sem restrição de data e idioma de publicação, bem como de idade ou sexo dos participantes. Os estudos incluídos deveriam comparar os níveis de adipocinas na saliva ou no FGC de pacientes obesos e não obesos.

Foram estabelecidos os seguintes critérios de exclusão: estudos não conduzidos em humanos (laboratoriais), estudos não controlados (avaliavam apenas indivíduos obesos ou não obesos), pesquisas desenvolvidas em populações seletivas, tais como indivíduos com diabetes ou doença periodontal sem um grupo controle, além de cartas ao editor, resumos em congressos, revisões narrativas, relatos de caso e séries de casos.

4.5 Levantamento de dados

A busca da literatura foi realizada em quatro bases de dados eletrônicas: Pubmed (http://www.pubmed.gov), Medline via Ovid (http://gateway.ovid.com), Web of Science (http://www.isiknowledge.com) e Scopus (https://www.scopus.com). Uma busca da literatura cinzenta foi conduzida no Google Scholar, limitando-se aos primeiros 100 resultados da busca. Adicionalmente, foi feita uma busca manual nas listas de referências dos artigos incluídos.

Os resultados da busca foram importados para a ferramenta online *Endnote Web* (https://access.clarivate.com/#/login?app=endnote&pageview=) e as duplicatas foram removidas. O programa *Reference Manager Software*® (Reference Manager Version 12.0.3, Thomson Reuters, Toronto, Canada) foi utilizado com o intuito de organizar a lista de estudos a serem lidos, com suas devidas referências e resumos.

4.6 Estratégia de busca

A estratégia de busca utilizada foi específica para cada base de dados. Para o Pubmed foi utilizada a seguinte estratégia: ((**Adipokines** [Mesh] OR **Adipokine** OR **Adipocytokines** OR **Biomarkers** [Mesh] OR **Biomarker** OR "**Biologic Markers**" OR "**Biological Markers**" OR **Adiponectin** [Mesh] OR **Adipsin** OR "**Complement Factor D**" [Mesh] OR "**Angiopoietin like protein 2**" OR **Apelin** [Mesh] OR **Cardiotrophin-1** [Mesh] OR **Chemerin** OR **CTRP1** OR **CTRP9** OR **CTRP12** OR **Adipolin** OR "**Fatty acid-binding protein 4**" OR **Ghrelin** [Mesh] OR **Obestatin** OR **Hepcidin** OR "**Hepatocyte Growth Factor**" [Mesh] OR **Interferon-gamma** [Mesh] OR **Interleukin-10** [Mesh] OR **Interleukin-6** [Mesh] OR **Interleukin-8** [Mesh] OR **irisi*** OR **irsin** OR "**FNDC5 protein**" [Mesh] OR **Leptin** [Mesh] OR **Lipocalin-2** [Mesh] OR "**Monocyte Chemotactic Protein-1**" OR **Nesfatin-1** OR "**Nephroblastoma Overexpressed protein**" [Mesh] OR **Intelectin-1** OR **Oment*** OR "**Plasminogen Activator Inhibitor 1**" [Mesh] OR **Progranulin** OR **GRN protein** [Mesh] OR **Prokineticin** OR **Resistin** [Mesh] OR "**Secreted Frizzled-related protein 5**" [Mesh] OR **Taurine** [Mesh] OR "**Tumor necrosis factor-α**" [Mesh] OR **Vaspin** OR **Serpin** OR **Visfatin** OR "**Nicotinamide phosphoribosyltransferase**" [Mesh]) AND (**Saliva** [Mesh] OR "**Gingival crevicular fluid**" [Mesh] OR **salivary**)

AND (“**weight gain**” [Mesh] OR **obesity** [Mesh] OR **overweight** [Mesh] OR **adiposity** [Mesh] OR “**body fat distribution**” [Mesh] OR “**waist circumference**” [Mesh] OR “**body mass index**” [Mesh] OR “**intra-abdominal fat**” [Mesh] OR “**abdominal fat**” [Mesh] OR **obese** OR “**abdominal circumference**” OR “**body weight**” [Mesh] OR “**anthropometric measurement**” OR “**anthropometric measurements**” OR “**anthropometric measure**”).

A estratégia de busca utilizada na base de dados Web of Science foi: ((**Adipokines** OR **Adipokine** OR **Adipocytokines** OR **Biomarkers** OR **Biomarker** OR **Biologic Markers** OR **Biological Markers** OR **Adiponectin** OR **Adipsin** OR **Complement Factor D** OR **Angiopoietin like protein 2** OR **Apelin** OR **Cardiotrophin-1** OR **Chemerin** OR **CTRP1** OR **CTRP9** OR **CTRP12** OR **Adipolin** OR **Fatty acid-binding protein 4** OR **Ghrelin** OR **Obestatin** OR **Hepcidin** OR **Hepatocyte Growth Factor** OR **Interferon-gamma** OR **Interleukin-10** OR **Interleukin-6** OR **Interleukin-8** OR **irisi*** OR **irsin** OR **FNDC5 protein** OR **Leptin** OR **Lipocalin-2** OR **Monocyte Chemotactic Protein-1** OR **Nesfatin-1** OR **Nephroblastoma Overexpressed protein** OR **Intelectin-1** OR **Oment*** OR **Plasminogen Activator Inhibitor 1** OR **Progranulin** OR **GRN protein** OR **Prokineticin** OR **Resistin** OR **Secreted Frizzled-related protein 5** OR **Taurine** OR **Tumor necrosis factor-α** OR **Vaspin** OR **Serpin** OR **Visfatin** OR **Nicotinamide phosphoribosyltransferase**) AND (**Saliva** OR “**Gingival crevicular fluid**”) AND (**obesity** OR **overweight** OR **adiposity** OR **obese**)).

Na base de dados Scopus a estratégia de busca utilizada foi a seguinte: ((**Adipokines** OR **Adipokine** OR **Adipocytokines** OR **Biomarkers** OR **Biomarker**) AND (**Saliva** OR “**Gingival crevicular fluid**”) AND (**obesity** OR **overweight** OR **adiposity** OR **obese**)).

Para realização da busca na base de dados Medline Ovid, utilizou-se a seguinte estratégia de busca: ((**Adipokines** OR **Adipokine** OR **Adipocytokines** OR **Biomarkers** OR **Biomarker** OR **Biologic Markers** OR **Biological Markers**) AND (**Saliva** OR **Gingival crevicular fluid** OR **Salivary**) AND (**obesity** OR **overweight** OR **adiposity** OR **obese**)).

4.7 Seleção dos artigos

O processo de seleção dos artigos foi conduzido de forma independente por dois autores (LFD e APH), em duas fases. A primeira fase consistiu da leitura e avaliação dos títulos/resumos. Para isso, ambos os autores passaram por um processo de calibração, aplicando-se os critérios de elegibilidade em 20% dos títulos/resumos recuperados. Foram realizadas discussões acerca dos critérios de inclusão e exclusão e o exercício de calibração foi repetido até que uma concordância adequada por meio do coeficiente Kappa de Cohen (Kappa: 0,789 a 0,825) fosse obtida. Nessa primeira fase, se o título/resumo contivesse informações insuficientes para uma decisão de inclusão ou exclusão, o texto completo era obtido e avaliado na segunda fase. Na segunda fase foram lidos os textos completos e incluídos aqueles que atendessem aos critérios de elegibilidade. Em ambas as fases, em casos de divergência entre os autores, era realizada uma discussão até que se atingisse um consenso. Caso a divergência persistisse, um terceiro autor de revisão (TAS) era consultado.

4.8 Extração de dados

Os textos completos selecionados passaram por avaliação cuidadosa realizada por dois examinadores independentes (LFD e APH) com o intuito de extrair dados relevantes para análise da revisão sistemática. Divergências foram resolvidas a partir de discussões e consenso. Novamente, em caso de persistência das divergências, um terceiro autor (TAS) era consultado.

Foram elaboradas tabelas para extração e anotação dos dados e toda informação pertinente aos trabalhos. Os seguintes itens foram coletados: nome dos autores; país onde o estudo foi conduzido; ano de publicação do trabalho; desenho de estudo; características da amostra (tamanho da amostra, idade dos participantes, perdas amostrais); índice utilizado para diagnóstico de obesidade; foco do estudo (avaliação de alguma alteração na saúde bucal ou alteração sistêmica na população do estudo); as adipocinas avaliadas e qual o método de análise das mesmas; fluido bucal coletado (saliva ou FGC); principais resultados de interesse (médias, números, valores de p) e as análises estatísticas utilizadas no estudo. Para aqueles estudos em que a avaliação da associação entre os níveis de adipocinas na saliva ou FGC e

obesidade era um objetivo secundário foi realizada uma classificação adicional (direcionada para análise desses desfechos secundários de interesse para esta revisão sistemática).

4.9 Avaliação da qualidade metodológica dos estudos

Para avaliação da qualidade foram verificadas determinadas características dos estudos incluídos para a determinação do risco de viés. Esta avaliação foi realizada por dois examinadores independentes (LFD e APH). Para solução de discordâncias, foi realizada uma discussão ou, quando necessário, uma consulta a um terceiro autor (TAS).

Uma vez que todos os estudos incluídos apresentavam desenho transversal, para análise de qualidade utilizou-se a versão original da ferramenta para análise de qualidade para estudos transversais do Instituto Joanna Briggs da Universidade de Adelaide (*Joanna Briggs Institute Critical Appraisal tool for Cross Sectional Studies*) (MOOLA *et al*., 2017) e uma versão adaptada pelos autores dessa mesma ferramenta. A versão original foi aplicada para estudos cujo objetivo principal foi avaliar alterações nos níveis de adipocinas na saliva ou no FGC em indivíduos obesos e não obesos. A versão modificada foi aplicada aos estudos, cujo foco de interesse não era semelhante ao questionamento desta revisão sistemática, mas que apresentavam desfechos secundários que respondiam a pergunta PECO. A modificação da ferramenta foi realizada com o intuito de adaptá-la às análises secundárias realizadas por cada estudo. Cada item da ferramenta foi discutido e avaliado pelos autores da presente revisão afim de garantir a congruência entre a versão modificada e a ferramenta original.

O sistema de análise de qualidade baseia-se na classificação do artigo incluído em “yes”, “no”, “unclear” ou “not applicable” para os seguintes critérios avaliados: definição clara do critério de elegibilidade, descrição adequada da amostra, uso de uma ferramenta válida e confiável para a avaliação da exposição, critério objetivo para avaliação da condição, identificação dos fatores de confusão, estratégias para ajuste dos fatores de confusão, uso de ferramenta válida e confiável para mensuração do desfecho e uso apropriado de análises estatísticas (MOOLA *et*

al., 2017). Na versão modificada, os dois critérios de elegibilidade relacionados aos fatores de confusão não foram utilizados.

4.10 Síntese dos resultados

O objetivo da síntese dos dados em uma revisão sistemática é agrupar os achados dos estudos primários incluídos. Essa síntese pode ser realizada por meio de uma descrição qualitativa dos dados ou, quando viável, utilizam-se técnicas estatísticas, como a meta-análise.

Todos os estudos incluídos na revisão sistemática foram avaliados quanto à heterogeneidade metodológica. Tal avaliação foi realizada por dois autores independentes (LFD e APH). A heterogeneidade metodológica foi avaliada analisando-se o tipo de fluido e a adipocina avaliada no estudo primário, o método utilizado para quantificação da adipocina e de mensuração da obesidade, bem como a faixa etária e os critérios para seleção dos participantes. Artigos com homogeneidade metodológica tiveram seus resultados agrupados através da meta-análise.

Os estudos incluídos na meta-análise foram submetidos à análise de heterogeneidade estatística, utilizando-se o teste I^2. Para as meta-análises cujo valor de I^2 era superior a 40%, utilizou-se o modelo de efeitos randomizados. Para meta-análises com valores de I^2 inferiores a 40%, o modelo de meta-análise fixo foi aplicado.

4.11 Interpretação da evidência

Foram utilizados tabelas e gráficos para apresentação dos resultados. O gráfico *forest plot* foi usado com o intuito de demonstrar, visualmente, os resultados da meta-análise, por meio de uma estimativa visual dos resultados dos agrupamentos e da heterogeneidade estatística dos estudos.

5 ARTIGO CIENTÍFICO

Os capítulos de resultados e discussão serão apresentados sob a forma de artigo científico, formatado segundo as normas do periódico: “Obesity Reviews”; Fator de impacto: 7,883; Qualis CAPES: A1.

ASSOCIATION BETWEEN OBESITY AND ADIPOKINES IN SALIVA AND GINGIVAL CREVICULAR FLUID: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Running title: SALIVARY AND GINGIVAL CREVICULAR FLUID ADIPOKINES: A SYSTEMATIC REVIEW

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CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interest.

Key words

Obesity; Adipokines; Saliva; Gingival crevicular fluid

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ABSTRACT

The objective of this systematic review was to evaluate the association between obesity and the concentration of adipokines in gingival crevicular fluid (GCF) and saliva. The search was conducted in four databases. Manual and Google Scholar searches were also conducted. Two calibrated authors performed study selection, data extraction and quality assessment of included articles. Thirty four articles were included. Meta-analysis demonstrated that TNF-α concentration in saliva was statistically increased in individuals with obesity compared with individuals without obesity. In contrast, concentrations of resistin, adiponectin, leptin, ghrelin and IL-6 in saliva and of resistin, adiponectin, leptin, IL-6, IL-8, TNF-α and PAI-1 in GCF, were statistically similar in individuals with and without obesity. Overall, the scientific evidence regarding altered levels of specific adipokines in saliva and or GCF among persons with obesity is weak, except for salivary TNF-α. The limited availability and heterogeneity of data do not allow us to state whether changes of adipokines in GCF and saliva are associated with obesity or otherwise.

Introduction

Obesity is a disease characterized by accumulation of fat in adipose tissue and in different organs and tissues.[1] The number of individuals with obesity is increasing worldwide.[1] This inflated figure may contribute to increase the prevalence of chronic disorders, such as cardiovascular diseases, type 2 diabetes mellitus and metabolic syndrome.[2]

Adipose tissue has currently been described as an endocrine organ, which secretes metabolic active molecules, such as adipose-derived hormones, inflammatory cytokines and adipokines[3]. Adipokines play an important role in metabolic systemic regulation as well as in inflammatory response.[4;5] Several molecules are classified as adipokines e.g. adiponectin, resistin, leptin, omentin, lipocalin-2, visceral adipose tissue-derived serpin (vaspin) and chemerin.[6-8] These molecules are highly assorted in terms of protein structure and physiological function. While some adipokines have showed to be reduced in the blood of individuals with obesity, such as adiponectin,[9;10] others such as resistin were identified at increased levels in subjects with obesity.[11;12] Moreover, due to the chronic systemic inflammatory response associated with obesity,[13] some of the classical inflammatory mediators e.g. tumor necrosis factor alpha (TNF-α),[14] interleukin 6 (IL-6)[15] and CC chemokine ligand 2 / Monocyte chemoattractant protein-1 (MCP-1)[16] have also been assigned to the group of adipokines when expressed in the context of obesity.

Emerging data demonstrate significant changes in the levels of adipokines e.g. adiponectin;[17] resistin;[18-20] leptin;[17;20-24] chemerin;[25] vaspin;[26] ghrelin;[27-29] irisin;[30] omentin-1;[26] lipocalin-2;[31] TNF-α[24;26;32;33] and IL-6[25;34] in saliva and gingival crevicular fluid (GCF) of individuals with obesity. Thus, the concentration of adipokines in oral fluids might be indicative of obesity or other metabolic disorder.[23;35] The objective of the present study was to systematically review and to appraise the quality of the available evidence of human studies investigating levels of adipokines in saliva and GCF and their association with obesity.

Materials and Methods

Protocol and registration

The report of this systematic review was based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[36] A protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42017078518.

Eligibility criteria

The question of relevance was as follows: Is obesity associated with changes in adipokines' levels in saliva and GCF? The follow PECO strategy has been applied:

P = individuals

E = obesity

C = no obesity

O = adipokines' levels in saliva and GCF

Original articles comparing adipokines' levels in saliva and GCF between individuals with and without obesity were included. No restriction was imposed for date or language of publication. Studies not conducted on humans; studies evaluating only people with obesity or individuals with a normal weight; studies conducted on highly selective populations, such as patients with diabetes or with periodontitis without a control group were excluded. Meeting abstracts, editorials, letters to the editor and literature reviews were also excluded.

Information sources

Electronic searches were conducted in PubMed (http://www/pubmed.gov), Web of Science (http://www.isiknowledge.com), Scopus (https://www.scopus.com), Medline via Ovid (http://gateway.ovid.com) from their date of inception up to August 2017. An update was carried out in October 2018. Grey literature search was also conducted in Google Scholar, limiting the search to the first 100 hits. Finally, the reference lists of the included

articles were manually searched. So were the reference lists of systematic reviews, theoretical reviews and additional articles of potential relevance. The Reference Manager Software® (Reference Manager Version 12.0.3, Thomson Reuters, Toronto, Canada) was used to organize the list of studies. Duplicate hits were removed upon identification.

Search strategy

The following search strategy was used in Pubmed: ((Adipokines [Mesh] OR Adipokine OR Adipocytokines OR Biomarkers [Mesh] OR Biomarker OR "Biologic Markers" OR "Biological Markers" OR Adiponectin [Mesh] OR Adipsin OR "Complement Factor D" [Mesh] OR "Angiopoietin like protein 2" OR Apelin [Mesh] OR Cardiotrophin-1 [Mesh] OR Chemerin OR CTRP1 OR CTRP9 OR CTRP12 OR Adipolin OR "Fatty acid-binding protein 4" OR Ghrelin [Mesh] OR Obestatin OR Hepcidin OR "Hepatocyte Growth Factor" [Mesh] OR Interferon-gamma [Mesh] OR Interleukin-10 [Mesh] OR Interleukin-6 [Mesh] OR Interleukin-8 [Mesh] OR irisi* OR irsin OR "FNDC5 protein" [Mesh] OR Leptin [Mesh] OR Lipocalin-2 [Mesh] OR "Monocyte Chemotactic Protein-1" OR Nesfatin-1 OR "Nephroblastoma Overexpressed protein" [Mesh] OR Intelectin-1 OR Oment* OR "Plasminogen Activator Inhibitor 1" [Mesh] OR Progranulin OR GRN protein [Mesh] OR Prokineticin OR Resistin [Mesh] OR "Secreted Frizzled-related protein 5" [Mesh] OR Taurine [Mesh] OR "Tumor necrosis factor-α" [Mesh] OR Vaspin OR Serpin OR Visfatin OR "Nicotinamide phosphoribosyltransferase" [Mesh]) AND (Saliva [Mesh] OR "Gingival crevicular fluid" [Mesh] OR salivary) AND ("weight gain" [Mesh] OR obesity [Mesh] OR overweight [Mesh] OR adiposity [Mesh] OR "body fat distribution" [Mesh] OR "waist circumference" [Mesh] OR "body mass index" [Mesh] OR "intra-abdominal fat" [Mesh] OR "abdominal fat" [Mesh] OR obese OR "abdominal circumference" OR "body weight" [Mesh] OR "anthropometric measurement" OR "anthropometric measurements" OR "anthropometric measure")).

Search strategies were tailored for the other electronic databases. The search strategies for Web of Science, Scopus and Medline Ovid are shown in Supplementary File 1.

Study selection

Study selection was carried out independently by two review authors (LFD and APH) in two phases. In phase one, the review authors evaluated titles/abstracts. Both review authors were calibrated, applying the eligibility criteria on 20% of the retrieved titles/abstracts. Review authors thoroughly discussed the inclusion and exclusion criteria and the calibration exercise was repeated until adequate agreement by means of the Cohen's Kappa coefficient (Kappa = 0.82) was obtained. In phase one, if the title/abstract contained insufficient information for a decision on inclusion or exclusion, the full text was obtained and evaluated in phase two. In the second phase, full texts meeting the eligibility criteria were included. In both phases, if divergence between the review authors took place, a discussion was performed until consensus. If the divergence persisted, a third review author (TAS) decided.

Data Extraction and data items

Data extraction was also conducted by two independent review authors (LFD, APH). Divergences were resolved by discussion and consensus. If necessary, a third part (TAS) participated. The following items were extracted: authors' names, year and language of publication and country where the study was conducted, study design, sample size, sample's characteristics and losses, index used for obesity diagnosis, focus of the study, method of assessment of adipokines, body fluid evaluated (saliva or GCF), statistical analysis used, main results regarding the association between obesity and adipokines' levels. For the studies, in which the main objective was not the evaluation of such an association, an additional classification of study design was provided, according to the analysis of interest for this systematic review (association between adipokines' levels and obesity).

Assessment of Methodological Quality

The quality of the studies was assessed by two review authors (APH and LFD) using the original and a modified version of the Joanna Briggs Institute Critical Appraisal tool for Cross Sectional Studies.[37] The original version was applied for the studies in which the main objective was to evaluate alterations in adipokines' levels in saliva or GCF among patients with and without obesity. Whenever the articles presented such data, but the phenomena of interest were not the main objective of the study, a modified version of the Joanna Briggs Institute tool was used. The modification was performed to adapt the critical appraisal tool for the analysis of secondary data. Each item of appraisal was evaluated to guarantee the reliability of the modified version of the critical appraisal instrument.

The tool allows the assessors to provide "yes", "no", "unclear" or "not applicable" to the following parameters: clear definition of eligibility criteria, adequate description of participants and study setting, valid and reliable measurement of the exposure, objective standard criteria for measurement of the condition, identification of confounding factors, adequate statement of strategies to deal with confounding factors, valid and reliable measurement of the outcome and appropriate use of statistical analysis. For the modified version, the two eligible categories about confounding factors were removed.

Summary measures and synthesis of results

Methodological heterogeneity among studies was evaluated. Assessment of methodological heterogeneity was carried out by means of comparisons among studies regarding the fluid and the adipokine assessed, the method used to evaluate the adipokine and participants' age. Meta-analysis was considered for articles that were methodologically homogeneous and appropriate for pooling. Feasible meta-analyses were submitted to the evaluation of statistical heterogeneity by means of the I^2 test. For meta-analyses, in which the I^2 value was under 40%, the fixed model was used. For meta-analyses, in which the I^2 value was higher than 40%, a random model was used.

Results

Study selection

The electronic searches retrieved 929 titles/abstracts. After the removal of duplicate references, 613 titles/abstracts remained and were evaluated by two review authors. Two references were identified by means of the manual search. Based on the evaluation of title/abstracts, 505 records were excluded, as they did not meet the inclusion criteria. A total of 108 studies were selected for full text assessment. After this analysis, 34 studies met the eligibility criteria and were included in this systematic review. Figure 1 shows the flowchart of the study.

Study characteristics

All articles included were published in English. Studies were conducted in different countries: Brazil,[24] Canada,[32;38] Chile,[39] China,[29;33] Germany,[27;28;40;41] Greece,[42] India,[18;22;23;31;43;44] Italy,[45] Portugal,[46] Sweden,[47-49] Thailand,[50] Turkey,[25;26;30;51] United States of America,[17] Saudi Arabia,[52] Poland,[19] United Kingdom,[20] Malaysia[53] and United Arab Emirates.[54;55] All studies were published between 2001 and 2018. Among the 34 included articles, 22 were cross-sectional studies with a control group;[18;19;22-27;29-31;33;39;41;43-46;48;49;51;53] ten were cross-sectional studies;[17;28;32;38;40;42;47;50;54;55] one was a cohort study[20] and one was a clinical trial.[52]

Each study was also classified regarding whether the information of interest of this systematic review (association between adipokines' levels and obesity) was part of the study's main objective or otherwise. In five articles,[19;29;32;45;55] the main objective was to evaluate the relationship between adipokines' levels in saliva or GCF and obesity. In 29 studies, the relationship between obesity and adipokines' levels was evaluated as a secondary outcome.[17;18;20;22-28;31;33;38-44;46-54;56]

The sample size of the included studies ranged between 25[28] and 744[17] participants, including male and female individuals. Ten articles included only children and adolescents,[17;20;29;32;33;38;46;48;49;51] while 21 included only adults.[18;19;23-28;30;31;39;41-45;50;52-55] Three articles included children, adolescents and adults.[22;40;47]

Among the 34 included articles, 18 different adipokines were analyzed. Evaluation of adipokines in saliva was carried out in 17 articles.[17;19;22;28-30;39-42;45;46;50;52-55] Analysis of GCF was done in 15 articles.[18;20;23-26,31-33;38,43;44;47-49] Two studies[27;51] evaluated adipokines in both saliva and GCF. The most used method for quantification of adipokines´ levels in GCF was enzyme-linked immunosorbent assay (ELISA) (n=16)[18;23-27;31-33;38;43;44;47-49;51] and ELISA multiplex (n=1).[20] In saliva, the adipokines´ levels were measured by means of ELISA (n=15);[19;20;22;27;29;39;42;45;46;50;52;53;51;54;55] ELISA multiplex (n=1);[17] radioimmunoassay (n=2)[40;41] and western blot (n=2).[28;40]

Risk of bias within studies

Articles in which the main objective was to evaluate the association between adipokines' levels and obesity

Five articles[19;29;32;45;55] used objective standard criteria for determination of the condition, by means of a valid and reliable tool for the measurement of the outcome and an appropriate strategy for statistical analysis. No article measured the exposure in a valid and reliable way, as they did not provide calibration process, intra or inter examiner agreement or kappa values. Three articles[19;29;45] failed in providing a clear description of participants and two failed in providing clear identification of confounding variables.[29;45;55] In one article,[45] the eligibility criteria were unclear and in other it was not mentioned.[55] In two articles[19;29;55] no statement on strategies to deal with confounding factors was provided (Supplementary File 2).

Articles in which the evaluation of the association between adipokines' levels and obesity was a secondary outcome

In ten studies,[19;28;38;40-42;46;47;49;53] the eligibility criteria were not described and in two articles[33;50] the information was unclear, as only the exclusion criteria was provided. Fifteen studies[17;18;20;23-26;31;38;43;44;49;51;52;54] clearly described the sample, addressing the following aspects: demographic data, study setting and the recruitment period. In 14 studies[22;27;28;30;33;40-42;46-50;53] information on at least two of these characteristics was missing. No article provided information whether the exposure was measured in a valid and reliable way, as the studies did not provide calibration process, intra or inter examiner agreement or kappa values. Two articles[28;42] did not use objective standard criteria for measurement of the condition and in two articles[41;30] this information was unclear. All included articles used a valid and reliable measurement of outcome assessment and only one study[38] did not use an appropriate statistical analysis for the evaluation of the association between adipokines' levels and obesity (Supplementary File 3).

Results of individual studies

Nineteen different adipokines have been identified across the studies. Taking into account that these molecules have particular characteristics, the results were reported separately. Detailed information regarding the characteristics and the results on the 34 studies is displayed in Supplementary File 4. Moreover, major conclusions whether the levels of adipokines were unchanged, increased or reduced in GCF and saliva of individuals with obesity are presented in Table 1.

Resistin

Five studies[17;19;42;51;52] evaluated the levels of resistin in saliva showing no significant difference between individuals with and without obesity and one study[54] showed increased levels in individuals with obesity. As regards to GCF, two articles[49;51] showed no significant difference between groups. Conversely, one study[24] found significantly decreased levels of resistin in individuals with obesity compared to non-obese. Another study[18] showed a

positive, but weak, correlation between resistin levels and body mass index (BMI), suggesting increased levels of this adipokine in the GCF of patients with obesity. One study[20] showed increased resistin levels in GCF of individuals with obesity.

Adiponectin

Five studies[19;42;45;50;53] showed no significant difference for adiponectin levels in saliva of individuals with and without obesity. In contrast, two studies[17;55] that the levels of adiponectin in saliva of subjects with obesity were significantly lower than non-obese. The four studies[20;24;48;49] that evaluated adiponectin levels in GCF showed no significant difference between people with and without obesity.

Leptin

Three studies[17;22;40] obtained that individuals with obesity had significantly higher levels of leptin in saliva compared to those without this condition. In a similar way, three studies[20;23;24] demonstrated significantly higher levels of leptin in GCF of individuals with obesity compared to non-obese. In contrast, comparing individuals with and without obesity, one study found similar leptin levels in GCF[49] and three studies showed similar levels of this adipokine in saliva.[17;46;50]

Adipisin

One study[49] that evaluated levels of adipisin in GCF showed no significant difference comparing individuals with and without obesity. No study assessed adipisin in saliva of individuals with and without obesity.

Chemerin

One study[27] evaluated the concentration of chemerin in saliva and found no significant difference between individuals with and without obesity. This same study evaluated chemerin in GCF and similar levels were found in two groups. For this latter comparison, however, no

p-value was provided. In contrast, one study[25] demonstrated that the levels of chemerin in GCF of individuals with obesity were higher than their peers with normal weight.

Ghrelin

One study[29] demonstrated a weak and positive correlation between BMI and ghrelin concentration in saliva. Otherwise, Groschl *et al.* (2005) found a weak and negative correlation between BMI and ghrelin in saliva. Three other studies[17;27;41] have observed no significant difference between salivary production of ghrelin in individuals with and without obesity. One study[27] did measure ghrelin levels in GCF and the findings suggested significantly higher levels in individuals with obesity compared to their peers with normal weight. However, no *p*-value was provided for such comparison.

Lipocalin-2

Lipocalin-2 was evaluated only in GCF. There was a significantly higher expression of this adipokine in GCF of individuals with obesity compared to the levels observed in non-obese.[31]

Irisin

Irisin was assessed only in saliva.[30] There was significant lower concentration of this adipokine in the saliva of individuals with obesity compared to those without obesity.

Serpin

Higher levels of serpin were detected in saliva of individuals with obesity compared to individuals without obesity.[19]

Vaspin

There is no study assessing vaspin levels in saliva. Two studies[26;43] did analyze vaspin in GCF. One[26] found significantly higher levels in individuals with obesity than in non-obese individuals. The other study[43] demonstrated a positive, but weak, correlation between BMI and vaspin concentration in GCF.

MCP-1

Two studies[17;19] evaluated MCP-1 in saliva. One study[17] showed no significant difference in the levels of this adipokine in the saliva of individuals with and without obesity. On the other hand, another study[19] found increased levels of MCP-1 in the saliva of individuals with obesity.

Visfatin.

Only one study evaluated visfatin[42] and no significant difference was observed in the levels of this adipokine in the saliva of individuals with and without obesity.

Omentin-1

Omentin-1 levels were assessed only in GCF. There was a significantly increased concentration of this adipokine in the GCF of individuals without obesity.[26]

Progranulin

Progranulin was examined in GCF by one study.[44] A positive weak correlation between BMI and progranulin concentration in GCF was observed. The levels of progranulin in GCF seemed to be higher in individuals with obesity than in non-obese. However, the *p*-value provided was obtained from a test comparing all groups and not only the two groups (obese and non-obese) of interest.

TNF-α

Three studies[17;19;51] determined the levels of TNF-α in saliva and nine studies evaluated it in GCF.[24;26;32;33;38;47-49] Five studies[38;47;48;49;51] found no significant differences in GCF comparing individuals with and without obesity, while four studies[24;26;32;33] demonstrated significantly elevated TNF-α levels in GCF of individuals with obesity. Regarding saliva, two studies[17;51] showed no difference in TNF-α concentration in saliva of individuals with and without obesity. In contrast, two studies[19;55] demonstrated higher levels of TNF-α in saliva of individuals with obesity.

IL-6

The majority of studies that evaluated IL-6 in saliva[17;39;52] or in GCF[24;49] did not find significant difference between participants with and without obesity. On the other hand, Balli *et al* (2016a) found higher levels of IL-6 in GCF of individuals with obesity compared to non-obese. In one study,[48] the comparison between the groups was not reported.

Interleukin 8 (IL-8)

Only one study[17] analyzed the levels of IL-8 in saliva, but no significant difference was found comparing individuals with and without obesity. With respect to GCF, one study[48] demonstrated significantly lower levels of IL-8 in individuals without obesity in comparison to individuals with obesity. Two studies[47;49] did not find significant differences in IL-8 levels in GCF between participants with and without obesity.

Interleukin 10 (IL-10)

Two studies[17;55] demonstrated similar levels of IL-10 in saliva of participants with and without obesity. However, in one study[17] the *p*-value was not reported. No study assessed IL-10 levels in the GCF.

Plasminogen activator inhibitor-1 (PAI-1)

One study[19] assessed the levels of PAI-1 in saliva and showed increased levels in the individuals with obesity. Two studies[48;49] obtained that there was no significant difference between the levels of PAI-1 in GCF of individuals with and without obesity.

Synthesis of results

The meta-analysis was conducted from the pool of studies with homogeneity in the adipokine evaluated, the fluid, the test used for identification and the form of data presentation. For the nineteen studies with unavailable data[17;19;25-29;32;38;39;41;42;46-48;50;51;53;55] personal contact with authors was made. Eleven authors answered, but only nine provided data.[17;19;27;29;46;48;51;53;55] According to the meta-analysis, there was no difference in resistin,

adiponectin, leptin, ghrelin and IL-6 levels in saliva of individuals with and without obesity (Figure 2 A-D and Figure 3 A), however TNF-α was increased in saliva of individuals with obesity (Figure 3 B). There was no difference in levels of resistin, adiponectin, leptin, IL-6, IL-8, TNF-α, IL-8 and PAI-1 in GCF of individuals with and without obesity (Figures 4 A-C and Figure 5 A-D).

Discussion

Adipokines are mainly produced by adipose tissue but altered levels of these molecules in a number of tissues and fluids,[30;57;58] including those from the oral cavity[17-34] were associated with obesity. The aim of this systematic review was to assess whether levels of adipokines in saliva and GCF are significantly influenced by obesity. Overall, the retrieved studies revealed that the adipokines fluctuation in oral fluids exhibit a variable profile in individuals with obesity. Therefore, unequivocal evidence on this association is generally still lacking. In contrast, TNF-α was showed to be increased in the saliva of individuals with obesity.

Methodological heterogeneity might explain some of the discrepancies among studies' findings. The main differences were related to sample selection criteria, exposure and outcomes measures. With respect to the sample characteristics, most studies had a limited number of participants, which may lead to unreliable results. Participants' age ranged from 6[33] to 85 years old[40] and both male and female individuals were evaluated. All included studies used BMI for obesity evaluation, and waist circumference was employed as an additional parameter in a number of publications.[18;23-26;31;43;44;49;50;55] Though flawed by the lack of correspondence of fatness among different individuals and the low sensitivity in the results related to the levels of body fat,[59] the BMI is the most widely used method for obesity assessment[1] due to the simplicity of application, especially in epidemiological studies. Four studies[30;41;42;50] used the BMI, but the numeric scale used to classify normal weight or obesity was not specified. Moreover, none of the included studies clearly mentioned inter- or intra-examiner calibration process for obesity assessment. These aspects may have compromised the validity and reliability of exposure measurements.

The concentration of a specific adipokine in individuals with obesity (even when analyzing the same fluid and the same age group) varied from high to low levels. Those

variations may rely on the different techniques used for samples' collection and adipokine measurement and also because only few studies for each investigated adipokine were retrieved. Therefore, caution should be exercised when comparing the findings presented herein. As regards the outcome assessments, the most used assay to measure the concentration of adipokines in saliva and GCF was ELISA. Even using the same assay, different kits or brands of reagents and the variability in the standardization of the technique might account for significant variation. Thus, even when similar methods are used, the homogeneity of the results and consequently the estimate pooling by means of a meta-analysis is not guaranteed. For these reasons, only few data could be pooled to conduct meta-analysis. The results showed no statistically significant difference in any adipokines concentrations in saliva and GCF, when comparing individuals with and without obesity, except for TNF-α in saliva, that was in increased levels in individuals with obesity. Interestingly, salivary concentrations of different adipokines were found to be lower[57;60-62] or higher compared to blood.[30;42] In contrast, no correlation was achieved in the evaluation of adipokine concentrations in blood and GCF.[63] Differences can be explained by distinct molecular size, structure, kinetics and secretory pattern of these molecules.[42] For future studies, the concomitant analysis of adipokines in blood, saliva and GCF may contribute to determine the association of these molecules with obesity and their kinetics within these fluids.

Other important variable that must be taken into account is the oral status of sample subjects.[64] As demonstrated, periodontal disease interferes with adipokines' levels in blood,[64] saliva[27] and GCF.[25] Moreover, other conditions affecting the oral cavity, such as squamous cell carcinoma[65] and dental caries[66;67] may also impact the production of inflammatory markers in saliva and GCF. Some studies[35;63] were not included in this systematic review because they did not evaluate the impact of obesity and periodontitis independently on adipokines production. It is important to stress that several studies included in the present

systematic review did not report the evaluation of oral health status of participants.[28;29;30;39;40;41;42;45;46;50;55] Consequently, these confounding variables were not incorporated into adjusted models of statistical analysis, which suggests a possible bias.

The composition of saliva may be influenced by systemic conditions, which makes saliva a potential diagnostic fluid. However, results of salivary concentration of a particular substance may be deeply influenced by the type of saliva collected (stimulated or unstimulated), daytime collection, storage conditions, contamination with blood, oral health condition and others. For the studies included in this review, scarce information regarding these aspects is mentioned. Furthermore, an specific adipokine, ghrelin, was demonstrated to be produced by salivary glands.[40] Thus, the precise relationship of this adipokine evaluated in oral fluids with obesity deserves a particular interpretation. The contribution of salivary glands for the levels of other adipokines in saliva needs to be further defined.

The lack of significance in adipokine concentrations of saliva and GCF from subjects with and without obesity does not allow us to reject the hypothesis of an association. The increase of TNF-α concentration in the saliva of individuals with obesity, demonstrated by the meta-analysis, reinforce the idea that the evaluation of these fluids can be promising, mainly because they are less invasive. Further well-designed studies will require complete oral examination of recruited subjects; the application of standardized methods for obesity diagnosis as well as for GCF and saliva sampling and storage. Moreover, sample size calculation as well as case-control studies with non-obese age and gender-matched controls are worth performing. Follow-up with at least two time points of evaluation is warranted.

This review used a systematic approach to examine whether saliva and GCF are significantly impacted by obesity. In conclusion, while TNF-α in saliva was associated with obesity, the limited availability and the heterogeneity of data do not allow us to define if changes of remaining adipokines in GCF and saliva are related or not with obesity.

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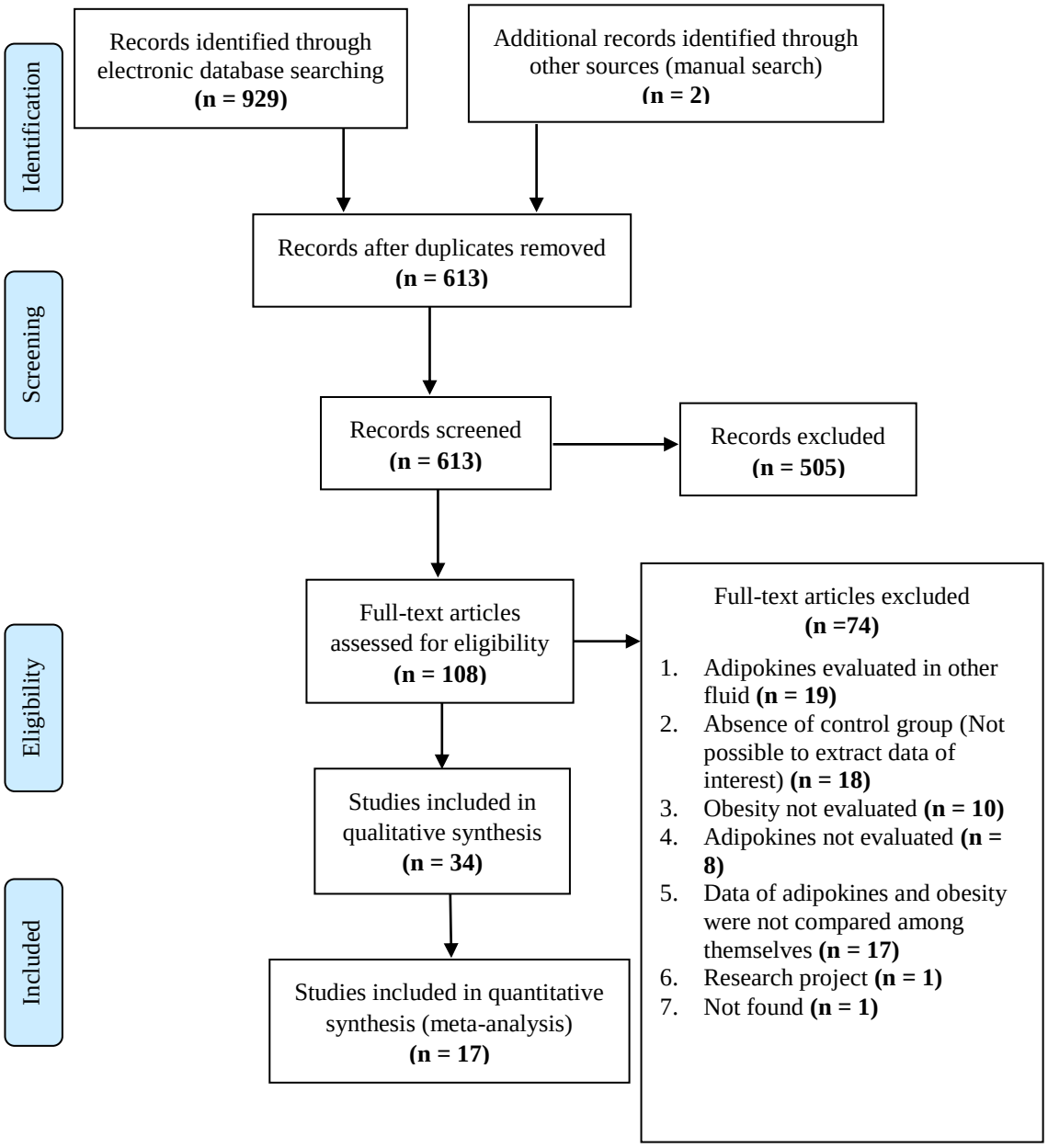

Figure 1 Screening of articles**.** Four-phase PRISMA flow-diagram for study selection, showing the number of studies identified, screened, eligible, and included in the review and meta-analysis.

Table 1: Major findings of adipokines fluctuation in saliva and GCF of obese subjects

Adipokine	Saliva	GCF
Resistin	(=)[17;19;42;51;52] (↑)[54]	(=)[49;51] (↑)[18;20] (↓)[24]
Adiponectin	(=)[19;42;45;50;53] (↓)[17;55]	(=)[20;24;48;49]
Leptin	(=)[19;46;50] (↑)[17;22;40]	(=)[49] (↑)[20;23;24]
Adipisin	NR	(=)[49]
Chemerin	(=)[27]	(=)[27] (↑)[26]
Ghrelin	(=)[17;27;41] (↑)[29] (↓)[28]	(↑)[27]
Lipocalin-2	NR	(↑)[31]
Irisin	(↓)[56]	NR
Serpin	(↑)[19]	NR
Vaspin	NR	(↑)[25;43]
MCP-1	(=)[17] (↑)[19]	NR
Visfatin	(=)[42]	NR
Omentin-1	NR	(↓)[25]
Progranulin	NR	(↑)[44]
PAI-1	(↑)[19]	(=)[48;49]
TNF-α	(=)[17;51] (↑)[19;55]	(=)[38;47-49;51] (↑)[24;25;32;33]
IL-6	(=)[17;39;52]	(=)[24;49] (↑)[26]
IL-8	(=)[17]	(=)[47;49] (↑)[48]
IL-10	(=)[17;55]	NR

NR, not-reported; ↑, increased concentrations of adipokine in individuals with obesity; ↓, decreased concentrations of adipokine in individuals with obesity; =, not alteration in concentration levels of adipokine in individuals with obesity.

Adipokines in saliva

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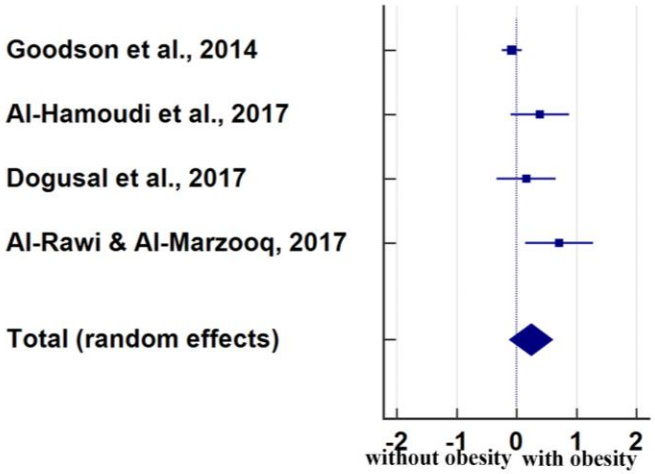

Resistin in saliva

Study	Obese Mean	Obese SD	Obese N	Non-obese Mean	Non-obese SD	Non-obese N	SMD	95% CI	Weight (%) Random
Goodson et al., 2014	2206.95	2643.92	186	2485.33	3989.53	558	-0.0752	-0.242 to 0.0903	34.98
Al-Hamoudi et al., 2017	2200	200	34	2100	300	33	0.389	-0.0982 to 0.876	22.61
Dogusal et al., 2017	9726.25	5088.05	32	8852.70	5423.33	33	0.164	-0.327 to 0.654	22.49
Al-Rawi & Al-Marzooq, 2017	14.4	3.6	26	10.8	6.1	26	0.708	0.142 to 1.274	19.92
Total (random effects)								-0.120 to 0.598	

I^2 (95% CI) = 69.35% p=0.0205

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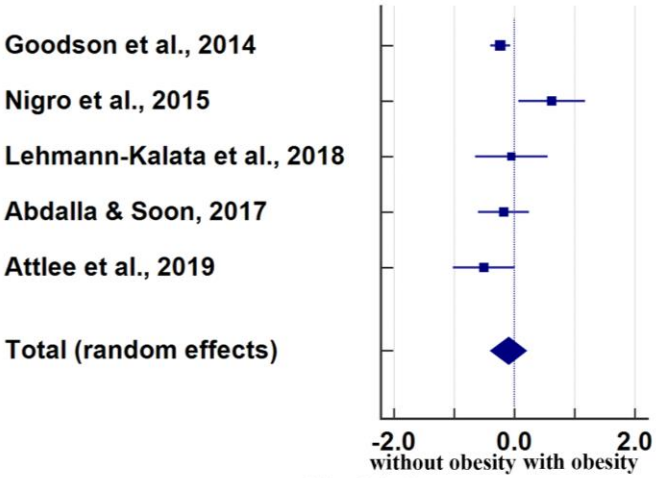

Adiponectin in saliva

Study	Obese Mean	Obese SD	Obese N	Non-obese Mean	Non-obese SD	Non-obese N	SMD	95% CI	Weight (%) Random
Goodson et al., 2014	4253.65	4647.18	186	6662.65	11798.13	558	-0.230	-0.396 to -0.0631	31.14
Nigro et al., 2015	6100	1300	27	4800	2600	27	0.623	0.0718 to 1.175	16.21
Lehmann-Kalata et al., 2018	6650	5350	19	7040	8770	25	-0.0511	-0.654 to 0.552	14.78
Abdalla; Soon, 2017	18100	8300	41	19600	8600	47	0.176	-0.598 to 0.246	20.62
Attlee et al., 2019	39000	42000	30	60000	40000	30	-0.505	-1.024 to 0.0130	17.24
Total (random effects)								-0.678 to 0.991	

I^2 (95% CI) = 62.44% p=0.0308

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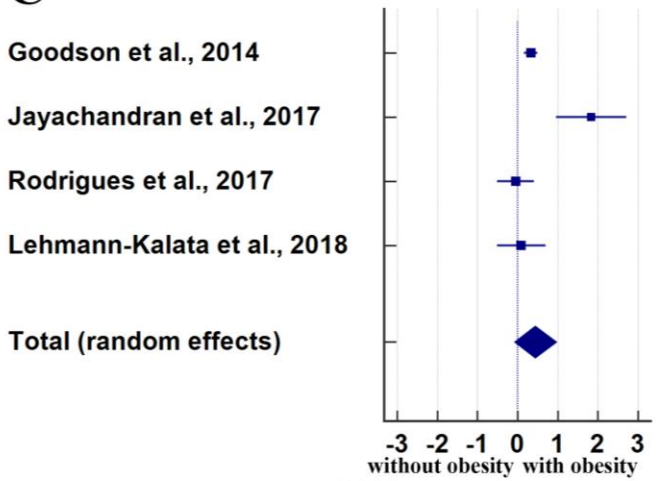

Resistin in saliva

Study	with obesity Mean	with obesity SD	with obesity N	without obesity Mean	without obesity SD	without obesity N	SMD	95% CI	Weight (%) Random
Goodson et al., 2014	2206.95	2643.92	186	2485.33	3989.53	558	-0.0752	-0.241 to 0.0909	54.37
Al-Hamoudi et al., 2017	2200	200	34	2100	300	33	0.389	-0.0982 to 0.876	22.92
Dogusal et al., 2017	9726.25	5088.05	32	8852.70	5423.33	33	0.164	-0.327 to 0.655	22.71
Total (random effects)								-0.197 to 0.368	

I^2 (95% CI) = 46.94% p=0.1519

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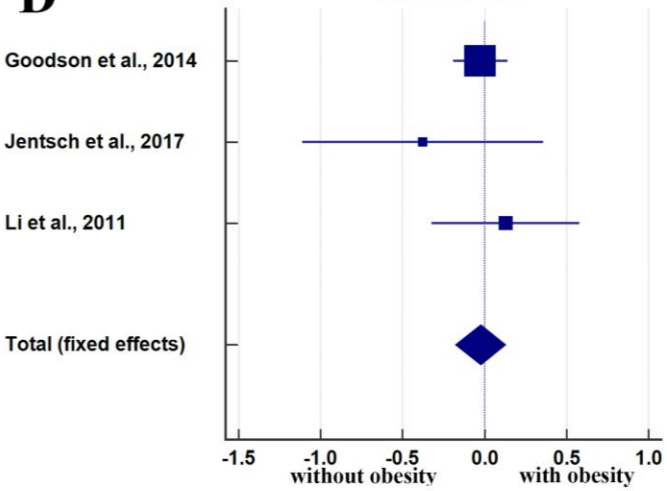


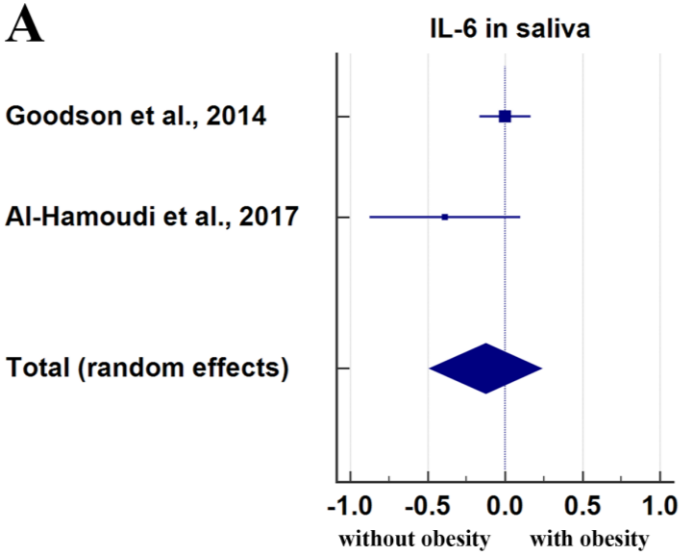
Ghrelin in saliva

Study	with obesity Mean	with obesity SD	with obesity N	without obesity Mean	without obesity SD	without obesity N	SMD	95% CI	Weight (%) Fixed
Goodson et al., 2014	5.08	7.05	186	5.29	8.41	558	-0.0259	-0.192 to 0.140	83.73
Jentsch et al., 2017	124.30	100.44	15	174.32	153.21	15	-0.376	-1.110 to 0.359	4.66
Li et al., 2011	381.80	421.92	45	325.01	458.85	33	0.128	-0.324 to 0.581	11.61
Total (fixed effects)								-0.176 to 0.128	

I^2 (95% CI) = 0.00% p=0.4934

Adipokines in saliva

A



Study	with obesity Mean	SD	N	without obesity Mean	SD	N	SMD	95% CI	Weight (%) Random
Goodson et al., 2014	15.17	27.56	186	15.16	28.08	558	0.000357	-0.166 to 0.166	67.27
Al-Hamoudi et al., 2017	2.1	0.4	34	2.3	0.6	33	-0.389	-0.876 to 0.0982	32.73
Total (random effects)								-0.486 to 0.231	

I^2 (95% CI) = 56.02% p=0.1316

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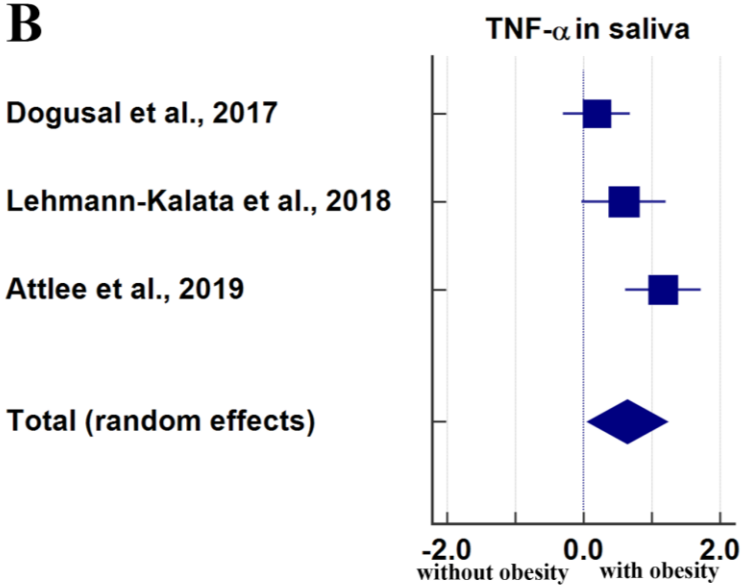

Study	Obese Mean	SD	N	Non-obese Mean	SD	N	SMD	95% CI	Weight (%) Random
Dogusal et al., 2017	204.99	151.60	32	177.41	132.71	33	0.191	-0.300 to 0.682	35.45
Lehmann-Kalata et al., 2018	3.23	5.00	19	1.19	1.14	25	0.592	-0.0246 to 1.208	31.25
Attlee et al., 2019	1.38	1.12	30	0.43	0.22	30	1.162	0.609 to 1.714	33.30
Total (random effects)								0.0576 to 1.222	

I^2 (95% CI) = 71.02% p=0.0317

Adipokines in GCF

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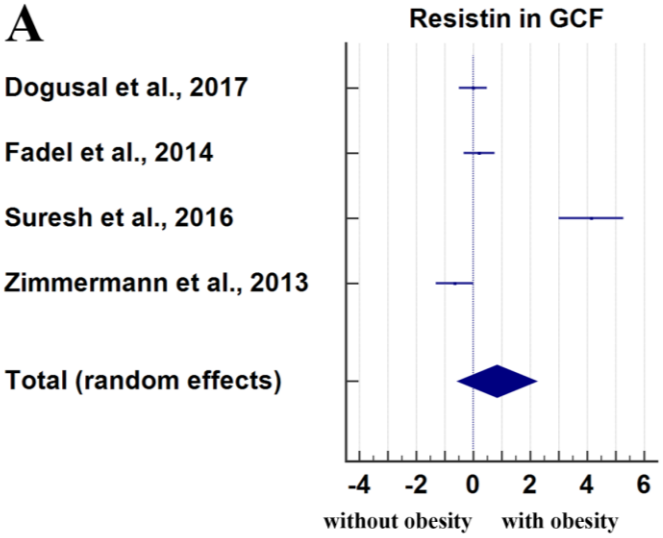

Resistin in GCF

Study	with obesity Mean	SD	N	without obesity Mean	SD	N	SMD	95% CI	Weight (%) Random
Dogusal et al., 2017	10132.01	7126.37	32	10137.35	4727.28	33	-0.000875	-0.491 to 0.489	25.99
Fadel et al., 2014	6.5125	4.5823	27	5.5839	4.0744	28	0.211	-0.323 to 0.746	25.84
Suresh et al., 2016	9.0680	0.77545	25	5.4107	1.00264	15	4.139	3.000 to 5.278	22.82
Zimmermann et al., 2013	2830	3430	18	5580	4630	20	-0.655	-1.318 to 0.00737	25.35
Total (random effects)								-0.533 to 2.198	

I^2 (95% CI) = 94.69% p<0.0001

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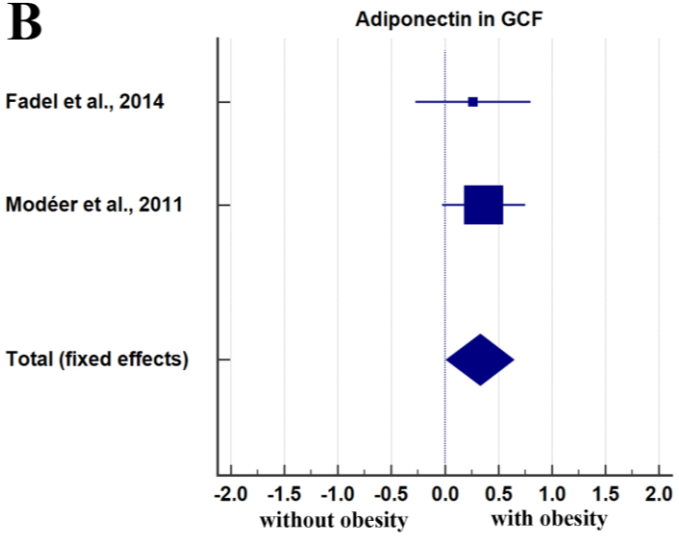

Adiponectin in GCF

Study	with obesity Mean	SD	N	without obesity Mean	SD	N	SMD	95% CI	Weight (%) Fixed
Fadel et al., 2014	1368.9	778.9	27	1155	809.3	28	0.264	-0.272 to 0.799	35.07
Modéer et al., 2011	2540	2815	52	1481	2972	52	0.364	-0.0254 to 0.753	64.93
Total (fixed effects)								0.0163 to 0.641	

I^2 (95% CI) = 0.00% p=0.7620

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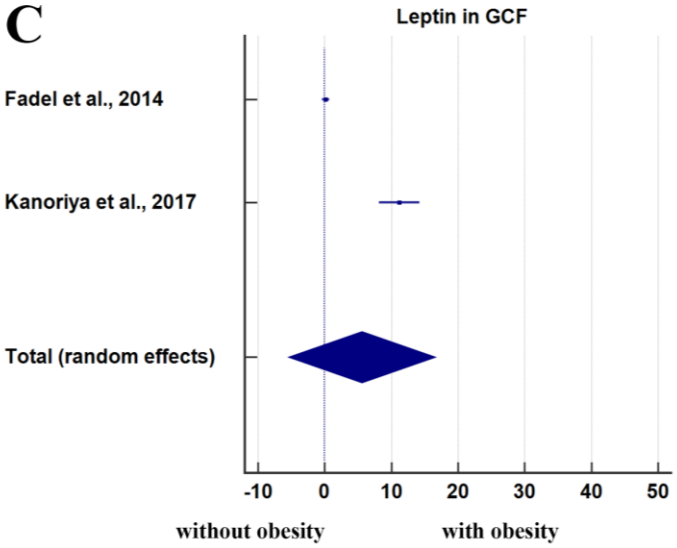

Leptin in GCF

Study	with obesity Mean	SD	N	without obesity Mean	SD	N	SMD	95% CI	Weight (%) Random
Fadel et al., 2014	45.7	23.4	27	42.1	21.1	28	0.159	-0.375 to 0.693	50.88
Kanoriya et al., 2017	330.93	8.31	15	231.33	9.02	15	11.174	8.131 to 14.217	49.12
Total (random effects)								-5.383 to 16.522	

I^2 (95% CI) = 98.12% p< 0.0001

Adipokines in GCF

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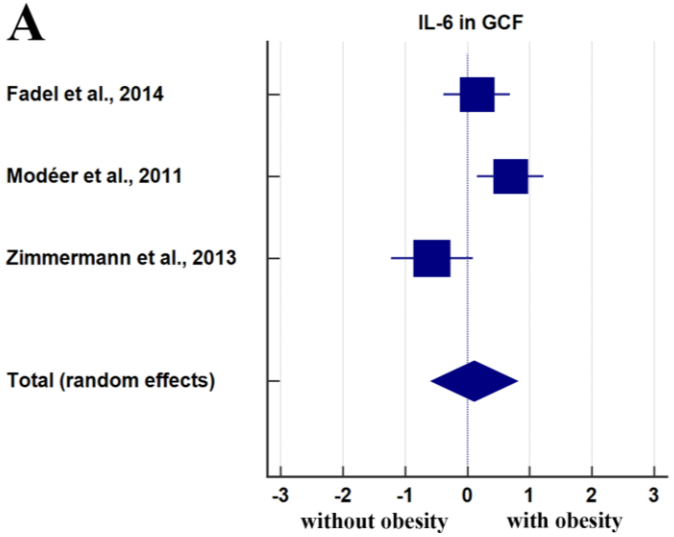

IL-6 in GCF

Study	with obesity Mean	SD	N	without obesity Mean	SD	N	SMD	95% CI	Weight (%) Random
Fadel et al., 2014	1.8	1.7	27	1.6	0.7	28	0.153	-0.381 to 0.687	34.34
Modéer et al., 2011	11600	14900	40	3200	2500	23	0.691	0.160 to 1.222	34.37
Zimmermann et al., 2013	260	500	18	840	1290	20	-0.569	-1.227 to 0.0896	31.29
Total (random effects)								-0.577 to 0.801	

I^2 (95% CI) = 77.84% p= 0.0110

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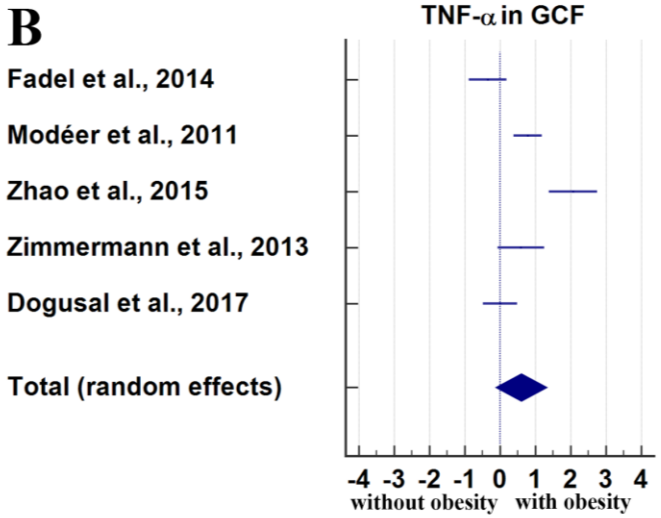

TNF-α in GCF

Study	with obesity Mean	SD	N	without obesity Mean	SD	N	SMD	95% CI	Weight (%) Random
Fadel et al., 2014	2.6	1.5	27	3.1	1.3	28	-0.352	-0.889 to 0.186	20.17
Modéer et al., 2011	1.0	0.2	52	0.8	0.3	52	0.779	0.378 to 1.179	21.15
Zhao et al., 2015	219.91	24.57	30	169.31	23.62	23	2.063	1.383 to 2.743	18.95
Zimmermann et al., 2013	590	790	18	200	500	20	0.585	-0.0747 to 1.244	19.20
Dogusal et al., 2017	125040	92270	32	125170	72870	33	-0.00155	-0.491 to 0.488	20.53
Total (random effects)								-0.125 to 1.318	

I^2 (95% CI) = 89.34% p<0.0001

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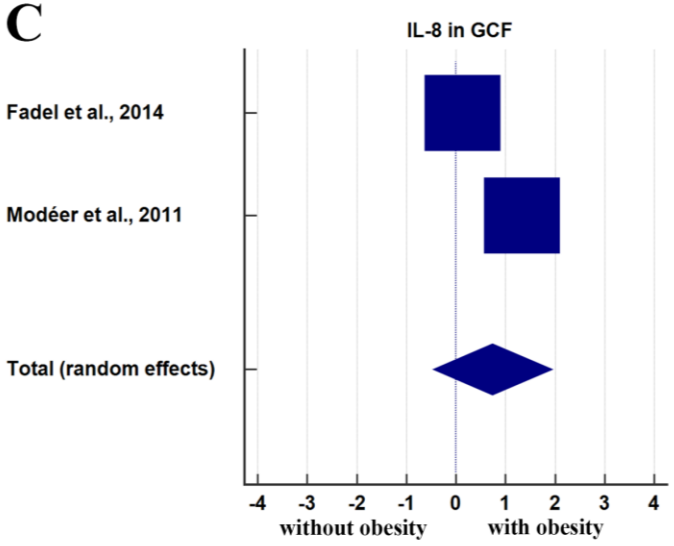

IL-8 in GCF

Study	with obesity Mean	SD	N	without obesity Mean	SD	N	SMD	95% CI	Weight (%) Random
Fadel et al., 2014	91.4	68.7	27	84.5	33.9	28	0.126	-0.408 to 0.660	49.16
Modéer et al., 2011	173	91	52	77	44	52	1.333	0.906 to 1.761	50.84
Total (random effects)								-0.452 to 1.932	

I^2 (95% CI) = 91.95% p= 0.0004

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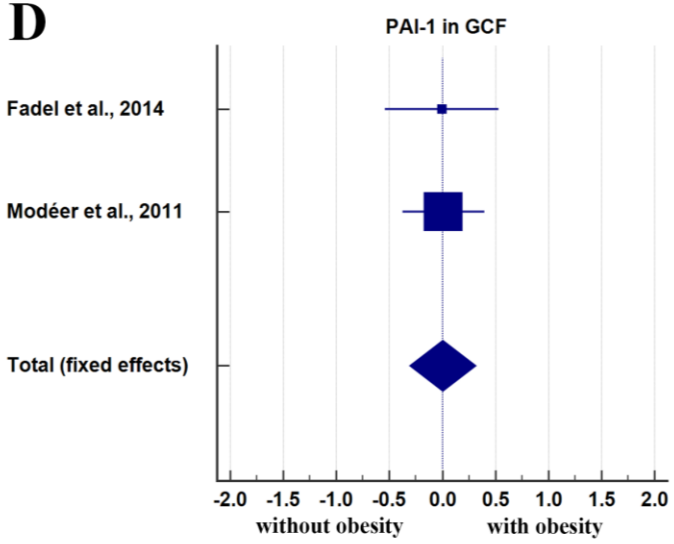

PAI-1 in GCF

Study	with obesity Mean	SD	N	without obesity Mean	SD	N	SMD	95% CI	Weight (%) Fixed
Fadel et al., 2014	160.8	134.4	27	161.4	84.4	28	-0.00529	-0.539 to 0.528	34.90
Modéer et al., 2011	102	68	52	101	113	52	0.0106	-0.375 to 0.397	65.10
Total (fixed effects)								-0.305 to 0.315	

I^2 (95% CI) = 0.00% p=0.9614

Supplementary File 1 Search strategies for Web of Scence, Scopus and Medline Ovid

Database	Search Strategie
Web of Science	((Adipokines OR Adipokine OR Adipocytokines OR Biomarkers OR Biomarker OR Biologic Markers OR Biological Markers OR Adiponectin OR Adipsin OR Complement Factor D OR Angiopoietin like protein 2 OR Apelin OR Cardiotrophin-1 OR Chemerin OR CTRP1 OR CTRP9 OR CTRP12 OR Adipolin OR Fatty acid-binding protein 4 OR Ghrelin OR Obestatin OR Hepcidin OR Hepatocyte Growth Factor OR Interferon-gamma OR Interleukin-10 OR Interleukin-6 OR Interleukin-8 OR irisi* OR irsin OR FNDC5 protein OR Leptin OR Lipocalin-2 OR Monocyte Chemotactic Protein-1 OR Nesfatin-1 OR Nephroblastoma Overexpressed protein OR Intelectin-1 OR Oment* OR Plasminogen Activator Inhibitor 1 OR Progranulin OR GRN protein OR Prokineticin OR Resistin OR Secreted Frizzled-related protein 5 OR Taurine OR Tumor necrosis factor-α OR Vaspin OR Serpin OR Visfatin OR Nicotinamide phosphoribosyltransferase) AND (Saliva OR "Gingival crevicular fluid") AND (obesity OR overweight OR adiposity OR obese))
Scopus	((Adipokines OR Adipokine OR Adipocytokines OR Biomarkers OR Biomarker) AND (Saliva OR "Gingival crevicular fluid") AND (obesity OR overweight OR adiposity OR obese))
Medline via Ovid	((Adipokines OR Adipokine OR Adipocytokines OR Biomarkers OR Biomarker OR Biologic Markers OR Biological Markers) AND (Saliva OR Gingival crevicular fluid OR Salivary) AND (obesity OR overweight OR adiposity OR obese))

Supplementary File 2 Quality assessment of studies according to The Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross Sectional Studies

Author	Critical Appraisal Criterias							
	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?
KHOSRAVI *et al*., 2009	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
LI *et a*l., 2011	Yes	No	No	Yes	No	No	Yes	Yes
NIGRO *et al*., 2015	Unclear	No	No	Yes	No	Yes	Yes	Yes
LEHMANN-KALATA *et al*., 2018	Yes	No	No	Yes	Yes	No	Yes	Yes
ATTLEE *et al*., 2019	No	Yes	No	Yes	No	No	Yes	Yes

NA, not applicable

Supplementary File 3 Quality assessment of studies according to an adaptation from the University of Adelaide (JBI) appraisal checklist for analytical cross sectional studies

Author	Critical Appraisal Criterias					
	Were the criteria for inclusion in the sample clearly defined?	Were the study subjects and the setting described in detail?	Was the exposure measured in a valid and reliable way?	Were objective, standard criteria used for measurement of the condition?	Were the outcomes measured in a valid and reliable way?	Was appropriate statistical analysis used?
ACURIO *et al.*, 2014	Yes	No	No	Yes	Yes	Yes
AYDIN *et al*., 2013	Yes	No	No	Unclear	Yes	Yes
BALLI *et al*., 2016 a	Yes	Yes	Unclear	Yes	Yes	Yes
BALLI *et al*., 2016 b	Yes	Yes	Unclear	Yes	Yes	Yes
BENEDIX et al., 2011	No	No	No	Unclear	Yes	Yes

FADEL *et al*., 2014	No	Yes	No	Yes	Yes	Yes
GOODSON *et al.*, 2014	No	Yes	No	Yes	Yes	Yes
GRÖSCHL *et al.*, 2001	No	No	No	Yes	Yes	Yes
GRÖSCHL *et al.*, 2005	No	No	No	No	Yes	Yes
JAYACHANDRAN *et al*., 2017	Yes	No	No	Yes	Yes	Yes
JENTSCH *et al*., 2017	Yes	No	No	Yes	Yes	Yes
KÂ *et al.*, 2014	No	Yes	No	Yes	Yes	No

KANORIYA *et al*., 2017	Yes	Yes	No	Yes	Yes	Yes
LUNDIN *et al*., 2004	No	No	No	Yes	Yes	Yes
MAMALI *et al*., 2012	No	No	No	No	Yes	Yes
MODÉER *et al*., 2011	Yes	No	No	Yes	Yes	Yes
PRADEEP *et al*., 2012	Yes	Yes	No	Yes	Yes	Yes
PRADEEP *et al*., 2016a	Yes	Yes	No	Yes	Yes	Yes
PRADEEP *et al*., 2016b	Yes	Yes	No	Yes	Yes	Yes
RODRIGUES *et al*., 2017	No	No	No	Yes	Yes	Yes
SURESH *et al*., 2016	Yes	Yes	No	Yes	Yes	Yes

THANAKUN *et al.*, 2014	Unclear	No	No	Yes	Yes	Yes
ZHAO *et al.*, 2015	Unclear	No	No	Yes	Yes	Yes
ZIMMERMANN *et al.*, 2013	Yes	Yes	Unclear	Yes	Yes	Yes
AL-HAMOUDI *et al.*, 2018	Yes	Yes	No	Yes	Yes	Yes
DOGUSAL et al., 2017	Yes	Yes	No	Yes	Yes	Yes
SALOOM *et al.*, 2017	Yes	Yes	Unclear	Yes	Yes	Yes
ABDALLA; SOON, 2017	No	No	No	Yes	Yes	Yes
AL-RAWI; AL-MARZOOQ, 2017	Yes	Yes	No	Yes	Yes	Yes

NA, not applicable

Supplementary File 4: Data extraction of full text analysis

Author, year (Country) Publication language	Study design	Design of the interest analysis	Sample size, characteristics and losses	Obesity diagnosis	Focus of Study	Adipokines evaluated (method of assessment)	Body fluid evaluated	Statistics (adjusted for confounders)	Results of the association between obesity and changes in adipokines' levels
ACURIO, J. *et al*., 2014 (Chile) English	**Controlled Cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 33 **Sample characteristics** Group 1: with obesity (n= 7) Gender: Male:1/Female:6 Mean age: 45.2 years Group 2: with overweight (n= 8) Gender: Male:4/Female:4 Mean age: 38.0 years Group 3: with normal weight (Control) (n=12) Gender: Male:4/Female:8 Mean age: 31.1 years **Sample losses** n=6 (inappropriate sample collections before or after vocal loading.)	**BMI** Normal weight: BMI <25Kg/m^2 Overweight: 25 Kg/ m^2 ≤ BMI < 30Kg/ m^2 Obese: BMI ≥ 30 Kg/ m^2	Vocal loading and it's influence in Voice alteration (acoustic parameters) and IL-6 levels	IL-6 (ELISA)	Saliva	Kruskal-Wallis nonparametric analysis of variance (ANOVA) followed by the Mann-Whitney U test was performed for comparing the data from normal, overweight, and obese teachers. In addition, BMI and IL-6 values were correlated with the other quantitative variables, including acoustic parameters, by using a Spearman test. (Not reported)	Concentrations of IL-6 in saliva were not correlated with BMI neither before (r = -0.15, p = 0.42) or after (r = -0.008; p= 0.66) vocal loading when all teachers were included. (r: correlation value) Mean (SD) (value in absorbance): With obesity: 0.488 (0.289) Without obesity: 0.426 (0.174)
AYDIN *et al*., 2013 (Turkey) English	**Controlled Cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 41 **Sample characteristics** Group1: Male subjects with obesity enrolled for Turkishbath. (n=7); Mean age: 40.50 years; Mean BMI: 34.84 kg/m^2 (± 4.01). Group2: Male subjects with normal weight enrolled for Turkishbath (n=7); Mean age: 44.14 years; Mean BMI: 26.92 kg/m^2 (±	**BMI** Obese: BMI ≥ 30 kg/m^2	Compare levels of irisin after exercise and showering at a Turkish bath	Irisin (ELISA)	Saliva	A one-way analysis of variance (ANOVA) was used to compare mean values in groups. (Not reported)	Significant correlations were observed between saliva irisin and BMI (r = -0.956, p = 0.003) in the obese subjects.

			6.28). Group3: Male subjects with obesity enrolled for moderate outdoor exercise (n=7); Mean age: 40.50 years; Mean BMI: 35.67 kg/m^2 (± 4.53). Group4: Male subjects with normal weight enrolled for moderate outdoor exercise (n=7); Mean age: 44.14 years; Mean BMI: 26.62 kg/m^2 (± 5.98). Group 5: Non-exercise and non-Turkishbath males subjects with normal weight (n=7); Mean age: 44.14 years; Mean BMI: 23.09 kg/m^2 (± 1.85). Group 6: Non-exercise and non-Turkishbath males subjects with obesity (n=6); Mean age: 40.50 years; Mean BMI: 34.23 kg/m^2 (± 3.52). **Sample losses** Not reported						

BALLI *et al*., 2016 a (Turkey) English	**Controlled Cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 80 **Sample characteristics** Group 1: Health periodontium and with normal weight (n= 20) Gender: Male:11/Female:9 Mean Age: 37.06 years Mean BMI = 22.75kg/m^2 Mean WHR = 0.81cm Group 2: Chronic periodontitis and with normal weight (n= 20) Gender: Male:10/Female:10 Mean Age: 39.67 years Mean BMI = 22.611kg/m^2 Mean WHR= 0.83cm Group 3: Health periodontium and with obesity (n=20) Gender: Male:11/Female:9 Age (range): 38.17 years Mean BMI = 33.99kg/m^2 Mean WHR= 0.94cm Group 4: Chronic periodontitis and with obesity (n=20) Gender: Male:9/Female:11 Mean Age: 40.56 years Mean BMI = 33.8kg/m^2 Mean WHR= 0.95cm **Sample losses** Not reported	**BMI and WHR** **BMI** Normal weight: 20 kg/m^2 ≥ BMI <25 kg/m^2 Obese: 30 kg/m^2 ≤ BMI < 40 kg/m^2 and **WHR** Normal weight: WHR < 0.85 cm/cm (females) or <0.90 cm/cm (males) Obese: WHR ≥0.85 cm/cm (females) or ≥0.90 cm/cm (males) If the BMI was indicative of normal weight and the WHR indicative of obesity, the participant was classified as normal weight	Chronic periodontitis (Clinical parameters)	Chemerin (ELISA) IL-6 (ELISA)	GCF	Kruskal-Wallis nonparametric. Bonferroni-adjusted. Mann–Whitney. U-test. Spearman's Rank. Correlation test (Not reported)	Total chemerin levels were higher in subjects with obesity compared to their normal-weight counterparts (p < 0.008). IL-6 levels were much greater in subjects with obesity in comparison with their control groups (p< 0.008). Spearman´s rank correlation (r): Chemerin to BMI: With normal weight: 0.350 (p>0.05) With obesity: 0.445 (p>0.05) IL-6 to BMI: With normal weight: 0.369 (p>0.05) With obesity: 0.328 (p>0.05)
BALLI *et al*., 2016 b (Turkey) English	**Controlled Cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 76 **Sample characteristics** Group 1: Health periodontium and with normal weight (n= 19) Gender: Male:10/Female:9	**BMI and WHR** **BMI** Normal weight: 20 kg/m^2 ≤ BMI < 25 kg/m^2	Chronic periodontitis (Clinical parameters)	Vaspin (ELISA) Omentin-1 (ELISA) TNF-α (ELISA)	GCF	Kruskal-Wallis nonparametrc and Spearman's rank correlation test. (Not reported)	Combined analysis of all clinical groups revealed that the total quantity of vaspin correlated positively with BMI (p< 0.05). There was statistically significant difference between the levels of vaspin in GCF of people with and without obesity.

			Mean Age: 39 years Mean BMI = 22.98kg/m^2 Group 2: Chronic periodontitis and with normal weight (n= 19) Gender: Male:8/Female:11 Mean Age: 40 years Mean BMI = 24.21kg/m^2 Group 3: Health periodontium and with obesity (n=19) Gender: Male:10/Female:9 Age (range): 40 years Mean BMI = 33.92kg/m^2 Group 4: Chronic periodontitis and with obesity (n=19) Gender: Male:9/Female:10 Mean Age: 42 years Mean BMI = 33.97kg/m^2 **Sample losses** Not reported	Obese: 30 kg/m^2 ≤ BMI < 40 kg/m^2 and **WHR** Normal weight: WHR < 0.85 cm/cm (females) or <0.90 cm/cm (males) Obese: WHR ≥0.85 cm/cm (females) or ≥0.90 cm/cm (males) If the BMI was indicative of normal weight and the WHR indicative of obesity, the participant was classified as normal weight.					The total quantity of omentin-1 correlated negatively with BMI (p< 0.05). Total amount of TNF- α in GCF is higher in individuals with obesity than in those without obesity. Spearman´s rank correlation (r): Vaspin to BMI: With normal weight: 0.254 (p>0.05) With obesity: 0.235 (p>0.05) Omentin-1 to BMI: With normal weight: -0.359 (p>0.05) With obesity: -0.481 (p<0.05) TNF-α to BMI: With normal weight: 0.311 (p>0.05) With obesity: 0.465 (p<0.05)
BENEDIX et al., 2011 (Germany) English	**Case-control**	**Controlled Cross-sectional**	**Sample size** N= 103 **Sample characteristics** Group 1: Individuals with morbidly obesity (n= 41) Gender: Male/Female ratio: 1:1.4 Mean Age: 42.6 years Mean BMI = 53.1kg/m^2 (range: 35.6 to 77.2) Group 2: Health participants (lean) (n= 45) Gender: Male/Female ratio: 1:1.6 Mean Age: 40.2 years Mean BMI = 22.7kg/m^2	**BMI** Normal weight (health participants): BMI < 25 kg/m^2 The BMI for the other 2 groups was not defined	Metastatic carcinoma, morbid obesity	Ghrelin (Radioimmunoassay)	Saliva	ANOVA (Not reported)	Ghrelin (mean concentration): With morbidly obesity: 1.56 ng/mL Healthy controls: 1.57 ng/mL (p=0.357) No significant correlation between salivary ghrelin and BMI could be demonstrated (r=-0.003; p=0.977)

			(range: 18.6 to 24.8) Group 3: Patients with metastatic disease from solid gastrointestinal tumors (n=17) Gender: Male/Female ratio: 1.2:1 Mean age: 65.7 years Mean BMI = 23.16kg/m^2 (range: 18.8 to 34.8) **Sample losses** Not reported						
FADEL *et al*., 2014 (Sweden) English	**Case-control**	**Controlled Cross-sectional**	**Sample size** N= 55 **Sample characteristics** Group 1: Individuals with obesity (n=27) Gender: Male: 15 /Female: 12 Mean Age: 15 years Mean BMI: 37Kg/m^2 Mean WC: 110cm Mean WHR: 0.9 Group 2: Individuals with normal-weight (n=28) Gender: Male: 14 /Female: 14 Mean Age: 16 years Mean BMI: 20Kg/m^2 Mean WC: 71cm Mean WHR: 0.8 **Sample losses** Not reported	**BMI, WC and WHR** **BMI (age and sex specific):** Obese: corresponding to an adult BMI (35 kg/m^2 ≤ BMI < 40 kg/m^2) **WC (age and sex specific):** International Obesity Task Force (IOTF) **WHR (age and sex specific):** International Obesity Task Force (IOTF)	Indicators for Dental Caries (clinical and radiographic parameters) and periodontal health	IL-6 (ELISA) IL-8 (ELISA) TNF-α (ELISA) Leptin (ELISA) Resistin (ELISA) PAI-1 (ELISA) Adiponectin (ELISA) Adipisin (ELISA)	GCF	Two sample t test, Fisher's exact test, Pearson's chi-square and Wilcoxon rank test, Multiple linear regression analysis (Smoking, Age, Gender, Medication)	Mean concentration (SD) IL-6: With normal-weight: 1.6 pg/mL (0.7) With obesity: 1.8 pg/mL (1.7) p=0.508 IL-8 With normal-weight: 84.5 pg/mL (33.9) With obesity: 91.4 pg/mL (68.7) p=0.636 TNF-α With normal-weight: 3.1 pg/mL (1.3) With obesity: 2.6 pg/mL(1.5) p=0.152 Leptin With normal-weight: 42.1 pg/mL (21.2) With obesity: 45.7 pg/mL (23.4) p=0.549 Resistin With normal-weight: 5583.9 pg/mL (4074.4) With obesity: 6512.5 pg/mL (4582.3) p=0.430 PAI-1 With normal-weight: 161.4 pg/mL (84.4) With obesity: 160.8 pg/mL (134.4) p=0.984 Adiponectin

									With normal-weight: 1155 pg/mL (809.3) With obesity: 1368.9 pg/mL (778.9) p=0.325 Adipisin With normal-weight: 194.9 pg/mL (214.2) With obesity: 299.6 pg/mL (204.5) p=0.070
GOODSON *et al*., 2014 (USA) Sample from Kuwaiti and USA English	**Cross-sectional**	**Cross-sectional**	**Sample size** N= 744 **Sample characteristics** Individuals with underweight (n=186) Male (64) Mean Age: 11.76 years Mean BMI: 14.13kg/m^2 Mean WC: 60.48cm Female (122) Mean Age: 11.51 years Mean BMI: 13.86 kg/m^2 Mean WC: 54.90cm Individuals with normal weight (n=186) Male (93) Mean Age: 11.52 years Mean BMI: 17.46 kg/m^2 Mean WC: 58.50cm Female (93) Mean Age: 11.39 years Mean BMI: 17.73 kg/m^2 Mean WC: 61.64cm Individuals with overweight (n=186) Male (93) Mean Age: 11.55 years Mean BMI: 22.12 kg/m^2 Mean WC: 70.19cm Female (93) Mean Age: 11.44 years	**BMI (z-score)** Underweight: BMI < 5^{th} percentile Normal weight: $5^{th} \leq$ BMI < 85^{th} percentile Overweight: $85^{th} \leq$ BMI < 95^{th} percentile Obese: BMI ≥ 95^{th} percentile	Non-invasive approach to study inflammatory parameters and metabolic disease	IL-10 (ELISA multiplex) IL-6 (ELISA multiplex) IL-8 (ELISA multiplex) MCP-1 (ELISA multiplex) TNF-a (ELISA multiplex) Ghrelin (ELISA multiplex) Leptin (ELISA multiplex) Resistin (ELISA multiplex) Adiponectin (ELISA multiplex)	Saliva	Wilcoxon regression method, Kruskal-Wallis (Age, Sex)	Concentration´s median (interquartile range): Leptin: With obesity: Male: 3.39pg/mL (12.44) Female: 4.77 pg/mL (11.75) With normal weight: Male: 1.04 pg/ml (7.65) Female: 0.67 pg/ml (8.59) (p < 0.0001) Adiponectin: With obesity: Male: 6337 pg/ml (3550) Female: 7740 pg/ml (5233) With normal weight: Male: 8919 pg/ml (7590) Female: 11426 pg/ml (10123) (p < 0.0001) Other adipokines: No significant changes when analyzed by body weight categories. Mean concentration (SD) (pg/mL): Adiponectin: With obesity: 4253.65 (4647.18) Wiithout obesity: 6662.65 (11798.13) Ghrelin: With obesity: 5.08 (7.05) Without obesity: 5.29 (8.41)

			Mean BMI: 22.86 kg/m^2 Mean WC: 72.59cm Individuals with obesity (n= 186) Male (93) Mean Age: 11.50 years Mean BMI: 28.79 kg/m^2 Mean WC: 83.49cm Female (93) Mean Age: 11.43 years Mean BMI: 28.80 kg/m^2 Mean WC: 84.69cm **Sample losses** Not reported						IL-6: With obesity: 15.17 (27.56) Without obesity: 15.16 (28.08) Leptin: With obesity: 4.8 (6.01) Without obesity: 2.92 (5.55) Resistin: With obesity: 2206.95 (2643.92) Without obesity: 2485.33 (3989.53)
GRÖSCHL *et al*., 2001 (Germany) English	**Cross-sectional**	**Cross-sectional**	**Sample size** N= 66 **Sample characteristics** Group 1: Healthy adult males (n=23) Age: 28 to 80 years BMI: 20 to 50 kg/m^2 Group 2: Healthy adult females (n=25) Age: 22 to 85 years BMI: 19.5 to 54 kg/m^2 Group 3: Healthy adolescents (n=18) Gender: Male: 13 / Female: 5 Age: 10 to 18 years BMI: 15 to 39.9 kg/m^2 **Sample losses** Not reported	**BMI** Lean: BMI < 20 Kg/m^2 Obese: BMI > 25 Kg/m^2	Identify and characterize the presence of leptin in saliva	Leptin (Radioimmunoassay; Western blott)	Saliva	Spearman; Passing/Bablock regression; ANOVA; Bonferroni (Not reported)	The correlation between salivary leptin and the BMI was r^2=0.52.

GRÖSCHL *et al*., 2005 (Germany) English	**Cross-sectional**	**Cross-sectional**	**Sample size** N= 25 **Sample characteristics** Gender: Male: 11 / Female: 14 Age range: 17 to 51 years BMI: 19.5 to 35 Kg/m^2 **Sample losses** Not reported	**BMI** Healthy individuals: 18 kg/m^2 < BMI < 27 kg/m^2	Potential ghrelin functions	Ghrelin (Western Blot)	Saliva	Linear regression analysis (Not reported)	Salivary ghrelin concentrations were higher in people without obesity than in individuals with obesity (correlation (r^2) = 0.314; p=0.019)
JAYACHANDRAN *et al*., 2017 (India) English	**Controlled Cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 30 **Sample characteristics** Group 1: Individuals with normal weight (n=15) Gender: Female: 15 Age: 14 to 28 years BMI: 18.5 to 25 Kg/m^2 Group 2: Individuals with overweight (n=15) Gender: Female: 15 Age: 14 to 30 years BMI: 25 to 30 Kg/m^2 **Sample losses** Not reported	**BMI** Normal weight: 18.5 ≤ BMI < 25 Kg/m^2 Overweight: 25 ≤ BMI < 30 Kg/m^2	Tooth movement (Clinical parameters)	Leptin (ELISA)	Saliva	Student's t-tests and Shapiro Wilk's test, repeated-measures analysis of variance (It is mentioned that adjustment for multiple comparisons were performed, but the variables are not reported)	Mean concentration (SD): Leptin: T_0 (Before orthodontic force application) With normal weight: 322.9289 ng/100µL (99.83514) With overweight: 748.1269 ng/100µL (303.0905) p<0.01
JENTSCH et al., 2017 (Germany) English	**Controlled cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 60 **Sample characteristics** Group 1: Individuals with normal weight and with chronic periodontitis (n=15) Gender: Male: 2 /Female: 13 Mean Age: 46.7 years Mean BMI = 22.9 kg/m^2 Group 2: Individuals with overweight/obesity and with chronic periodontitis (n=15)	**BMI** Normal weight: BMI < 25 kg/m^2 Overweight: 25 ≤ BMI < 30 kg/m^2 Obese: BMI ≥30 kg/m^2	Chronic Periodontitis (Clinical parameters)	Ghrelin (ELISA) Chemerin (ELISA)	Saliva GCF	Kruskal-Wallis test and Mann-Whitney *U*-test (Not reported)	GCF: Ghrelin: The amount of total ghrelin in GCF differed significantly between the groups. Group 1: median: 140 pg per site Group 2: median: 118 pg per site Group 4: median: 145 pg per site p= 0.038 Mean concentration (SD): With obesity: 306.9748 (238.95228) Without obesity: 175.3737 (148.4829)

			Gender: Male: 8 /Female: 7 Age: 50.3 years Mean BMI = 29.9 kg/m^2 Group 3: Individuals with normal weight and without chronic periodontitis (n=15) Gender: Male: 3 /Female: 12 Mean Age: 37.2 years Mean BMI = 21.4 kg/m^2 Group 4: Individuals with overweight/obesity and without chronic periodontitis (n=15) Gender: Male: 9 /Female: 6 Age: 38.9 years Mean BMI = 29.3 kg/m^2 **Sample losses** Not reported						Chemerin: There was no statistically significant difference related to the body weight for chemerin levels in GCF. Group 1: median: 45.8 pg per site Group 2: median: 37.5 pg per site Group 3: median: 33.4 pg per site p<0.05 Mean concentration (SD): With obesity: 38.1257 (34.16061) Without obesity: 26.4485 (21.55879) SALIVA: Ghrelin: Ghrelin was highest in the group 1 than in group 3 and 4. p=0.022 Mean concentration (SD): With obesity: 124.3078 (100.44429) Without obesity: 174.3210 (153.21941) Chemerin: No significant differences between any groups. Mean concentration (SD): With obesity: 461.3149 (397.57209) Without obesity: 285.0730 (336.30802)

KÂ *et al.*, 2014 (Canada) English	**Cross-sectional**	**Cross-sectional**	**Sample size** N= 120 **Sample characteristics** Gender: Male: 67 /Female: 53 Mean Age: 9.6 years Mean BMI: • With normal weight (n=79): percentile = 53.94 • With overweight/obesity (n=41): percentile = 94.87 **Sample losses** Not reported	**BMI (Sex and age-specific)** Normal weight: BMI < 85th percentile Overweight: 85th ≤ BMI < 95th percentile Obese: BMI ≥ 95th percentile	Circulating Undercarboxylated osteocalcin	TNF-α (ELISA)	GCF	Linear regression analyses (age, gender, family income, sexual maturity stage, daily physical activity)	There was no statistically significant association between obesity and GCF TNF-a level in the sample (p=0.944).
KANORIYA *et al*., 2017 (India) English	**Controlled Cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 70 **Sample characteristics** Group 1: Individuals without obesity and without chronic periodontitis (n=15) Gender: Male: 8 /Female: 7 Mean Age: 33.1 years Mean BMI = 20.44 kg/m^2 Group 2: Individuals with obesity and without chronic periodontitis (n=15) Gender: Male: 8 /Female: 7 Mean Age: 35.33 years Mean BMI = 28.18 kg/m^2 Group 3: Individuals without obesity and with chronic periodontitis (n=20) Gender: Male: 10 /Female: 10 Mean Age: 35.1 years Mean BMI = 20.45 kg/m^2 Group 4: Individuals with obesity and with chronic	**BMI and WC** **BMI** Non-obese: 18.5 ≤ BMI ≤ 22.9 kg/m^2 Obese: BMI ≥ 25 kg/m^2 and with **WC** Obese: WC ≥90 cm (men) and WC ≥80 cm (women)	Chronic Periodontitis (clinical and radiographic parameters)	Leptin (ELISA)	GCF	ANOVA; Scheffe's test, Pearson's correlation coefficient (Not reported)	Mean Leptin concentration (SD): Individuals without obesity and without chronic periodontitis: 231.33 pg/mL (9.02) Individuals with obesity and without chronic periodontitis: 330.93 pg/mL (8.31) Comparison between Individuals without obesity and without chronic periodontitis, and individuals with obesity and without chronic periodontitis: Mean difference: 98.648 (p <0.001) Significant correlation was found between GCF leptin concentration with BMI in Groups I and II. (p<0.001)

			periodontitis (n=20) Gender: Male: 9 /Female: 11 Mean Age: 34.75 years Mean BMI = 29.09 kg/m^2 **Sample losses** Not reported						
KHOSRAVI *et al*., 2009 (Canada) English	**Cross-sectional**	**Cross-sectional**	**Sample size** N= 178 **Sample characteristics** Group 1: Boys (n=102) Mean Age: 9.6 years BMI: With normal weight: n= 61 / With overweight: n=21 / With obesity: n=20 Group 2: Girls (n=76) Mean Age: 9.5 years BMI: With normal weight: n= 46 / With overweight: n=10 / With obesity: n=20 **Sample losses** Not reported	**BMI (age- and sex-specific percentiles)** Normal weight: BMI < 85th percentile Overweight: 85th ≤ BMI < 95th percentile Obese: BMI ≥ 95th percentile	Adiposity and TNF-a	TNF-α (ELISA)	GCF	Kruskal–Wallis; Multiple Linear Regression (age in months and a SEP indicator (Family income))	Mean concentration of TNF-a (SD): Boys: 38 pg/µL (72) Girls: 32 pg/µL (55) Bivariate correlation analysis between GCF-TNF-a levels and BMI (Median (IQR): Boys With normal weight: 22 (62) With overweight: 48 (74) With obesity: 67 (100) p=0.016 Girls With normal weight: 30 (50) With overweight: 34 (69) With obesity: 32 (74) p=0.986 Tests for the variation of GCF-TNF-a levels in relation to variation in BMI: After controlling for all covariates, BMI remained positively associated with GCF-TNF-a level. Boys with obesity were associated with 37% increase of TNF- a level in GCF. Multiple linear regression (R^2) analysis of TNF-a and BMI (β= regression coefficient (CI)): With normal weight: Reference With overweight: β= 26.6 (-0.3 - 53.6) (p=0.053) With obesity: β= 37.1 (9.6 - 64.5) (p=0.009) R^2=0.085

									Girls With normal weight: Reference With overweight: β=-0.4 (-36.7 – 35.9) (p=0.981) With obesity: 1.5 (-25.7 – 28.7) (p=0.912) R^2=0.001
LI *et al*., 2011 (China) English	**Controlled Cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 194 **Sample characteristics** Group 1: Lean participants (n=79) Gender: Male: 29 /Female: 50 Mean Age: 12.51 years Mean BMI = 16.94 kg/m^2 Group 2: Individuals with normal weight (n=33) Gender: Male: 14 /Female: 19 Mean Age: 13.06 years Mean BMI = 21.17 kg/m^2 Group 3: Individuals with overweight (n=37) Gender: Male: 23 /Female: 14 Mean Age: 13.49 years Mean BMI = 24.62 kg/m^2 Group 4: Individuals with obesity (n=45) Gender: Male: 8 /Female: 7 Mean Age: 13.36 years Mean BMI = 28.63 kg/m^2 **Sample losses** Not reported	**BMI** (age- and sex-specific according to WHO criteria)	Ghrelin and its relation with weight	Ghrelin (ELISA)	Saliva	Oneway ANOVA; Student–Newman–Keuls; LSD post hoc; Dunnett's T3; Bivariate correlation analysis. (Not reported)	The saliva ghrelin level was lower for lean subjects than for the other 3 groups ($p < 0.05$, $p< 0.05$, and $p < 0.01$, respectively). Saliva ghrelin levels was significantly correlated with BMI ($r = 0.374$ / $p < 0.01$) Mean concentration pg/mL (SD): Lean: 58.34 (144.87) With normal weight: 325.01 (458.85) With overweight: 281.12 (396.63) With obesity: 381.80 (421.92)

LUNDIN *et al*., 2004 (Sweden) English	**Cross-sectional**	**Cross-sectional**	**Sample size** N= 33 **Sample characteristics** Gender: Male: 11 /Female: 22 Mean Age: 17.8 years Mean BMI: 38.6 Kg/m^2 12 subjects presented BMI $\geq$ 40 **Sample losses** There was a sample loss (1 female), but the paper does not explain the reason	**BMI** (Cole et al., BMJ, 2000, 320; 1240-3)	Association between BMI and adipokines. Periodontal status was also evaluated (Clinical and radiographic parameters)	TNF-α (ELISA) IL-8 (ELISA)	GCF	Pearson correlation; Student's t (Not reported)	Correlation between BMI and TNF-α or IL-8 (r = correlation coefficients): BMI x TNF-a (pg/mL): r= 0.02 (p>0.05) BMI x IL-8 (pg/mL): r=0.15 (p>0.05) When the subjects were divided in BMI≥40 or BMI<40: Mean concentration of TNF-a and IL-8 (SD): BMI < 40: TNF-a: 3.6 (2.7) IL-8 (pg/mL): 131 (107) BMI ≥ 40: TNF-a: 2.4 (2.4) IL-8 (pg/mL): 151 (88) There was a positive and significant correlation between BMI≥40 and TNF-α. (r=0.74; p<0.01); but not with BMI < 40 and TNF-a - (r= 0.18 / p>0.05). No significant correlation was found between the level of IL-8 and BMI.
MAMALI *et al*., 2012 (Greece) English	**Cross-sectional**	**Cross-sectional**	**Sample size** N= 50 **Sample characteristics** Gender: Male: 17 /Female: 33 Mean Age: 33.96 years Mean BMI: 22.39Kg/m^2 Mean Body fat percentage: 22.45 **Sample losses** Not reported	**BMI** (Not reported)	New method for measuring salivary adipokines and compare to serum levels	Resistin (ELISA) Visfatin (ELISA) Adiponectin (ELISA)	Saliva	Kolmogorov–Smirnov; Pearson product-moment correlation; Multiple linear regression. (Not reported)	Resistin: There were no significant correlations between resistin levels in saliva and BMI. Visfatin: There was no statistically significant correlation between salivary visfatin levels and BMI Adiponectin: There was no statistically significant correlation between salivary adiponectin levels and BMI.

MODÉER *et al*., 2011 (Sweden) English	**Controlled Cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 104 **Sample characteristics** Group 1: Individuals with obesity (n=52) Gender: Male: 29 /Female: 23 Mean Age: 14.5 years Mean BMI = 37.0 kg/m^2 Group 2: Individuals with normal weight (n=52) Gender: Male: 29 /Female: 23 Mean Age: 14.5 years Mean BMI = 19.7 kg/m^2 **Sample losses** Not reported	**BMI (adjusted for age and sex (BMI-SDS)** Obese: BMI ≥ 30 kg/m^2 Normal weight: BMI < 25 kg/m^2	Obesity and periodontal risk indicators	Adiponectin (ELISA) IL-6 (ELISA) IL-8 (ELISA) PAI-1 (ELISA) TNF-α (ELISA)	GCF	ANOVA; Chi-square; Logistic regression; Wald test (It was reported confounders for other analysis – not related to the association between obesity and adipokines)	Mean concentration (SD): Adiponectin: With obesity: 2540 pg/mL (2815) With normal weight: 1481 pg/mL (2972) p=0.072 IL-6: With obesity (n=40): 11.6 ng/mL (14.9) With normal weight (n=23): 3.2 ng/mL (2.5) IL-8: With obesity: 173 pg/mL With normal weight: 77 pg/mL p=0.002 PAI-1: With obesity: 102 pg/mL With normal weight: 101 pg/mL p=0.966 TNF- α: With obesity: 1.0 pg/mL With normal weight: 0.8 pg/mL p=0.060
NIGRO *et al*., 2015 (Italy) English	**Case-Control**	**Controlled Cross-sectional**	**Sample size** N= 54 **Sample characteristics** Group 1: Individuals with obesity (n=27) Gender: Male: 27 Age: 21-29 years: n=9 / 30-36 years: n=4 42-47 years: n=7 52-58 years: n=5 64-68 years: n=2 Obese class I: 7 Obese class II: 4 Obese class III: 16 Group 2: Individuals with normal weight (n=27) Gender: Male: 27 Age: 20-27 years: n=10	**BMI** Normal weight: 18.5 ≤ BMI ≤ 24.9 Kg/m^2 Obese class I: 30.0 ≤ BMI ≤ 34.9 Kg/m^2 Obese class II: 35.0 ≤ BMI ≤ 39.9 Kg/m^2 Obese class III: BMI≥ 40.0 Kg/m^2	Salivary adiponectin profile in obese patients	Adiponectin (ELISA)	Saliva	Student's t; Mann–Whitney U, ANOVA (Not reported)	Mean concentration of Adiponectin (SD): With obesity: 6.1 ng/mL (± 1.3) Median: 5.59 ng/mL Without obesity: 4.8 ng/mL (± 2.6) Median: 4.9 ng/mL Two-tailed unpaired Student's t-test p = 0.16 Mann–Whitney U-test p = 0.17

			30-39 years: n=7 40-48 years: n=6 51-52 years: n=3 60 years: n=1 **Sample losses** Not reported						
PRADEEP *et al*., 2012 (India) English	**Controlled Cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 40 **Sample characteristics** Group 1: Individuals without obesity and without chronic periodontitis (n=10) Gender: Male: 6 /Female: 4 Mean Age: 32.42 years Mean BMI = 20.84 kg/m^2 Group 2: Individuals with obesity and without chronic periodontitis (n=10) Gender: Male: 5 /Female: 5 Mean Age: 35.2 years Mean BMI = 28.16 kg/m^2 Group 3: Individuals without obesity and with chronic periodontitis (n=10) Gender: Male: 4 /Female: 6 Mean Age: 35.22 years Mean BMI = 20.63 kg/m^2 Group 4: Individuals with obesity and with chronic periodontitis (n=10) Gender: Male: 5 /Female: 5 Mean Age: 36.87 years Mean BMI = 31.95 kg/m^2 **Sample losses** Not reported	**BMI and WC** **BMI** Non-obese: 18.5 < BMI < 22.9 kg/m^2 Obese: BMI ≥ 25 kg/m^2 **WC** Non-obese: WC < 90 cm (men) and < 80 cm (women) Obese: WC ≥ 90 cm (men) and ≥80 cm (women)	Chronic Periodontitis (Clinical and radiographic parameters)	Progranulin (ELISA)	GCF	ANOVA; Pearson's correlation coefficient (Not reported)	Mean GCF progranulin concentration: Group 1: 71.8 ng/mL (2.54) Group 2: 197.8 ng/mL (3.22) Correlation of progranulin to BMI: Group 1: 0.4851 (p>0.05) Group 2: 0.0074 (p<0.05) A significant difference in the GCF levels of progranulin were found between the four groups.

PRADEEP *et al*., 2016a (India) English	**Controlled Cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 40 **Sample characteristics** Group 1: Individuals without obesity and without chronic periodontitis (n=10) Gender: Male: 5 /Female: 5 Mean Age: 31.4 years Mean BMI = 19.9 kg/m^2 Group 2: Individuals with obesity and without chronic periodontitis (n=10) Gender: Male: 5 /Female: 5 Mean Age: 31 years Mean BMI = 27.56 kg/m^2 Group 3: Individuals without obesity and with chronic periodontitis (n=10) Gender: Male: 5 /Female: 5 Mean Age: 30.9 years Mean BMI = 20.24 kg/m^2 Group 4: Individuals with obesity and with chronic periodontitis (n=10) Gender: Male: 5 /Female: 5 Mean Age: 32.5 years Mean BMI = 27.46 kg/m^2 **Sample losses** Not reported	**BMI and WC** **BMI** Non-obese: 18.5 < BMI < 22.9 kg/m^2 Obese: BMI ≥ 25 kg/m^2 **WC** Non-obese: WC < 90 cm (men) and WC < 80 cm (women) Obese: WC ≥90 cm (men) and WC ≥80 cm (women)	Chronic Periodontitis (Clinical and radiographic parameters)	Lipocalin-2 (ELISA)	GCF	ANOVA; Scheff's test; Pearson's correlation coefficient (Not reported)	Mean GCF Lipocalin 2 concentration: Group 1: 57.65 µg/L (6.4) Group 2: 80.9 µg/L (6.93) Pairwise comparison using the Scheff's test for GCF lipocalin-2 levels and BMI (Mean difference): Group 1 and group 2: -23.25 (p<0.001) The correlation between levels of lipocalin-2 in GCF and BMI was statistically significant in all four groups (p< 0.001).
PRADEEP *et al*., 2016b (India) English	**Controlled Cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 40 **Sample characteristics** Group 1: Individuals without obesity and with clinically-healthy periodontium (n=10) Gender: Male: 5 /Female: 5 Mean Age: 34.4 years Mean BMI = 21.24 kg/m^2 Group 2: Individuals with	**BMI and WC (The Asia Pacific Perspective)** **BMI** Non-obese: 18.5 ≤ BMI ≤ 22.9 kg/m^2 Obese: BMI	Chronic Periodontitis (Clinical and radiographic parameters)	Vaspin (ELISA)	GCF	ANOVA; Pearson's correlation coefficient (Not reported)	Mean GCF vaspin concentration: Group 1: 0.65ng/mL (0.02) Group 2: 0.95 ng/mL (0.26) Correlation between GCF and BMI: Group 1: 0.001 (p < 0.001) Group 2: 0.001 (p < 0.001)

			obesity and with clinically-healthy periodontium (n=10) Gender: Male: 5 /Female: 5 Mean Age: 35.6 years Mean BMI = 28.92 kg/m^2 Group 3: Individuals without obesity and with chronic periodontitis (n=10) Gender: Male: 5 /Female: 5 Mean Age: 35.1 years Mean BMI = 20.74 kg/m^2 Group 4: Individuals with obesity and with chronic periodontitis (n=10) Gender: Male: 5 /Female: 5 Mean Age: 33.8 years Mean BMI = 33.77 kg/m^2 **Sample losses** Not reported	≥25 kg/m^2 **WC** Non-obese: WC <90 cm (men) and <80 cm (women) Obese: WC ≥90 cm (men) and ≥80 cm (women)					
RODRIGUES *et al*., 2017 (Portugal) English	**Controlled Cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 121 **Sample characteristics** Gender: Male: 60 /Female: 61 Age: 9 and 10 years With normal weight: Girls (n=30) / Boys (n=34) With preobesity: Girls (n=16) / Boys (n=15) With obesity: Girls (n=12) / Boys (n=13) **Sample losses** Not reported	**BMI** Overweight (preobese + obese): BMI ≥ 85th percentile (+ 1 SD). Coincident to BMI ≥ 25 kg/m^2 of adult age.	Salivary leptin levels and the perception of basic tastes (sweet and bitter) and its association with BMI	Leptin (ELISA)	Saliva	Kolmogorov-Smirnoff; Levene. (Not reported)	Salivary leptin concentration (pg/mL) did not differ between children with normal weight, preobesity, and obesity (p=0.099). Correlation between salivary leptin (pg/min) and BMI: r= 0.226 (p=0.018) *with a tendency for higher salivary leptin levels in children with obesity, comparatively to those with normal weight. Mean concentration (SD) (pg/mL): With obesity: 9.8 (4.4) Without obesity: 10.1 (6.4)

SURESH *et al*., 2016 (India) English	**Controlled Cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 90 **Sample characteristics** Gender: Male: 39 /Female: 51 Group 1: Individuals with overweight or obesity and with chronic periodontitis (n=25) Mean Age: 38.56 years Mean BMI: 31.84 kg/m^2 Mean WC: 99.56 cm Group 2: Individuals with overweight or obesity and without chronic periodontitis (n=25) Mean Age: 31.4 years Mean BMI: 31.08 kg/m^2 Mean WC: 102.68 cm Group 3: Individuals without obesity and with chronic periodontitis (n=25) Mean Age: 35.96 years Mean BMI: 22.4 kg/m^2 Mean WC: 77.36 cm Group 4: Individuals without obesity and without chronic periodontitis (n=15) Mean Age: 31.4 years Mean BMI: 22.47 kg/m^2 Mean WC: 79.07 cm **Sample losses** Not reported	**BMI and WC** **BMI** Overweight and obese: BMI > 25 kg/m^2 **WC** Overweight and obese: WC >90cm (men) and >80cm (women)	Chronic periodontitis (Clinical parameters)	Resistin (ELISA)	GCF	One way ANOVA; t-test; Pearson correlation (Not reported)	Mean GCF resistin levels: Group 2: 9.0680 ng/ml (0.77545) Group 4: 5.4107 ng/ml (1.00264) Correlation between GCF resistin levels and BMI: Correlation: 0.341(p=0.001)
THANAKUN *et al.*, 2014 (Thailand) English	**Controlled Cross-sectional**	**Cross-sectional**	**Sample size** N= 128 **Sample characteristics** Group 1: Healthy participants (n=46)	**BMI and WC** **BMI** Not reported **WC**	Metabolic Syndrome (diagnosed when three of the following five factors	Adiponectin (ELISA) Leptin (ELISA)	Saliva	Kolmogorov-Smirnov; Mann-Whitney U test, logistic regression analysis (controlling for the effect of covariates)	Median salivary adiponectin concentration (25^{th} – 75^{th} percentile): Health subjects: 2.92 µg/mL (7.91-6.23) Patients with metabolic syndrome: 2.78 µg/mL (1.05-6.48)

			Gender: Male:13 / Female: 33 Mean Age: 44.5 years Mean BMI: 21.82 kg/m^2 Mean WC: 81 cm (male) / 75 cm (female) Group 2: Metabolic syndrome participants (n=82) Gender: Male: 40 / Female: 42 Mean Age: 48 years Mean BMI: 27.26 kg/m^2 Mean WC: 91 cm (male) / 90.5 cm (female) **Sample losses** Not reported	Elevated WC: WC ≥85 cm (men) and ≥80 cm (women)	were present: (1) elevated WC circumference (2) elevated raised triglyceride level; (3) reduced lowered high density lipoprotein cholesterol; (4) elevated blood pressure (5) elevated fasting plasma glucose)				Median salivary leptin concentration (25th – 75th percentile): Health subjects: 33.80 pg/mL (14.66-102.8) Patients with metabolic syndrome: 34.88 pg/mL (17.07-54.77) The correlation between salivary adiponectin levels and BMI or salivary leptin levels and BMI was not significant. (p>0.05)
ZHAO *et al.*, 2015 (China) English	**Controlled Cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 53 **Sample characteristics** Age: 6 to 14 years Group 1: Individuals with obesity (n=30) Group 2: Individuals without obesity (n=23) **Sample losses** Not reported	**BMI (Specific for age and sex; article's table 1)**	Periodontal status	TNF-α (ELISA)	GCF	Student´s t-test (Not reported)	Mean concentration of TNF-α in GCF (SD): Without obesity: 169.31 pg/mL (23.62) With Obesity: 219.91 pg/mL (24.57) t-value: 2.844 (p=0.006)
ZIMMERMANN *et al.*, 2013 (Brazil) English	**Controlled Cross-sectional**	**Controlled Cross-sectional**	**Sample size** N= 78 **Sample characteristics** Group 1: Individuals with normal weight and without chronic periodontitis (n=20) Gender: Male: 6 /Female: 14 Mean Age: 42.9 years Mean BMI: 23.4 kg/m^2 Mean WHR: 0.8	**BMI and WHR** **BMI** Normal weight: 20 Kg/m^2 ≤ BMI ≤ 24.9 Kg/m^2 Obese: 30 Kg/m^2 ≤ BMI < 40Kg/m^2	Chronic periodontitis (Clinical parameters)	Resistin (ELISA) Adiponectin (ELISA) Leptin (ELISA) TNF-α (ELISA)	GCF	Kolmogorov-Smirnov; ANOVA; Kruskal-Wallis; Mann-Whitney U; t-test; Wilcoxon; Multivariable logistic regression (Not reported)	Concentration of adipokines in GCF of Shallow sites: Resistin (ng/µL): Group 1: 5.58 (4.63) Group 3: 2.83 (3.43) p>0.05 Adiponectin (ng/µL): Group 1: 0.00 (0.0) Group 3: 3.4 (17.0) p-value not reported

			Group 2: Individuals with normal weight and with chronic periodontitis (n=20) Gender: Male: 5 /Female: 15 Mean Age: 47.8 years Mean BMI: 23.0 kg/m^2 Mean WHR: 0.8 Group 3: Individuals with obesity and without chronic periodontitis (n=18) Gender: Male: 4 /Female: 14 Mean Age: 43.2 years Mean BMI: 33.9 kg/m^2 Mean WHR: 1.0 Group 4: Individuals with obesity and with chronic periodontitis (n=20) Gender: Male: 6 /Female: 14 Mean Age: 51.5 years Mean BMI: 33.2 kg/m^2 Mean WHR: 1.0 **Sample losses** Not reported	**WHR** Normal weight: WHR < 0.85 (women) and < 0.90 (men) Obese: WHR ≥ 0.85 (women) and ≥ 0.90 (men)		IL-6 (ELISA)			Leptin (pg/µL): Group 1: 0.00 (0.0) Group 3: 4.11 (19.04) p<0.05 TNF-α (pg/µL): Group 1: 0.20 (0.50) Group 3: 0.59 (0.79) p<0.05 IL-6 (pg/µL): Group 1: 0.84 (1.29) Group 3: 0.26 (0.50) p-value not reported
AL-HAMOUDI *et al*., 2018 (Saudi Arabia) English	**Clinical Trial**	**Cross-sectional**	**Sample size** N= 137 **Sample characteristics** Group 1: Individuals with and without obesity and with chronic periodontitis (n=70) (Male: 70 / Female: 0) Obese (n= 35) Mean Age: 39.5 years Mean BMI: 35.2 kg/m^2 Non-obese (n=35) Mean Age: 36.3 years Mean BMI: 21.6 kg/m^2 Group 2: Individuals with and without obesity and without chronic periodontitis	**BMI** (Not reported)	Chronic periodontitis (Clinical and radiographic parameters)	Resistin (ELISA) IL-6 (ELISA)	Saliva	Kolmogorov-Smirnov; Shapiro-Wilk; Q-Q Plots; One-way analysis of variance; Bonferroni post-hoc.	Mean concentration of resistin in saliva (SD): Individuals without chronic periodontitis at baseline (ng/mL): Obese: 2.2 (0.2) Non-obese: 2.1 (0.3) Individuals without chronic periodontitis at 6 months' follow up (ng/mL): Obese: 0.8 (0.2) Non-obese: 1.1 (0.3) Mean concentration of IL-6 in saliva (SD): Individuals without chronic periodontitis at baseline (pg/mL): Obese: 2.1 (0.4) Non-obese: 2.3 (0.6) Individuals without chronic periodontitis at 6

			(n=67) (Male: 65 / Female: 2) Obese (n= 34) Mean Age: 37.5 years Mean BMI: 33.6 kg/m^2 Non-obese (n=33) Mean Age: 36.2 years Mean BMI: 22.4 kg/m^2 **Sample losses** Not reported						months' follow up (pg/mL): Obese: 1.3 (0.4) Non-obese: 1.5 (0.2) p>0.05
DOGUSAL et al., 2017 (Turkey) English	**Cross-sectional**	**Cross-sectional**	**Sample size** N= 130 **Sample characteristics** Group 1: Individuals with obesity and gingivitis (n=33) Mean Age: 10.6 years Mean BMI: 26.14 kg/m^2 Group 2: Individuals with obesity and healthy periodontium (n=32) Mean Age: 10.6 years Mean BMI: 26.51 kg/m^2 Group 3: Individuals with normal weight and gingivitis (n=32) Mean Age: 10.98 years Mean BMI: 17.78 kg/m^2 Group 4: Individuals with normal weight and healthy periodontium (n=33) Mean Age: 10.98 years Mean BMI: 17.79 kg/m^2 **Sample losses** Not reported	**BMI** (age- and sex-specific according to WHO criteria) Normal weight: 5^{th} < BMI < 85^{th} With obesity: BMI ≥ 95^{th}	Periodontal Health (clinical parameters)	Resistin (ELISA) TNF-α (ELISA)	Saliva GCF	Shapiro Wilk; Brunner and Langer; Chi-square; Spearman's Rank Correlation Analysis	Childhood obesity is not associated with GCF and salivary resistin and TNF-α levels. Levels of adipokines in the different groups are exposed by graphs, with p-value >0.05. Correlation between BMI and salivary resistin: 0.007 (p>0.05) Correlation between BMI and salivary TNF-α: 0.071 (p>0.05) Correlation between BMI and GCF resistin: -0.045 (p>0.05) Correlation between BMI and GCF TNF-α: 0.109 (p>0.05) Mean concentration of resistin in GCF (SD) (pg/µL): With normal weight and health periodontium: 10137.35 (4727.28) With obesity and health periodontium: 10132.01 (7126.37) Mean concentration of resistin in saliva (SD) (pg/mL): With normal weight and health periodontium: 8852.70 (5423.33) With obesity and health periodontium: 9726.25 (5088.05) Mean concentration of TNF-α in GCF (SD)

									(pg/µL): With normal weight and health periodontium: 125.17 (72.87) With obesity and health periodontium: 125.04 (92.27) Mean concentration of TNF-α in saliva (SD) (pg/mL): With normal weight and health periodontium: 177.41 (132.71) With obesity and health periodontium: 204.99 (151.60)
LEHMANN-KALATA *et al*., 2018 (Poland) English	**Cross-sectional**	**Cross-sectional**	**Sample size** N= 110 **Sample characteristics** Group 1: Individuals without obesity (n=25) Gender: Male: 0 /Female: 25 Mean Age: 31.1 years Mean BMI: 22.1 kg/m^2 Mean WHR: 0.76 Group 2: Individuals with obesity (n=19) Gender: Male: 0 /Female: 19 Mean Age: 32.7 years Mean BMI: 38.7 kg/m^2 Mean WHR: 0.90 **Sample losses** 31 individuals with obesity (comorbidities/medication, incomplete clinical data and men as underrepresented) 35 individuals without obesity (not fulfilling matching criteria)	**BMI** Individuals with obesity: BMI ≥ 30 Kg/m^2 Individuals without obesity: BMI < 30 Kg/m^2	Relation between adipokines levels in saliva and obesity	TNF-α (ELISA) MCP-1 (ELISA) PAI-1 (ELISA) Leptin (ELISA) Adiponectin (ELISA) Serpin (ELISA) Resistin (ELISA)	Saliva	Chi-squared; Fisher-Freeman-Halton; Lilliefors; t-Student; Mann-Whitney; Spearman´s rank correlation	Mean concentration of TNF-α in saliva (SD) (pg/mL): With obesity: 3.23 (5.00) Without obesity: 1.19 (1.14) Mean concentration of MCP-1 in saliva (SD) (pg/mL): With obesity: 112 (118) Without obesity: 45 (50) Mean concentration of PAI-1 in saliva (SD) (pg/mL): With obesity: 453 (434) Without obesity: 214 (358) Mean concentration of leptin in saliva (SD) (pg/mL): With obesity: 45 (28) Without obesity: 43 (14) Mean concentration of adiponectin in saliva (SD) (ng/mL): With obesity: 6.65 (5.35) Without obesity: 7.04 (8.77) Mean concentration of serpin in saliva (SD) (pg/mL):

									With obesity: 262 (325) Without obesity: 51 (82) Median concentration of resistin in saliva (interquartile ranges) (ng/mL): With obesity: 9.33 (2.92-17.59) Without obesity: 1.87 (1.00-6.53) p=0.013
SALOOM *et al*., 2017 (United Kingdom) English	**Cohort**	**Cross-sectional**	**Sample size** N= 55 **Sample characteristics** Group 1: Individuals with normal weight (n=28) Gender: Male: 15 /Female: 13 Mean Age: 15.1 years Mean BMI: 19.4 kg/m^2 Group 2: Individuals with obesity (n=27) Gender: Male: 12 /Female: 15 Mean Age: 15.1 years Mean BMI: 30.2 kg/m^2 **Sample losses** None	**BMI** Individuals with normal weight: BMI-centile 91-98 Individuals with obesity: BMI-centile > 98	Orthodontic tooth movement (clinical parameters)	Adiponectin (ELISA multiplex) Leptin (ELISA multiplex) Resistin (ELISA multiplex)	GCF	t-Student; Chi-square; Mann-Whitney; Regression models	Mean concentration of adiponectin in GCF (SD) (pg/mL): With normal weight: 6.55 (0.42) With obesity: 6.66 (0.23) p=0.237 Mean concentration of leptin in GCF (SD) (pg/mL): With normal weight: 6.40 (14.65) With obesity: 19.15 (24.45) p=0.031 Mean concentration of resistin in GCF (SD) (pg/mL): With normal weight: 5.30 (0.55) With obesity: 5.92 (0.36) p< 0.001
ABDALLA; SOON, 2017 (Malaysia) English	**Cross-sectional**	**Cross-sectional**	**Sample size** N= 88 **Sample characteristics** Gender: Male: 88 /Female: 0 Mean Age: 20.64 years Mean BMI: 24.92 kg/m^2 Mean WHR: 0.85 Mean hip circumference: 100.24 Mean WC: 85.4 Mean total fat percentage: 20.10 Mean visceral fat level: 8.59	**BMI** Individuals with overweight and obesity: BMI > 24.9 Kg/m^2 Individuals without obesity: BMI < 24.9 Kg/m^2	Anthropometric measures and fat distribution	Adiponectin (ELISA)	Saliva	Regression analysis; chi-square; degree of freedom; probability level; root mean residual; goodness of fit index; normed fit index; incremental fit index; root mean square error of approximation.	Mean concentration of adiponectin in saliva (SD) (ng/mL): With normal weight: 19.6 (8.6) With obesity: 18.1 (8.3) p>0.05

			Mean subcutaneous whole-body-fat: 14.39 Individuals with overweight and obesity: n=41 Individuals without obesity: n=47 **Sample losses** Not reported						
AL-RAWI; AL-MARZOOQ, 2017 (United Arab Emirates) English	**Cross-sectional**	**Controlled cross-sectional**	**Sample size** N= 78 **Sample characteristics** Group 1: Individuals with obesity and diabetes (n=26) Mean Age: 51.1 years Mean BMI: 34.3 kg/m^2 Group 2: Individuals with obesity and without diabetes (n=26) Mean Age: 47.9 years Mean BMI: 34.2 kg/m^2 Group 3: Individuals without obesity and without diabetes (n=26) Mean Age: 47.4 years Mean BMI: 27.1 kg/m^2 **Sample losses** Not reported	**BMI** Individuals with obesity: BMI ≥ 30 Kg/m^2 Individuals without obesity: BMI < 30 Kg/m^2	Resistin levels, periodontopathogenic bacteria, diaetes and obesity	Resistin (ELISA)	Saliva	Mann-Whitney U; Kruskal-Wallis; Spearman's correlation	Mean concentration of resistin in saliva (SD) (ng/mL): With obesity and without diabetes: 14.4 (3.6) Without obesity and without diabetes: 10.8 (6.1) p=0.010
ATTLEE *et al*., 2019 (United Arab Emirates) English	**Cross-sectional**	**Controlled cross-sectional**	**Sample size** N= 90 **Sample characteristics** Gender: Female: 90 Age: 18 to 35 years Group 1: Woman with normal weight (n=30) Median Age: 21 years Median BMI: 21.3 kg/m^2	**BMI** Individuals with normal weight: 18.5 Kg/m^2 ≤ BMI ≤ 24.9 Kg/m^2 Individuals with overweight: 25 Kg/m^2 ≤ BMI < 30 Kg/m^2	Salivary adipokines; diet quality; physical activity; obesity	Adiponectin (ELISA) TNF-α (ELISA) IL-10 (ELISA)	Saliva	Shapiro-Wilk; Kruskal-Wallis; Chi-square test; Spearmen's correlation	Median of concentration of adiponectin in saliva (IQR) (ug/mL): With normal weight: 0.64 (0.67) With overweight: 0.236 (0.53) With obesity: 0.27 (0.73) p=0.03 Median of concentration of TNF-α in saliva (IQR) (pg/mL): With normal weight: 0.47 (0.28)

			Median WC: 76.9 cm Group 2: Woman with overweight (n=30) Median Age: 21 years Median BMI: 26.75 kg/m^2 Median WC: 87.1 cm Group 3: Woman with obesity (n=30) Median Age: 20.5 years Median BMI: 32.5 kg/m^2 Median WC: 98.9 cm **Sample losses** Not reported	Individuals with obesity: BMI ≥ 30 Kg/m^2 **WC** Not reported					With overweight: 0.96 (2.08) With obesity: 1.03 (1.56) p<0.001 Median of concentration of IL-10 in saliva (IQR) (pg/mL): With normal weight: 40.77 (32.13) With overweight: 44.04 (35.5) With obesity: 31.8 (17.56) p=0.32 Correlation of BMI and total adiponectin in saliva: -0.28 p=0.009 Correlation of BMI and TNF-α levels in saliva: 0.37 p=0.002 Correlation of BMI and IL-10 levels in saliva: -0.17 p>0.05

GCF, Gingival Crevicular Fluid; BMI, Body Mass Index; WHR, Ratio of waist-to-hip circumference (cm/cm); WC, waist circumference; IQR, inter-quartile range

6 CONSIDERAÇÕES FINAIS

A obesidade é uma condição cada vez mais presente na sociedade, podendo estar relacionada ao desenvolvimento de diversas doenças com alto índice de mortalidade, como por exemplo as alterações cardiovasculares. A obesidade pode estar relacionada a uma piora na qualidade de vida de um indivíduo, da infância à vida adulta, visto que pode dificultar seu convívio social, devido aos padrões de beleza estabelecidos na sociedade, além de dificultar a realização de atividades corriqueiras.

Muitas vezes a obesidade é uma doença silenciosa, a qual só é percebida quando ocorre o aumento de peso. A identificação de diferentes métodos para caracterização desse quadro pode contribuir para um diagnóstico precoce, evitando possíveis sequelas desencadeadas pela obesidade. A identificação de adipocinas em níveis alterados na saliva e no FGC é um método diagnóstico em potencial, uma vez que pode detectar alterações moleculares relacionadas à obesidade de forma não invasiva, sendo preferível ao sangue, principalmente em estudos epidemiológicos.

O pequeno número amostral dos estudos, a heterogeneidade metodológica, bem como a falta de padronização na mensuração dessas moléculas corroboraram para que as meta-análises não demonstrassem diferenças estatísticas na expressão da maioria das adipocinas, com exceção do TNF-α que apresentou concentrações aumentadas na saliva de indivíduos com obesidade quando comparado aos sem obesidade.

A princípio, houve a intenção de realizar uma análise agrupando os estudos segundo as faixas etárias, afim de caracterizar o comportamento de adipocinas, tanto na saliva como no FGC, em crianças e adolescente e em adultos. Entretanto, a heterogeneidade metodológica dos estudos não permitiu essa avaliação.

A dificuldade no agrupamento de dados ocorreu não apenas pela diversidade metodológica, mas também pela forma de apresentação dos dados. Para realização das meta-análise, poderiam ser agrupados dados referentes à média e ao desvio padrão da concentração das adipocinas em indivíduos com

obesidade e sem obesidade, ou por meio do valor da correlação entre os níveis de adipocinas e o IMC. Nos casos dos artigos que não apresentavam esses dados, foi feito contato com os autores por meio de correspondência eletrônica, entretanto, nem todos os autores responderam ou forneceram os dados necessários.

Sugere-se a realização de estudos com amostras maiores, principalmente, mais bem controlados com relação à condição bucal dos participantes, afim de melhor estabelecer a relação entre os níveis de adipocinas nos fluidos bucais e a obesidade.

Apesar da evidência científica ser fraca, o TNF-α encontra-se aumentado na saliva em quadros de obesidade e existem estudos que sugerem uma alteração nos níveis salivares e no FGC de outras adipocinas em indivíduos acima do peso. Dessa forma, acredita-se que fluidos bucais podem, futuramente, representar um método diagnóstico adicional para identificação precoce de uma alteração sistêmica como a obesidade.

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