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Association between circulating adipocytokine concentrations and microvascular complications in patients with type 2 diabetes mellitus: A systematic review and meta-analysis of controlled cross-sectional studies

Alexander J. Rodríguez [a,1,2], Vania dos Santos Nunes [b,2], Claudio A. Mastronardi [a], Teresa Neeman [c], Gilberto J. Paz-Filho [a,*]

[a] Department of Genome Sciences, The John Curtin School of Medical Research, The Australian National University, Canberra, 131 Garran Rd, Acton, ACT, 2601, Australia
[b] Department of Internal Medicine, Botucatu Medical School, State University/UNESP, Sao Paulo, Faculdade de Medicina, Distrito de Rubião Júnior s/n, Botucatu, SP, CEP 18618-000, Brazil
[c] Statistical Consulting Unit, The Australian National University, Canberra, John Dedman Mathematical Sciences Building, 27 Union Lane, Acton, ACT, 2601, Australia

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ABSTRACT

Background: The adipocytokines leptin and adiponectin have been variously associated with diabetic microvascular complications. No comprehensive clinical data exist examining the association between adipocytokines and the presence of these complications.
Methods: This is a systematic review of cross-sectional studies comparing circulating adipocytokines in patients with type 2 diabetes mellitus (T2DM), with and without microvascular complications. Studies were retrieved from MEDLINE, EMBASE, Scopus and Cochrane databases. Study quality was evaluated using a modified Newcastle–Ottawa Scale. Meta-analysis was performed using an inverse-variance model, providing standardised mean differences (SMD) and 95% confidence intervals (CI). Heterogeneity was determined by I^2 statistic.
Results: Amongst 554 identified studies, 28 were included in the review. Study quality range was 3.5–9 (maximum 11). Higher leptin levels were associated with microalbuminuria (SMD = 0.41; 95% CI = 0.14–0.67; n = 901; p = 0.0003), macroalbuminuria (SMD = 0.68; 95% CI = 0.30–1.06; n = 406; p = 0.0004), and neuropathy (SMD = 0.26; 95% CI = 0.07–0.44; n = 609; p = 0.008). Higher adiponectin levels were associated with microalbuminuria (SMD = 0.55; 95% CI = 0.29–0.81, n = 274; p < 0.001), macroalbuminuria (SMD = 1.37; 95% CI = 0.78–1.97, n = 246; p < 0.00001), neuropathy (SMD = 0.25; 95% CI = 0.14–0.36; n = 1516; p < 0.00001), and retinopathy (SMD = 0.38; 95% CI = 0.25–0.51; n = 1306; p < 0.00001). Meta-regression suggested no influence of body mass index and duration of diabetes on effect size, and a weak trend in terms of age on effect size.
Discussion: Our meta-analysis suggests leptin and adiponectin levels are higher in T2DM patients with microvascular complications. Studies were limited by cross-sectional design. Large prospective analyses are required to validate these findings.

1. Introduction

Diabetes mellitus (DM), a chronic progressive disease characterised by altered glucose homeostasis, is a significant cause of global morbidity and mortality. In Australia, recent statistics suggest that approximately 3.61 million people are affected by diabetes mellitus, both type 1 and type 2 (Whiting, Guariguata, Weil, & Shaw, 2011). Based on studies from 110 countries, the International Diabetes Federation (IDF) estimated that in 2014 there were 387 million people with diabetes; this number is expected to rise to nearly 600 million by 2035 (IDF, 2014).

Due to chronic hyperglycaemia and associated metabolic abnormalities, patients with DM are at an increased risk for developing several macro- and microvascular complications (Hammes, 2003), namely retinopathy, nephropathy and neuropathy. Retinopathy affects approximately 25% of the population with diabetes, and is associated with blood vessel damage in the retina, with the potential to cause significant, and sometimes irreversible, vision loss (Klein,

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* Corresponding author at: 131 Garran Rd, Acton, ACT, 2601, Australia.
E-mail addresses: alexander.rodriguez@monash.edu (A.J. Rodríguez), vsnunes@fmb.unesp.br (V..S. Nunes), claudio.mastronardi@anu.edu.au (C.A. Mastronardi), teresa.neeman@anu.edu.au (T. Neeman), gilberto.pazfilho@anu.edu.au (G.J. Paz-Filho).
[1] Present address: Bone and Muscle Health Research Group, Department of Medicine, Monash University, Clayton, Victoria, Level 5, Block E, Monash Medical Centre (Monash University), 246 Clayton Rd, Clayton, VIC 3168, Australia.
[2] Equal contribution.

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Klein, Moss, Davis, & DeMets, 1984). Nephropathy has a prevalence of approximately 30% in patients with diabetes; it is associated with vascular injury in the nephrons, affecting renal function at different levels. Serious nephropathy can evolve into chronic kidney disease and eventual end-stage renal disease, meaning these patients must either enter long-term haemodialysis or require renal transplantation (Costacou, Ellis, Fried, & Orchard, 2007). Neuropathy is associated with vascular and neuronal damage (commonly peripheral, but also autonomic), leading to impairment of sensation, movement or organ/gland control. In more severe cases, impairment of sensation can result in ulceration requiring limb amputation. Within the population with diabetes, neuropathy has a prevalence as high as 25% (Dyck et al., 1993; Edwards, Vincent, Cheng, & Feldman, 2008).

Whilst the clinical aspects of these microvascular complications are well understood, their molecular mechanisms remain unclear. As type 2 diabetes mellitus (T2DM) is commonly associated with obesity, it has been proposed that adipocytokines, which are produced by the adipose tissue, can directly influence the pro-atherogenic and pro-inflammatory environment of the vascular walls (Cha et al., 2012). Leptin and adiponectin are the two most abundant adipocytokines, and have previously been linked with vascular complications in patients with T2DM (Hanai et al., 2010, 2014; Matsuda, Kawasaki, Inoue, et al., 2004; Matsuda, Kawasaki, Yamada, et al., 2004; Stehouwer, Lambert, Donker, & van Hinsbergh, 1997; Uckaya et al., 2000).

Leptin is a 16-kDa molecule synthesised primarily by the adipose tissue. It is the chief energy regulatory hormone, acting both centrally in the hypothalamus at the arcuate nucleus to produce sensations of satiety; and peripherally to stimulate fatty acid oxidation and glucose disposal (Paz-Filho et al., 2012). Furthermore, leptin has several cytokine-like actions. Importantly, leptin shares structural homology with the interleukin-6 (IL-6) molecule, which is a well-established pro-inflammatory effector (Mak, Cheung, Cone, & Marks, 2006). Leptin too has emerged as an important inflammatory molecule responsible for vascular inflammation, increased oxidative stress, endothelial dysfunction and proliferation of vascular smooth muscle cells (VSMC), and resultant intimal hyperplasia (Guzik, Marvar, Czesnikiewicz-Guzik, & Korbut, 2007).

Adiponectin is also an adipocytokine, but its function is complementary and antagonistic to leptin (Safai et al., 2015). For instance, whilst leptin promotes VSMC proliferation, *in vitro* studies indicate that adiponectin has the inverse effect and furthermore, adiponectin has been shown to inhibit TNF-α, an important inflammatory mediator which facilitates cell adhesion (Chandran, Phillips, Ciaraldi, & Henry, 2003; Okamoto et al., 2002; Yamauchi et al., 2001). Therefore, these adipocytokines are of direct clinical relevance to diabetic microvascular complications.

In patients with diabetes and obesity, leptin levels are increased and adiponectin, decreased (Goldstein, Scalia, & Ma, 2009; Havel, 2004). In this way, patients with T2DM may be exposed to an increased risk of leptin/adiponectin axis-mediated vascular inflammation, and subsequent damage leading to the development of microvascular complications (Niswender & Magnuson, 2007; Payne, Tune, & Knudson, 2014).

Despite several studies demonstrating the pathophysiological association between these adipocytokines and endothelial dysfunction (Van de Voorde, Pauwels, Boydens, & Decaluwé, 2013), clinical data have proved heterogeneous, and no study to date has systematically examined the evidence in this area. Consequently, we sought to survey the literature with the aim to (1) through a systematic review, synthesise and critically evaluate work done in this field and (2) through meta-analysis, clarify the results from this literature, to determine if there is an association between the adipocytokines leptin and adiponectin, and diabetic microvascular complications.

2. Methods

2.1. Study focus and eligibility criteria

To achieve our aims, we conducted a systematic review in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher, Liberati, Tetzlaff, & Altman, 2009) and sought original (observational) studies that examined the association between circulating concentrations of leptin, adiponectin or both (measured by any kind of assay), with the presence or absence of diabetic microvascular complications (retinopathy, nephropathy and neuropathy). Studies were considered eligible for systematic review if the investigation evaluated either concentrations of leptin or adiponectin (or both) in patients with T2DM whom were affected by at least one microvascular complication, and compared these concentrations against patients with T2DM without these complications.

Specific exclusion criteria were: studies not comparing two groups of patients with T2DM (e.g. diabetic complications versus non-diabetic complications), studies evaluating only a cohort of patients with type 1 diabetes, studies that did not present data that could be interpreted as a comparison of leptin or adiponectin between patients with and without microvascular complications, animal or cell-based studies, and individual case reports.

The diagnosis of T2DM was made according to the American Diabetes Association (ADA) guidelines (ADA, 2010). Further, in accordance with these guidelines, patients with urinary albumin excretion between 30 and 300 mg/day (or if urinary albumin excretion between 30 and 300 μg/g creatinine) were considered to have microalbuminuria; macroalbuminuria was defined as urinary albumin excretion >300 mg/day (or if urinary albumin excretion >300 mg/g creatinine), and normoalbuminuria was defined as urinary albumin excretion <30 mg/day (or if urinary albumin excretion <30 μg/g creatinine; i.e., absence of nephropathy) (Group, 2013). Diabetic retinopathy (DR) was classified as normal, non--proliferative and proliferative according to fundoscopic exam performed by an ophthalmologist. Non-proliferative DR was defined based on one or more of the following findings: exudates, microvascular abnormalities, microaneurysm, or haemorrhage. Proliferative DR was diagnosed in the presence of new vessels. For the diagnosis of peripheral or autonomic neuropathies, we considered only validated methods to be appropriate. Peripheral neuropathy was defined as patient reporting changes in sensations (subjectively, or objectively by employing validated screening instruments such as the Michigan Neuropathy Screening Instrument) (Jung, Kim, Mok, Kang, & Kim, 2014), altered clinical tests (monofilament test, vibration test and ankle reflex test) and/or abnormal electrophysiological studies. Autonomic neuropathy was diagnosed by abnormal cardiovascular reflex tests (Jung et al., 2012).

2.2. Units of measurement

Leptin levels were recorded as ng/mL. In order to have unit consistency across all the studies examining adiponectin, we applied a conversion factor of 0.03 to adiponectin results that were not reported as μg/mL. This was determined by contacting the manufacturer of the assay used in one study (Matsuda, Kawasaki, Inoue, et al., 2004; Matsuda, Kawasaki, Yamada, et al., 2004) that measured the 30 kDa form of adiponectin (personal correspondence).

2.3. Information sources and search strategy

We surveyed the MEDLINE (archives from 1966 to 2014), Scopus (1996–2014), EMBASE (1947–2014) and Cochrane Library (1992–2014) databases, and applied the following title/abstract terms ["leptin" OR "adiponectin"] AND ["retinopathy" OR "nephropathy" OR "neuropathy" OR "microvascular complication"] with no language restriction, on the 16th of August 2014. Additionally, we manually scanned the reference lists of eligible texts and the related articles lists that were generated, following a database search for other potential studies of interest. We termed these texts the "grey literature".

For eligible studies unavailable online, attempts were made to obtain full text manuscripts direct from authors and further data were also sought direct from authors in order to ensure study eligibility.

2.4. Meta-analysis eligibility

Studies were eligible for meta-analysis if they first satisfied the criteria for systematic review and reported data specifically relating mean leptin and/or adiponectin (serum or plasma) concentrations in a group of patients with at least one microvascular complication (case), against data relating mean leptin and/or adiponectin (serum or plasma) concentrations in a group of patients without microvascular complications (control). Studies were excluded from meta-analysis if the study did not specifically report leptin and/or adiponectin concentrations in patients with and without a specific microvascular complication (for example, a cohort comprising a mix of patients with retinopathy, patients with nephropathy and patients with neuropathy). Contact was made with authors requesting these specific data in an attempt to include as much literature as possible.

2.5. Study selection and data extraction process

Two reviewers (AJR and VSN) independently screened the records identified by the literature search for studies eligible for full-text review. Both reviewers extracted data using an extraction template. Information was compiled relating to: study design; study participants and baseline risk factors; outcome measurement and assessment; patient biochemical data (specifically of the adipocytokines of interest); statistical analysis of results; limitations highlighted by study investigators; and limitations not considered by investigators. For eligible cohort studies, data were extracted from baseline evaluation. Any discrepancies were resolved through iteration and consensus on the final output.

2.6. Quality assessment

In addition to data extraction, two reviewers (GP-F and CAM) independently performed a quality assessment of the studies included following screening. As no standardised quality assessment tool exists for investigations assessing adipocytokines in diabetic microvascular complications, we modified the previously validated Newcastle–Ottawa Quality Assessment Scale (scale widely used for quality assessment of observational studies), to suit our aims (Wells et al., 2009). In a "star rating system", each included study was judged in the following areas: sample representativeness; sample size; outcome definition and measurement; comparability of results; outcome assessment and statistical methods. For the final scoring, the average score given by both reviewers was calculated. A sample data extraction form and quality assessment tool is provided (Supplementary Material A.1).

2.7. Meta-analysis

Data were first tabulated into a format that allowed comparison of mean leptin and adiponectin concentrations in groups of patients with and without microvascular complications. As leptin and adiponectin levels can be influenced by renal insufficiency, we performed the adipocytokine analysis considering levels of albuminuria: microalbuminuria versus normoalbuminuria; macroalbuminuria versus normoalbuminuria; macroalbuminuria versus microalbuminuria. For diabetic retinopathy, the group analyses were: diabetic retinopathy (non-proliferative and proliferative) versus no retinopathy; non-proliferative retinopathy versus no diabetic retinopathy; proliferative versus non-proliferative. Neuropathy was evaluated as neuropathy or no neuropathy. Tabulated outcomes were then synthesised using the inverse-variance method, and as adipocytokines were measured in either plasma or serum, standardised mean differences (SMD) was used instead of mean difference. The 95% confidence interval (95% CI) was also reported. Heterogeneity was determined by the Q statistic (defined as the I^2 statistic and its degrees of freedom) and inconsistency percentage (I^2) was defined as the ratio of the difference between the Q statistic and degrees of freedom with the Q statistic "$[(Q - df)/Q] \times 100$" (Higgins & Thompson, 2002). Random or fixed effects models were applied based on whether I^2 was greater than 50% in each analysis. To assess any impact important confounders might have on the effect size, we also conducted meta-regression where effect sizes were regressed against study-level confounders, and trends were noted giving an indication whether confounder was related to the effect size. All statistical operations were performed in consultation with a statistician (TN) and using the software RevMan v5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration 2012).

2.8. Sensitivity analysis

In instances of a significant result in meta-analysis, to assess if one particular study contributed exceptionally to the result, we performed a leave-one-out sensitivity analysis. The meta-analysis was repeated with the exclusion of a single study, and was repeated for all the studies in the analysis (each time re-including the one study left out).

3. Results

3.1. Included literature

Initial database search identified 721 records, of which 167 were duplicates (i.e. appearing in more than one searched database), leaving 554 unique records available for abstract screening. Screening of abstracts removed a further 509 studies. This left 45 articles for full text review and of these, a further 17 studies were excluded for different reasons. Overall, 28 studies (Asakawa, Tokunaga, & Kawakami, 2001; Cha et al., 2012; Chan et al., 2004; Choe et al., 2013; Chung, Tsai, Chang, Shin, & Lee, 2005; Dossarps et al., 2014; Fruehwald-Schultes et al., 1999; Fujita et al., 2006; Gottsater, Ahren, & Sundkvist, 1999; Hanai et al., 2010; Jung et al., 2012, 2014; Kato et al., 2008; Komaba et al., 2006; Kopeisy, A. H. A., & Wasfy, 2011; Koshimura et al., 2004; Matsuda, Kawasaki, Inoue, et al., 2004; Matsuda, Kawasaki, Yamada, et al., 2004; Parveen & Zia Qureshi, 2013; Pradeepa et al., 2015; Ran et al., 2010; Saito et al., 2007; Sari, Balci, & Apaydin, 2010; Swellam, Sayed Mahmoud And, & Ali, 2009; Uckaya et al., 2000; Wilson, Nelson, Nicolson, & Pratley, 1998; Yilmaz et al., 2004, 2008) satisfied our inclusion and exclusion criteria for systematic review, and data from 21 of those studies were eligible for meta-analysis (Asakawa et al., 2001; Cha et al., 2012; Chan et al., 2004; Choe et al., 2013; Chung et al., 2005; Dossarps et al., 2014; Fruehwald-Schultes et al., 1999; Fujita et al., 2006; Hanai et al., 2010; Jung et al., 2012, 2014; Kato et al., 2008; Komaba et al., 2006; Kopeisy et al., 2011; Koshimura et al., 2004; Matsuda, Kawasaki, Inoue, et al., 2004; Matsuda, Kawasaki, Yamada, et al., 2004; Parveen & Zia Qureshi, 2013; Pradeepa et al., 2015; Ran et al., 2010; Saito et al., 2007; Sari et al., 2010; Swellam et al., 2009; Uckaya et al., 2000; Wilson et al., 1998; Yilmaz et al., 2004, 2008) (Fig. 1). Included studies are listed in Table 1. Funnel plots are also provided (Supplementary Fig. A.1–A.9), which are mostly symmetrical, as an indication into the lack of publication bias.

3.2. Study characteristics

All 28 studies were cross-sectional analyses, twelve studies assessed retinopathy (Asakawa et al., 2001; Choe et al., 2013; Dossarps et al., 2014; Jung et al., 2014; Kato et al., 2008; Matsuda, Kawasaki, Inoue, et al., 2004; Matsuda, Kawasaki, Yamada, et al., 2004; Parveen & Zia Qureshi, 2013; Pradeepa et al., 2015; Sari et al., 2010; Swellam et al., 2009; Uckaya et al., 2000; Yilmaz et al., 2004); twenty studies assessed nephropathy (Asakawa et al., 2001; Cha et al., 2012; Chan et al., 2004; Choe et al., 2013; Chung et al., 2005; Fruehwald-Schultes et al., 1999; Fujita et al., 2006; Hanai et al., 2010; Jung et al., 2014; Kato

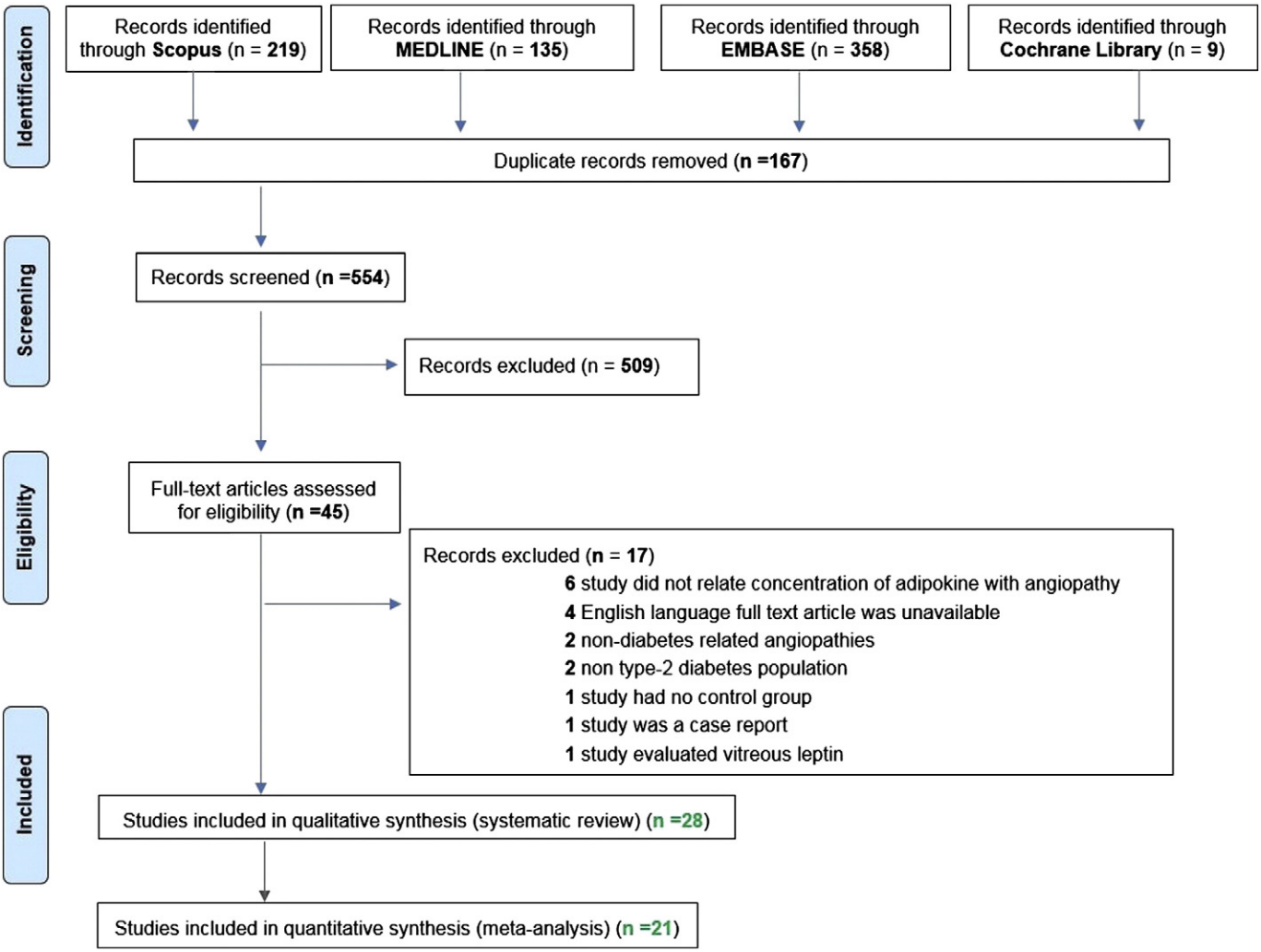

Fig. 1. PRISMA flow diagram of literature search protocol.

et al., 2008; Komaba et al., 2006; Kopeisy et al., 2011; Koshimura et al., 2004; Matsuda, Kawasaki, Inoue, et al., 2004; Matsuda, Kawasaki, Yamada, et al., 2004; Ran et al., 2010; Saito et al., 2007; Sari et al., 2010; Swellam et al., 2009; Wilson et al., 1998; Yilmaz et al., 2008) and eight studies examined neuropathy (Asakawa et al., 2001; Choe et al., 2013; Gottsater et al., 1999; Jung et al., 2012, 2014; Matsuda, Kawasaki, Inoue, et al., 2004; Matsuda, Kawasaki, Yamada, et al., 2004; Sari et al., 2010; Swellam et al., 2009). Nine studies assessed leptin from serum (Asakawa et al., 2001; Chan et al., 2004; Dossarps et al., 2014; Fruehwald-Schultes et al., 1999; Hanai et al., 2010; Jung et al., 2012, 2014; Kopeisy et al., 2011; Parveen & Zia Qureshi, 2013; Sari et al., 2010); seven studies measured plasma leptin (Cha et al., 2012; Chung et al., 2005; Gottsater et al., 1999; Matsuda, Kawasaki, Inoue, et al., 2004; Matsuda, Kawasaki, Yamada, et al., 2004; Sari et al., 2010; Uckaya et al., 2000; Wilson et al., 1998). Of the studies that assessed adiponectin, eight studies assessed serum adiponectin (Dossarps et al., 2014; Fujita et al., 2006; Jung et al., 2012, 2014; Kato et al., 2008; Koshimura et al., 2004; Pradeepa et al., 2015; Saito et al., 2007) and seven assessed plasma adiponectin (Choe et al., 2013; Matsuda, Kawasaki, Inoue, et al., 2004; Matsuda, Kawasaki, Yamada, et al., 2004; Ran et al., 2010; Swellam et al., 2009; Yilmaz et al., 2004, 2008) (Tables 1 and 2).

3.3. Quality assessment

Average quality assessment scores ranged from 3.5 to 9. Items #1, 3, 5 and 6 were the most reported items. These items related to sample representativeness (#1); outcome definition and measurement (#3); outcome assessment (#5) and employment of appropriate statistical methods (#6). Items #2 and #4 respectively relating to sample size and comparability of results were variously reported. Table 3 summarises the individual scores.

3.4. Patient profile

Study population cohorts ranged from n = 30 participants to n = 1480 (Chung et al., 2005; Fruehwald-Schultes et al., 1999). Mean age of study participants ranged from 45.9 to 70.4 years-old in case groups, and 45.8 to 67.2 years-old in control groups (Cha et al., 2012; Ran et al., 2010). Mean patient body mass index (BMI) ranged from 23.7 to 35.8 kg/m^2 in cases (Komaba et al., 2006; Parveen & Zia Qureshi, 2013) and 23.2 to 33.7 kg/m^2 in controls (Dossarps et al., 2014; Koshimura et al., 2004). Finally, mean diabetes duration ranged from 1.31 to 18.7 years in cases (Fruehwald-Schultes et al., 1999; Uckaya et al., 2000), and 1.2 to 13.9 years in controls (Fruehwald-Schultes et al., 1999; Uckaya et al., 2000). These data and further details on patient risk factors are found in the Supplementary Tables (Tables A.1, A.2, A.3 and A.4).

3.5. Meta-analysis

3.5.1. Leptin

3.5.1.1. Retinopathy. Leptin concentration was not significantly different in patients with diabetic retinopathy (n = 92) relative to patients without diabetic retinopathy (n = 288) from three studies

Table 1
Details of studies included in the systematic review.

Study	Year	Patients (n)	Outcome	Blood medium		Meta-analysis
				Leptin	Adiponectin	
Asakawa	2000	182	Retinopathy, nephropathy, neuropathy	Serum	n/a	*
Cha	2012	163	Nephropathy	Plasma	n/a	*
Chan	2003	46	Nephropathy	Serum	n/a	*
Choe[a]	2013	693	Retinopathy, nephropathy, neuropathy	n/a	Plasma	*
Chung	2005	1480	Nephropathy	Plasma	n/a	*
Dossarps	2013	179	Retinopathy	Serum	Serum	*
Fruehwald-Schultes	1999	30	Nephropathy	Serum	n/a	*
Fujita	2006	53	Nephropathy	n/a	Serum	
Gottsater	1999	82	Neuropathy	Serum	n/a	
Hanai	2010	502	Nephropathy	Serum	n/a	*
Jung	2012	142	Neuropathy	Serum	Serum	*
Jung	2014	153	Retinopathy, nephropathy, neuropathy	Serum	Serum	*
Kato	2008	198	Retinopathy, nephropathy	n/a	Serum	
Komaba	2006	179	Nephropathy	n/a	n/r	*
Kopiesy	2011	100	Nephropathy	Serum	n/a	*
Koshimura	2004	38	Nephropathy	n/a	Serum	*
Matsuda	2004	231	Retinopathy, nephropathy	Plasma	Plasma	*
Matsuda	2004	105	Neuropathy	n/a	Plasma	
Parveen	2013	86	Retinopathy	Serum	n/a	*
Pradeepa	2014	487	Retinopathy	n/a	Serum	*
Ran	2010	50	Nephropathy	n/a	Plasma	*
Saito	2007	280	Nephropathy	n/a	Serum	
Sari	2010	157	Retinopathy, nephropathy, neuropathy	Plasma	n/a	*
Swellam	2009	179	Retinopathy, nephropathy, neuropathy	n/a	Plasma	
Uckaya	2000	136	Retinopathy	Plasma	n/a	*
Wilson	1999	20	Nephropathy	Plasma	n/a	
Yilmaz	2004	74	Retinopathy	n/a	Plasma	*
Yilmaz	2008	123	Nephropathy	n/a	Plasma	*

n/a = not applicable; n/r = not reported.
[a] Only provided biochemical data for nephropathy as study examined association between adiponectin gene variants and incidence of diabetic microvascular complications.

(Jung et al., 2014; Sari et al., 2010; Uckaya et al., 2000). Standardised mean difference (SMD) of the effect size was 0.49 and the 95% confidence interval (CI) ranged from −0.38 to 1.36 (p = 0.27) (Supplementary Fig. B.1). Heterogeneity for this analysis was 91% as determined by the I^2 index (Table 4). When considering severity of retinopathy, leptin was not significantly different in patients with non-proliferative diabetic retinopathy (n = 45) compared to patients without diabetic retinopathy (n = 153) [SMD = 0.78; 95% CI = −0.70 to 2.25; p = 0.30; I^2 = 93%] from two studies (Sari et al., 2010; Uckaya et al., 2000) (Supplementary Fig. B.2, Table 4). Leptin was not significantly different in patients with proliferative diabetic retinopathy (n = 29) compared to patients with non-proliferative diabetic retinopathy (n = 45) [SMD = 0.41; 95% CI = −0.11 to 0.93; p = 0.12; I^2 = 16%] from two studies (Sari et al., 2010; Uckaya et al., 2000) (Supplementary Fig. B.3, Table 4). Leptin was not significantly different in patients with proliferative diabetic retinopathy (n = 29) compared to patients without diabetic retinopathy (n = 153) [SMD = 0.91; 95% CI = −0.53 to 2.36; p = 0.21; I^2 = 90%] from two studies (Sari et al., 2010; Uckaya et al., 2000) (Supplementary Fig. B.4, Table 4).

3.5.1.2. Nephropathy. Leptin was significantly elevated in patients with microalbuminuria (n = 318) relative to patients with normoalbuminuria (n = 583) [SMD = 0.41; 95% CI = 0.14–0.67; p = 0.003; I^2 = 58%] from six studies (Cha et al., 2012; Chung et al., 2005; Fruehwald-Schultes et al., 1999; Hanai et al., 2010; Kopeisy et al., 2011; Sari et al., 2010) (Supplementary Fig. C.1, Table 4). A leave-one-out sensitivity analysis confirmed this result (Supplementary Fig. C.2). Leptin was significantly elevated in patients with macroalbuminuria (n = 157) relative to patients with normoalbuminuria (n = 249) [SMD = 0.68; 95% CI = 0.30–1.06; p = 0.0004; I^2 = 57%] from six studies (Cha et al., 2012; Chung et al., 2005; Fruehwald-Schultes et al., 1999; Kopeisy et al., 2011; Sari et al., 2010; Wilson et al., 1998) (Supplementary Fig. D.1, Table 4). A leave-one-out sensitivity analysis confirmed this result (Supplementary Fig D.2). Leptin was significantly elevated in patients with macroalbuminuria (n = 137) relative to patients with microalbuminuria (n = 150) [SMD = 0.44; 95% CI = 0.20–0.68; p = 0.0003; I^2 = 0%] from four studies (Cha et al., 2012; Chung et al., 2005; Kopeisy et al., 2011; Sari et al., 2010) (Supplementary Fig. E, Table 4).

3.5.1.3. Neuropathy. Higher leptin concentration was observed in patients with diabetic neuropathy (n = 184) compared to patients without neuropathy (n = 425) [SMD = 0.26; 95% CI = 0.07–0.44; p = 0.008; I^2 = 0%] from four studies (Asakawa et al., 2001; Jung et al., 2012, 2014; Sari et al., 2010) (Supplementary Fig. F, Table 4).

3.5.2. Adiponectin

3.5.2.1. Retinopathy. Adiponectin was significantly elevated in patients with diabetic retinopathy (n = 324) compared to patients without diabetic retinopathy (n = 983) [SMD = 0.38; 95% CI = 0.25–0.51; p < 0.00001; I^2 = 0%] from three studies (Choe et al., 2013; Jung et al., 2014; Pradeepa et al., 2015) (Supplementary Fig. G.1, Table 4). When considering severity of retinopathy, adiponectin was not significantly different in patients with non-proliferative diabetic retinopathy (n = 221) compared to patients without diabetic retinopathy (n = 547) [SMD = −0.51; 95% CI = −2.45 to 1.43; p = 0.61; I^2 = 96%] from four studies (Dossarps et al., 2014; Kato et al., 2008; Pradeepa et al., 2015; Yilmaz et al., 2004) (Supplementary Fig. G.2, Table 4). Adiponectin did not differ significantly between patients with non-proliferative diabetic retinopathy (n = 43) relative to patients with proliferative diabetic retinopathy (n = 26) [SMD = −0.16; 95% CI = −1.52 to 1.20; p = 0.82; I^2 = 83%] from two studies (Kato et al., 2008; Yilmaz et al., 2004) (Supplementary Fig. D.3, Table 4).

3.5.2.2. Nephropathy. Adiponectin was significantly elevated in patients with microalbuminuria (n = 92) relative to patients with normoalbuminuria (n = 182) [SMD = 0.55; 95% CI = 0.29–0.81; p < 0.0001; I^2 = 0%] from four studies (Kato et al., 2008; Komaba et al., 2006; Koshimura et al., 2004; Ran et al., 2010) (Supplementary

Table 2
Outcome definition details of studies included in systematic review.

Study	Outcome	Outcome definition	Criterion	Case (n)	Controls (n)
Asakawa	Retinopathy	Retinopathy	n/r	39	139
	Nephropathy	Microalbuminuria	AER >30 mg/day	39	139
	Neuropathy	Peripheral neuropathy	Signs/symptoms of peripheral neuropathy	47	135
Cha	Nephropathy	Macroalbuminuria	AER ≥300 mg/day	76	40
		Microalbuminuria	AER 30–299 mg/day		
Chan	Nephropathy	Microalbuminuria	ACR >25 mg/mmol	34	12
Choe	Nephropathy	Microalbuminuria	ACR >30 mg/g	245	448
			AER >30 mg/day		
Chung	Nephropathy	Microalbuminuria	ACR 30–300 mg/g	113	50
		Macroalbuminuria	ACR >300 mg/g		
Dossarps	Retinopathy	Retinopathy	Fundoscopic examination	69	110
Fruehwald-Schultes	Nephropathy	Macroalbuminuria	AER >300 mg/day	20	20
		Microalbuminuria	AER 30–300 mg/day		
Fujita	Nephropathy	Microalbuminuria	ACR 30–299 mg/g	18	19
		Macroalbuminuria	ACR ≥300 mg/g	16	
Gottsater	Neuropathy	Parasympathetic	R-R interval variation	24	58
Hanai	Nephropathy	Microalbuminuria	ACR >25–355 mg/g (women); 17–250 mg/g (men)	158	344
Jung 2012	Neuropathy	Cardiac autonomic neuropathy	n/r	46	96
Jung 2014	Retinopathy	Retinopathy	Fundoscopic examination	18	135
	Nephropathy	Microalbuminuria	AER 20–200 μg/min; ACR 30–300 mg/g	20	133
		Macroalbuminuria	AER >200 μg/min		
			ACR >300 mg/g		
	Neuropathy	n/sp	Self-assessment	87	66
Kato	Retinopathy	Simple	Mild vascular changes	37	119
		Pre-proliferative	Ophthalmologist diagnosis	23	
		Proliferative	Ophthalmologist diagnosis	11	
	Nephropathy	Microalbuminuria	ACR 30–300 mg/g	47	116
		Macroalbuminuria	ACR ≥300 mg/g	24	
		Overt nephropathy	Serum creatinine ≥177 μmol/L	5	
Komaba	Nephropathy	Microalbuminuria	ACR 30–300 mg/g	93	86
		Macroalbuminuria	ACR ≥300 mg/g		
Kopiesy	Nephropathy	Microalbuminuria	AER 30–300 mg/day	20	60
		Macroalbuminuria	AER >300 mg/day		
Koshimura	Nephropathy	Microalbuminuria	ACR 30–300 mg/g	20	18
		Macroalbuminuria	ACR >300 mg/g		
Matsuda	Retinopathy	Proliferative retinopathy	Fundoscopic examination	191	263
	Nephropathy	Macroalbuminuria	ACR 3.4–33.9 g/mol	83	148
Matsuda	Neuropathy	Nerve conduction velocity	Motor and sensory nerve function	n/r	n/r
Pradeepa	Retinopathy	Proliferative retinopathy	Retinal photography	81	487
	Nephropathy	Microalbuminuria	n/r	143	
	Neuropathy	n/sp	n/r	138	
Parveen	Retinopathy	Proliferative retinopathy	Neovascularisation or pre-retinal haemorrhages	21	39
		Non-proliferative retinopathy	Microaneurysms, dot or blot haemorrhages, hard or soft exudates or venous beadings	26	
Ran	Nephropathy	Microalbuminuria	ACR 30–300 mg/day	32	18
		Macroalbuminuria	ACR >300 mg/day		
Saito	Nephropathy	Albuminuria	stage I (no microalbuminuria) to V (under dialysis treatment)	204	76
Sari	Retinopathy	Proliferative retinopathy	New vessels, confirmed by angiography, or previous treatment by photocoagulation	37	120
	Nephropathy	Microalbuminuria	AER 30–300 mg/day	39	119
		Macroalbuminuria	AER >300 mg/day		
	Neuropathy	Sensorial neuropathy	Clinically and/or with electromyography	51	263
		Autonomic neuropathy	Orthostatic test		
Swellam	Retinopathy	n/r	n/sp	71	n/r
	Nephropathy	n/r	Elevated serum creatinine level; stage V, under dialysis treatment	76	n/r
	Neuropathy	n/r	Self-assessment	110	n/r
Uckaya	Retinopathy	Proliferative retinopathy	Vascular abnormalities	37	33
Wilson	Nephropathy	Albuminuria	ACR ≥300 mg/day	10	10
Yilmaz	Retinopathy	Proliferative retinopathy	Vascular abnormalities	44	30
Yilmaz	Nephropathy	Microalbuminuria	Urinary protein >500 mg/day	45	40

ACR = albumin-creatinine ratio; AER = albumin excretion rate; mg = milligrams; n/r = not reported; mol = moles; g = grams; > = greater than; n/sp = not specified; μg = micrograms; min = minute.

Fig. H, Table 4). Adiponectin was significantly elevated in patients with macroalbuminuria (n = 64) relative to patients with normoalbuminuria (n = 182) [SMD = 1.37; 95% CI = 0.78–1.97; p < 0.00001; I^2 = 67%] from four studies (Kato et al., 2008; Komaba et al., 2006; Koshimura et al., 2004; Ran et al., 2010) confirmed in a sensitivity analysis (Supplementary Figs. I.1 and I.2; Table 4). Adiponectin was significantly elevated in patients with macroalbuminuria (n = 64) relative to patients with microalbuminuria (n = 92) [SMD = 0.87; 95%CI = 0.23, 1.51; p = 0.007; I^2 = 67%] from four studies (Kato et al., 2008; Komaba et al., 2006; Koshimura et al., 2004; Ran et al., 2010) confirmed in a sensitivity analysis (Supplementary Figs. J.1 and J.2; Table 4).

3.5.2.3. Neuropathy. Adiponectin was significantly higher in patients with diabetic neuropathy (n = 506) relative to patients without diabetic neuropathy (n = 1010) [SMD = 0.25; 95% CI = 0.14–0.36; p < 0.00001; I^2 = 0%] from five studies (Choe et al., 2013; Jung et al.,

Table 3
Study quality scores using a modified Newcastle–Ottawa Scale.

Study	Item						Score
	1	2	3	4	5	6	
Asakawa 2001	**/**	*/–	**/**	*/**	**/**	*/*	9
Cha 2012	**/**	*/–	**/**	*/*	*/*	*/*	7.5
Chan 2004	*/**	—/—	**/**	–/*	*/*	*/*	6
Choe 2013	**/**	*/–	**/**	–/*	*/*	*/*	7
Chung 2005	***/**	*/–	**/**	**/*	*/–	*/*	8
Dossarps 2014	*/**	*/*	**/**	–/*	*/–	*/*	6.5
Fruehwald-Schultes 1999	*/*	–/–	**/**	*/*	*/**	*/*	6.5
Fujita 2006	**/*	–/–	**/**	**/*	*/*	*/*	7
Gottsater 1999	**/*	*/–	*/**	–/–	–/*	*/*	5
Hanai 2010	*/**	*/–	**/**	**/**	**/**	*/*	9
Jung 2012	*/*	*/–	**/**	*/**	**/**	*/*	8
Jung 2014	*/*	*/–	**/**	**/**	**/**	*/*	8.5
Kato 2008	**/*	*/–	**/**	**/**	**/**	*/*	9
Komaba 2006	**/**	*/*	**/**	*/*	*/–	*/–	7
Kopeisy 2011	*/**	–/*	**/**	–/**	*/–	*/*	6.5
Koshimura 2004	*/*	–/–	*/**	–/–	*/*	*/*	4.5
Matsuda 2004	*/*	*/–	**/**	*/**	*/**	*/*	7.5
Matsuda 2004	**/*	*/–	*/**	–/*	–/**	*/*	6
Pradeepa 2014	**/**	*/*	**/*	–/*	*/–	*/*	6.5
Parveen 2013	*/*	–/*	*/*	–/–	*/*	*/*	4.5
Ran 2010	**/*	–/*	**/**	–/*	*/–	*/*	6
Saito 2007	**/**	*/*	**/**	*/*	*/–	*/*	7.5
Sari 2010	**/**	*/*	**/**	–/*	*/–	*/*	7.5
Swellam 2009	*/**	*/*	*/*	*/*	*/–	*/*	6
Uckaya 2000	**/***	–/*	**/**	–/*	*/**	*/*	8
Wilson 1999	–/*	–/–	*/**	–/–	*/*	–/*	3.5
Yilmaz 2004	**/**	–/*	**/**	–/**	*/**	*/*	8
Yilmaz 2008	**/***	–/*	**/*	*/**	*/**	*/*	8.5

Scores were attributed by two reviewers, which were averaged to provide final scores. Itemised scoring criteria are provided in Supplementary Material A.1.

2012, 2014; Kato et al., 2008; Pradeepa et al., 2015) (Supplementary Fig. K, Table 4). The above results are summarised in Table 5.

3.5.3. Meta-regression

No relationship was found between BMI and duration of diabetes and effect sizes, however a slight trend was evident with respect to age (Supplementary Figs. L and M).

4. Discussion

4.1. Summary and highlight

Insulin-resistant T2DM affects a substantial proportion of the population, and is associated with debilitating microvascular complications such as retinopathy, nephropathy and neuropathy (Hammes, 2003). This investigation suggests that adipocytokines are relevant to microvascular disease and represents the first aggregated study to demonstrate the association between increased leptin levels and nephropathy/neuropathy, and between increased adiponectin levels and nephropathy/neuropathy/retinopathy.

4.2. Role of leptin and adiponectin in MV complications

Adipocytokines (also called adipokines) are adipose tissue-derived molecules with hormone-like actions. Adipocytokines are established metabolic regulators with functions in several other systems including inflammation (Tian, Chang, Loh, & Hsieh, 2014). Leptin and adiponectin are two of the most abundant adipocytokines. Adiponectin levels are inversely related to the degree of adiposity (Cnop et al., 2003), whilst leptin increases with adiposity (Ostlund, Yang, Klein, & Gingerich, 1996).

Diabetic microvascular complications are principally driven by vascular inflammation, and there is strong evidence to suggest that adipocytokines have important functions in vascular inflammation

Table 4
Summary of heterogeneity of the studies included in the systematic review.

Adipocytokine	Analysis	# studies	n	Heterogeneity χ^2 (p value)	Inconsistency I^2 (%)	Model
Leptin	Micro vs Normo	6	901	12.03 (0.03)	58	Random
	Micro vs Macro	4	287	1.62 (0.66)	0	Fixed
	Macro vs Normo	6	406	11.62 (0.04)	57	Random
	DR vs No DR	3	380	21.45 (<0.0001)	91	Random
	Non DR vs no PDR	2	198	14.86 (0.0001)	93	Random
	PDR vs Non PDR	2	74	1.19 (0.28)	16	Fixed
	PDR vs No DR	2	182	10.25 (0.001)	90	Random
	Neuro vs No Neuro	4	609	2.76 (0.43)	0	Fixed
Adiponectin	Micro vs Normo	4	274	2.78 (0.43)	0	Fixed
	Macro vs Normo	4	246	9.06 (0.03)	67	Random
	Macro vs Micro	4	156	9.19 (0.03)	67	Random
	DR vs No DR	3	1307	1.85 (0.4)	0	Fixed
	Non PDR vs No DR	4	768	23.29 (<0.00001)	96	Random
	Non PDR vs PDR	2	69	5.8 (0.02)	83	Random
	Neuro vs No Neuro	5	1516	2.54 (0.64)	0	Fixed

Micro: microalbuminuria; Macro: macroalbuminuria; Normo: normoalbuminuria; DR: diabetic retinopathy; PDR: proliferative diabetic retinopathy; Neuro: neuropathy.

Table 5
Summary of results from the meta-analyses.

Adipokine	Analysis	n (total)	SMD (95% CI)	p value
Leptin	**Micro vs Normo**	**901**	**0.41 [0.14, 0.67]**	**0.0003**
	Macro vs Normo	**406**	**0.68 [0.30, 1.06]**	**0.0004**
	Macro vs Micro	**287**	**0.44 [0.20, 0.68]**	**0.0003**
	Neuro vs No Neuro	**609**	**0.26 [0.07, 0.44]**	**0.008**
	DR vs No DR	380	0.49 [−0.38, 1.36]	0.27
	Non PDR vs No DR	198	0.78 [−0.70, 2.25]	0.30
	PDR vs Non PDR	74	0.41 [−0.11, 0.93]	0.12
	PDR vs No DR	182	0.91 [−0.53, 2.36]	0.21
Adiponectin	**Micro vs Normo**	**274**	**0.55 [0.29, 0.81]**	**<0.0001**
	Macro vs Normo	**246**	**1.37 [0.78, 1.97]**	**<0.00001**
	Macro vs Micro	**156**	**0.87 [0.23, 1.51]**	**0.007**
	DR vs No DR	**1,306**	**0.38 [0.25, 0.51]**	**<0.00001**
	Non PDR vs No DR	768	−0.51 [−2.45, 1.43]	0.61
	Non PDR vs PDR	69	−0.16 [−1.52, 1.20]	0.82
	Neuro vs No Neuro	**1,516**	**0.25 [0.14, 0.36]**	**<0.00001**

Micro: microalbuminuria; Macro: macroalbuminuria; Normo: normoalbuminuria; DR: diabetic retinopathy; PDR: proliferative diabetic retinopathy; Neuro: neuropathy. Bold indicates significant result.

and endothelial dysfunction; leptin has deleterious actions on the vasculature, and adiponectin, has extensive vasculo-protective actions (Jamroz-Wiśniewska et al., 2014; Martínez-Martínez et al., 2014; Nevelsteen et al., 2013).

4.3. Comparing and contrasting this investigation with the literature

Adiponectin is generally considered to be an anti-inflammatory adipocytokine, and this is supported by a recent meta-analysis of over 3000 T2DM patients, where adiponectin was negatively correlated with diabetic retinopathy (Fan et al., 2014). This result is in contradiction to the present study. However, the population under consideration in the present study is considerably more heterogeneous, compared to the population included in the meta-analysis by Fan and colleagues, which was composed predominantly of Han Chinese. In considering that adiponectin concentration is influenced by genetic background, we postulate that our genetically diverse study represents the more robust result and may explain the disparate findings (Morimoto et al., 2014). Furthermore, it may be reasonable to hypothesise that adiponectin in fact plays no role in the pathophysiology of diabetic microvascular complications, and is increased in an attempt to counteract leptin's deleterious effects or may have a novel as yet unknown effect on diabetic microvascular complications (Costacou & Orchard, 2008; Ebert & Fasshauer, 2011). Overall, cellular and clinical evidence presents leptin and adiponectin as relevant and important to diabetic microvascular complications as these complications are driven by a component of inflammation in pathways which are directly affected by these adipocytokines.

Adiponectin levels differ in the presence of macrovascular versus microvascular complications. Patients with macrovascular complication display low concentrations of plasma adiponectin levels (Boyle, 2007; Wang, Gao, Su, Xu, & Fu, 2015; Yazici et al., 2012), whereas it has been reported that microvascular complications are associated with increased circulating adiponectin levels (Frystyk, Tarnow, Krarup Hansen, Parving, & Flyvbjerg, 2005). Atherosclerosis is an essential aetiological component of macrovascular complications (Fowler, 2011). The process of atherosclerosis appears to involve the synergistic action of hyperglycaemia and hyperlipidaemia (Chait & Bornfeldt, 2009). In an *in vivo* study, it was shown that diabetic pigs develop atherosclerosis in presence of hyperlipidaemia, but not in its absence, suggestive of a synergistic interaction between hyperlipidaemia and glycaemia in the progression of macrovascular complication (Gerrity, Natarajan, Nadler, & Kimsey, 2001). Thus, it could be hypothesised that increased hyperlipidaemia, which is ultimately involved in macrovascular complications, might play a role in decreasing circulating adiponectin. Interestingly, low plasma adiponectin favours progression of atherosclerosis and vascular plaque formation (Broedl et al., 2009; Yazici et al., 2012). Therefore, the increased levels of circulating adiponectin observed in microvascular complications (as evident in this meta-analysis) could result from a compensatory mechanism to counter inflammatory processes that occur as part of the pathophysiology of microvascular disease complication, in the absence of macrovascular complications. In fact, a mounting body of evidence supports that adiponectin exerts vascular protective actions including anti-atherogenic effects (Broedl et al., 2009; Iwaki et al., 2003; Yazici et al., 2012).

Despite this literature, there has been little direct examination of the role of leptin and adiponectin in microvascular complications. We identified several studies that suggest leptin and adiponectin are relevant to these conditions (Asakawa et al., 2001; Cha et al., 2012; Chan et al., 2004; Choe et al., 2013; Chung et al., 2005; Dossarps et al., 2014; Fruehwald-Schultes et al., 1999; Fujita et al., 2006; Hanai et al., 2010; Jung et al., 2012, 2014; Kato et al., 2008; Komaba et al., 2006; Kopeisy et al., 2011; Koshimura et al., 2004; Matsuda, Kawasaki, Inoue, et al., 2004; Matsuda, Kawasaki, Yamada, et al., 2004; Parveen & Zia Qureshi, 2013; Pradeepa et al., 2015, Ran et al., 2010, Saito et al., 2007; Sari et al., 2010; Swellam et al., 2009; Uckaya et al., 2000; Wilson et al., 1998; Yilmaz et al., 2004, 2008). As this investigation attests, these studies have proven to be heterogeneous in their findings of associations between leptin and adiponectin and diabetic microvascular complications. In light of this, we have attempted to clarify these results by way of a systematic review and meta-analysis and found leptin and adiponectin to be significantly associated with diabetic microvascular complications.

4.4. Limitations of included studies

We identified some limitations of the included studies. All included studies were cross-sectional observational clinical studies. These studies leave open the possibility of selection bias as no randomisation was performed (recorded as part of the NOS). Therefore associations drawn in cross-sectional studies do not imply causation. Importantly, we did not exclude longitudinal studies from our literature search. In order to properly identify causative agents or assess the role of adipocytokines in microvascular complication development, large prospective trials are needed.

Another potential source of heterogeneity is the use of medications by the patients in this cohort. Generally, medication use was poorly reported and no instance exists where results (data relating to leptin and adiponectin with respect to patients with and without complications) were adjusted for medication use. Multiple co-morbidities are common in people with diabetes and many of these co-morbidities can be treated medically (e.g. fibrates for hypertriglyceridaemia) and these therapies are in addition to the many medical treatments patients with diabetes already receive for the diabetes itself (e.g. insulin, metformin or the glitazones). It is not known what effect these adjunct therapies have on adipocytokine levels in the blood in patients with microvascular complications.

Furthermore, several studies failed to report a method or criteria for evaluating diabetes in patients recruited, even if the presence of diabetes was part of the study inclusion criteria (Chan et al., 2004; Fruehwald-Schultes et al., 1999; Jung et al., 2012, 2014; Uckaya et al., 2000). This is important, as different countries have different standards for diabetes definitions. In considering that the studies included here were conducted in many different countries (e.g. Japan, Korea, Germany, Turkey and Egypt), we may be grouping some patients with poorly controlled diabetes together with patients with well-controlled diabetes according the definitions set in this country (Australia). Further to this, there was no direct assessment of possible leptin resistance in these patients. This is extremely relevant to the diabetes population as leptin resistance is a common finding in

patients with diabetes and obesity (Coppari & Bjørbæk, 2012). These effects may be mitigated by adjusting results according to baseline leptin levels, but this too was not performed in the studies included for meta-analysis.

There was also limited reporting of inflammatory markers which may be important in distinguishing the inflammatory effects of leptin and adiponectin from classic pro-inflammatory cytokines. Moreover, the duration of diabetes varied greatly and may have contributed to heterogeneity, as the risk of developing these chronic complications increases with longer diabetes duration. Finally, some studies were generally small in size, and as they included only patients with diabetes, the results may not be generalisable to patients with similar microvascular morbidities independent of diabetes.

4.5. Limitations of this meta-analysis

Our meta-analysis has some limitations. This meta-analysis was performed using aggregate data, and as such we did not have access to all primary data to enable adjustment of adipokine levels to factors strongly related to the risk of diabetic complications. However, we performed meta-regression analyses using the study-level confounders of age, BMI and duration of diabetes, representing the most important microvascular complication risk factors. No relationship between BMI and duration of diabetes was evident, suggesting that these study-level variables did not influence the effect size (SMD between leptin or adiponectin levels in case and control groups). A slight trend was evident with age: increasing age increased the effect size, suggesting that in patients with advanced age, the effect size (SMD between leptin or adiponectin levels in case and control groups) would be greater. However, it has been shown that the age-dependent changes in leptin and adiponectin levels are not very significant (Balaskó, Soós, Székely, & Pétervári, 2014).

In considering that leptin and adiponectin have been inconsistently associated with MV complications (some reporting no association, some reporting higher leptin or adiponectin to be associated and some reporting lower leptin or adiponectin to be associated), our study adds value to the literature in this area as a succinct, synthesised report. We cannot confirm whether the association of leptin with nephropathy is independent of hypertension. Increased leptin has variously been reported with normotension, hypertension and indeed may be elevated independent of hypertensive status (Almeida-Pititto, Gimeno, Freire, Ribeiro-Filho, & Ferreira, 2006; Tsuda & Nishio, 2004). Importantly, leptin does not mediate hypertension in human obesity and obesity is common amongst patients with T2DM suggesting increased leptin in nephropathy is occurring independently of hypertension (Brown, Meehan, & Gorden, 2015). However, to mitigate any potential effects, we attempted to include blood pressure in the meta-regression. As specific systolic or diastolic blood pressures were poorly reported by these studies, we sought these data directly from authors however we received no timely response. Other important sources of heterogeneity were sample sizes of some of the analyses, and that we grouped together results where adipocytokines were measured either in plasma or in serum. Also, ethnic and gender differences may account for possible bias in our results as we included studies from many racially and genetically distinct populations. Finally, we cannot discount any age or sex specific affects as possible sources of heterogeneity as for example, leptin levels tend to be higher in females.

5. Conclusion

Overall, we sought literature that examined the association between circulating levels of the adipocytokines leptin and adiponectin and diabetic microvascular complications. Our analysis revealed that higher leptin and adiponectin levels were associated with macro- and microalbuminuria and neuropathy. Further, elevated adiponectin was also associated with retinopathy. This meta-analysis represents the first comprehensive quantitative assessment of adipocytokines in diabetic microvascular complications, and the results here could be translated into diagnostics, surveillance tools or for risk prediction uses. This pool of participants is likely underpowered to determine the influence of adipocytokines in microvascular complication development, and therefore large prospective studies are required to confirm and validate these findings independent of known risk factors and determine their causality.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jdiacomp.2015.11.004.

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