Circulating leptin level, soluble leptin receptor level and their gene polymorphism in patients with systemic lupus erythematosus: a systematic review and meta-analysis

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ABSTRACT

Objective. *Initial studies investigating peripheral levels of leptin and soluble leptin receptor (LepR) in systemic lupus erythematosus (SLE) patients have generated a number of controversial results. Thus, we conducted a meta-analysis to evaluate the circulating leptin level, soluble LepR level and related gene polymorphism in SLE patients.*

Methods. *We performed a meta-analysis comparing the circulating leptin level, LepR level and their gene polymorphism in patients with SLE to controls, and evaluate the relationship between leptin levels, LepR levels and SLE disease activity. Pubmed, Embase, Cochrane, CNKI, WanFang and VIP databases were searched systematically without restricting languages and years (up to Feb. 2020). Stata v. 14.0 was used to calculate statistical data.*

Results. *34 articles involving 7337 SLE patients and 6866 healthy controls were included in this meta-analysis. Compared with healthy controls, SLE patients had a significantly higher level of leptin, in particular for active SLE patients, regardless of sample size, source, or assay method. The elevated leptin level was only found in the female SLE group, but not in the male SLE group. Apart from the South American subgroup, other ethnicity subgroups showed significantly higher levels of leptin in SLE patients. A marginally lower level of LepR in SLE patients was also observed. The LepR gene rs1137101 variant (i.e. AG+GG) was borderline significantly associated with the increased risk of SLE.*

Conclusion. *Our meta-analysis revealed SLE patients showed an elevated leptin level and a decreased LepR level. LepR gene rs1137101 mutation might be associated with the increased susceptibility to SLE.*

Introduction

Systemic lupus erythematosus (SLE) is a chronic multi-organ autoimmune disease which is characterised by the impaired clearance of apoptotic cells, loss of tolerance to self-antigens, aberrant activation of T cells and B cells, and chronic inflammation (1). The aetiology and pathogenesis of SLE are not clearly understood. Variably intertwined factors including genetic predisposition, environmental stimuli, and persistent immune dysfunction have been reported as being potential mediators of morbidity and mortality in SLE patients (2, 3).

Leptin, the forerunner of the adipokine superfamily, plays a pivotal role in regulating energy expenditure and neuroendocrine function. Research into leptin has revealed that not only does this hormone play an important role in metabolism, it also mediates the immune response by promoting inflammation through immunocyte activation and cytokine secretion (4). Leptin acts on receptors that are widespread throughout the body and that are expressed across many tissue types. The LepR gene encodes for six alternatively spliced isoforms: LepRa~f (5). Although soluble receptor (*i.e.* LepRe) failed to finish signal transduction, it is thought to be pivotal for leptin transport and degradation (5, 6). As a consequence, the abnormal expression of leptin and the mutations of LepR gene have been found to correlate with the increased susceptibility to a number of diseases, including cardiovascular diseases, cancers and autoimmune diseases.

SLE patients with increased adiposity have a heightened risk for disease-related complications, including neurocognitive decline, renal impairment, and dampened physical activity (7). It has been well-established that obesity is

closely associated with hypertension and diabetes, which may increase the risk of subclinical atherosclerosis in SLE and lead to poor prognosis (8). These suggest that the significance of leptin in the development of SLE is becoming increasingly prominent. Most investigations have described increased leptin levels in SLE patients compared with healthy controls and observed an inverse correlation between soluble LepR levels and SLE (9, 10). However, other studies have reported either unchanging leptin levels or decreased leptin levels in SLE patients (11, 12). Overall, conflicting associations are reported between leptin levels and SLE. Although there exists meta-analysis (published in 2015 and 2017) about the correlation between leptin levels and SLE, their pooled results are inconclusive or even contradictory (13, 14). Those meta-analyses involved only leptin levels, without soluble LepR levels and relevant gene polymorphism. Therefore, we carried out a meta-analysis of more studies to determine the relationship between leptin levels, soluble LepR levels as well as relevant gene polymorphism and SLE and investigate the association of circulating leptin level and LepR level with SLE disease activity.

Methods

Search strategies

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and was registered in the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY202040137). We carried out an electronic search of PubMed, Embase, Cochrane, China National Knowledge Infrastructure (CNKI), China WanFang and China Weipu (VIP) databases looking for previous studies on the correlation between leptin levels, LepR levels as well as relevant gene polymorphism and SLE. The final systematic search was conducted on February, 2020 with no limitations on language or the publication year. We used the following combined random words and MeSH terms: "leptin" and "systemic lupus erythematosus". The complete search strategies were shown in the supplementary material. The authors also searched the reference lists of relevant articles to ensure the comprehensiveness of this article.

Eligibility criteria

All observational studies, including cohort studies, case-control studies and cross-sectional studies, that provided data on the serum/plasma leptin levels, LepR levels and relevant gene polymorphism in SLE cases and control groups, were eligible for inclusion in this meta-analysis. In addition, studies that met the following inclusion criteria were selected: 1) predefined SLE criteria; 2) predefined measurement methods; 3) OR estimates with 95% CI and *p*-values, or values that could be calculated according to the reported raw data in the study.

Data extraction

Three reviewers evaluated each study for eligibility and extracted the following data independently: first author's name; publication year; location; study design; numbers of cases and controls; sex ratio of cases and controls; assay method; matched variables; genotype frequencies. Any differences of opinion between the three assessors were discussed until agreement was achieved. When necessary, an additional researcher would be contacted for extended discussions as another adjudicator.

Quality of included studies

The authors evaluated each of the included studies for quality assessment, based on the Newcastle-Ottawa Scale (NOS) for case-control studies. The following factors were taken into account: selection of cases and controls; comparability of cases and controls on the basis of the design or analysis; and exposure of cases and controls. Studies scored above or equal to the median NOS value were considered as high quality (lower risk of bias) and those scored below the median value were considered as low quality (higher risk of bias) (15).

Statistical analysis

All statistical analyses were performed on Stata statistical software (v. 14.0). The *p*-value of Hardy-Weinberg Equilibrium was evaluated based on the genotype frequency in the control group. Odds ratio (OR) and standardised mean difference (SMD) along with 95% confidence intervals (CI) were used and the analyses were carried out by using a random/fixed-effects model. OR was applied for statistical analysis of the dichotomous data, and SMD was applied to statistically analyze the continuous variables. Of note, $p<0.05$ was considered as statistically significant. We used the chi-squared test to evaluate the statistical heterogeneity between different studies. $p>0.1$ and $I^2< 50\%$ indicated low heterogeneity where a fixed effect model was used; $p<0.1$ and $I^2 >50\%$ indicated statistical heterogeneity where a random effect model was applied.

We carried out sensitivity analyses for identifying the source of heterogeneity and checking the robustness of the results. The leave-one-out method (removing one study each time and repeating the analysis) was employed, which allowed us to determine the implication of each study on the pooled effect size. In addition, we performed meta-regression analyses using the following variables: ethnicity (Asian, African, South American, North American and European), sample size ($n\leq30$ and $n>30$), source (Serum and Plasma), sex (female and male) and assay method (Radioimmunoassay, ELISA and Graphene pastes). The above pre-specified characteristics were then conducted in the subgroup analyses. We utilised descriptive analysis when significant heterogeneity still existed between the two groups.

We generated a funnel plot so that we could inspect publication bias visually. Begg's and Egger's tests were also conducted for analysing the publication bias quantitatively, where, $p<0.05$ was regarded as statistically significant. We validated the results of publication bias by establishing trim and fill funnel plot if required.

Results

Publication selection

The PRISMA flow diagram of study selection process is illustrated in Fig. 1. There were 371 studies in total

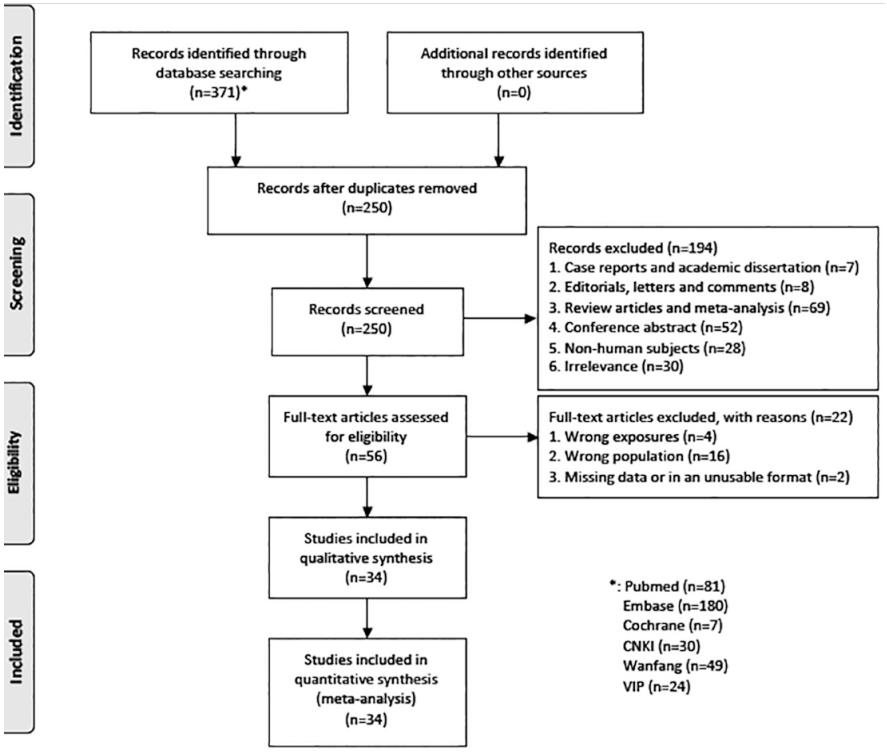

Fig. 1. PRISMA flow diagram of study selection.

from the initial retrieval, of which the duplicates (n=121); case reports and academic dissertation (n=7); editorials, letters and comments (n=8); review articles and meta-analysis (n=69) were excluded. After reviewing the abstract of 166 articles, a total of 110 articles were subsequently excluded for being conference abstract (n=52) and non-human subjects (n=28); irrelevance (n=30). Then, we completed the full test review of 56 articles and excluded 22 articles as a consequence of wrong exposures (n=4), wrong population (n=16), missing data or in an unusable format (n=2). We eventually included a total of 34 articles in the meta-analysis (9-12, 16-45).

The basic characteristics of the included studies are shown in Tables I and II. All of the included studies were journal articles, of which 3 articles were cohort studies; 30 articles were case-control studies; 1 article was cross-sectional study. However, all the cohorts in studies were further divided into SLE cases and healthy controls. We considered these as case-control studies. Of the included studies, eighteen were on Asian population (China [9, 16, 27, 33-41], India [11, 19], Iran [10], Korea [30] and Japan [25, 42]), six were on European (Germany [28], Poland [12, 22], Italy [26, 29] and Romania [23]), five with North American (Canada [43, 44], USA [32, 45] and Mexico [20]), two with South America (Brazil [31] and Venezuela [21]) and three studies on African participants (Egypt [17, 18, 24]).

Quality assessment of the selected publications

Quality assessment of the included studies using modified NOS for case-control studies is shown in Tables I and II. The median score of NOS was 6.5. Therefore, among the 34 studies, 73.5% of the studies, scored ≥6.5, were assessed as high methodological quality (low risk of bias). Nine studies scored lower than 6.5 were evaluated as low methodological quality (high risk of bias).

Meta-analysis results

– *Meta-analysis of leptin levels, soluble LepR levels and their gene polymorphism in SLE patients compared with healthy controls*

Our pooled data of twenty-nine studies revealed that circulating leptin level was significantly higher in the SLE group than in the control group (SMD=0.772, 95%CI (0.477–1.066), $p<0.001$) (Fig. 2a). Stratification by ethnicity showed a significantly elevated leptin level in the SLE group in Asian, African, North American and European (SMD=0.863, 95%CI (0.504–1.223), $p<0.001$; SMD=1.674, 95%CI (1.066–2.282), $p<0.001$; SMD=0.494, 95%CI (0.328–0.661), $p<0.001$; SMD=0.679, 95%CI (0.459–0.899), $p<0.001$), but not in the South American population (SMD=-0.750, 95%CI (-4.031–2.531), $p=0.654$) (Table III). Stratification by sample size showed a significantly higher leptin level in the SLE group in small (n≤30) and large (n>30) sample numbers (SMD=0.948, 95%CI (0.523–1.374), P<0.001; SMD=0.706, 95%CI (0.351–1.061), $p<0.001$) (Table III). Subgroup analysis by source of leptin showed a significantly higher leptin level in the SLE group by serum and plasma (SMD=0.778, 95%CI (0.447–1.109), $p<0.001$; SMD=0.721, 95%CI (0.105–1.337), $p=0.022$) (Table III). Subgroup analysis by sex showed a significantly higher leptin level in the SLE group in female population (SMD=0.861, 95%CI (0.418–1.305), $p<0.001$), but not in the male population (SMD=1.574, 95%CI (-0.563–3.711), $p=0.149$) (Table III). Stratification by assay method revealed a significantly higher leptin level in the SLE group by enzeme-linked immunosorbent assay and radioimmunoassay (SMD=0.642, 95%CI (0.303–0.980), $p<0.001$; SMD=1.095, 95%CI (0.461–1.729), $p=0.001$) (Table III). In addition, our combined results of seven studies indicated a trend toward a higher leptin level in the active SLE patients (SLEDAI ≥10) compared to the inactive SLE patients (SLEDAI <10), but it failed to reach statistical significance (SMD=0.215, 95%CI (-0.005–0.435), $p=0.055$) (Fig. 2b).

Six studies compared the LepR levels between the SLE cases and the healthy controls, with the pooled data indicating a trend toward a lower LepR level in the SLE group compared to the healthy group that did not reach statistical significance (SMD=-0.673, 95%CI (-1.441–0.096), $p=0.086$) (Fig. 3a). Four studies compared the LepR levels

Table I. Basic information about the patients involved in the studies.

Author	Year	Region	Study design	Case		Control		Assay method	Matched variables	NOS score
				n	Sex ratio	n	Sex ratio			
Han, X	2006	China	Case-control study	24	Not reported	31	22/9	Radioimmunoassay, ELISA	Age, gender, BMI	7
He, S	2016	China	Case-control study	36	30/6	20	12/8	ELISA	Age, gender, BMI	8
Hu, Q	2009	China	Case-control study	42	42/0	30	42/0	Radioimmunoassay	Age, gender, BMI	7
Li, J	2004	China	Case-control study	54	54/0	30	30/0	Radioimmunoassay	Age, gender, BMI	7
Li, J	2010	China	Case-control study	34	34/0	30	30/0	Radioimmunoassay	Age, gender, BMI	7
Lin, X	2008	China	Case-control study	42	31/11	35	21/14	Radioimmunoassay	Age, BMI	8
Liu, J	2011	China	Case-control study	28	22/6	21	17/4	ELISA	Age, gender, BMI	8
Xu, T	2007	China	Case-control study	45	36/9	15	Not reported	ELISA	Not reported	6
Zhu, L	2007	China	Case-control study	104	104/0	30	30/0	Radioimmunoassay	Age, BMI	8
Zhu, L	2007	China	Case-control study	30	30/0	30	30/0	Radioimmunoassay	Age, BMI	8
Afroze, D	2015	India	Case-control study	100	97/3	100	98/2	ELISA	Age, gender	8
Al, M	2009	Canada	Cohort study	105	84/21	77	56/21	ELISA	Not reported	6
Badawi, AIZ	2017	Egypt	Case-control study	30	Not reported	20	Not reported	ELISA	Age, gender	6
Barbosa Vde, S	2015	Brazil	Case-control study	52	52/0	33	33/0	ELISA	Not reported	5
Bagheri, K	2012	Iran	Case-control study	34	Not reported	34	Not reported	ELISA	Age, gender	6
Chougule, D	2018	India	Case-control study	60	Not reported	40	Not reported	ELISA	Age, gender	8
Chung, CP	2009	USA	Case-control study	109	100/9	78	67/11	ELISA	Age, gender, race, BMI	7
De Sanctis, JB	2009	Venezuela	Case-control study	60	51/9	60	54/6	ELISA	Age, gender	6
Elwakkad, ASE	2007	Egypt	Case-control study	12	10/2	21	Not reported	ELISA	Age, gender	7
Garcia-Gonzalez, A	2002	Mexico	Cross-sectional study	41	41/0	23	23/0	ELISA	Age, BMI	8
Härle, P	2004	Germany	Case-control study	32	24/8	54	26/28	ELISA	Not reported	6
Hrycek, E	2018	Poland	Case-control study	41	Not reported	38	Not reported	ELISA	Age, place of residence, BMI	7
Kim, HA	2010	Korea	Case-control study	70	Not reported	39	Not reported	ELISA	gender, BMI	8
Ma, L	2015	China	Case-control study	87	76/11	85	71/14	ELISA	Age, gender, BMI	8
Margiotta, D	2016	Italy	Case-control study	13	13/0	11	11/0	ELISA	Age, gender	7
McMahon, M	2011	USA	Case-control study	250	250/0	122	122/0	ELISA	Age, gender	7
Mohammed, SF	2018	Egypt	Case-control study	40	40/0	20	20/0	ELISA	Age, BMI	7
Sada, K.E	2006	Japan	Case-control study	37	Not reported	80	Not reported	Radioimmunoassay	Age, gender, BMI	8
Stanescu, II	2018	Romania	Case-control study	24	24/0	5	5/0	Graphene pastes	Not reported	5
Tanaka, N	2013	Japan	Cohort study	18	14/4	140	118/22	ELISA	gender, BMI	7
Vadacca, M.	2013	Italy	Case-control study	60	60/0	29	29/0	ELISA	Age, gender, BMI	7
Wislowska, M	2008	Poland	Case-control study	30	30/0	30	30/0	ELISA	Age, gender, BMI	7

Note: Sex ratio=female/male.

Table II. Distribution of LepR rs1137101 genotype among SLE patients and healthy controls.

Author	Year	Region	Case			Control			Hardy-Weinberg Equilibrium (*p*-value)	NOS score
			AA/A allele	AG+GG/G allele	n	AA/A allele	AG+GG/G allele	n		
Afroze, D	2015	India	18**	82$^{\#\#}$	100	31**	69$^{\#\#}$	100	0.54	8
			94*	106$^{\#}$	200	114*	86$^{\#}$	200		
Li, H	2017	China	10**	623$^{\#\#}$	633	9**	550$^{\#\#}$	559	0.97	8
Zhao, J	2015	Canada	4577*^{EA}	3355$^{\#EA}$	7932	4039*^{EA}	3047$^{\#EA}$	7086	Beyond calculation	6
			1344*^{AA}	1710$^{\#AA}$	3054	1642*^{AA}	1982$^{\#AA}$	3624		

*: A allele frequency of LepR gene rs1137101; $^{\#}$: G allele frequency of LepR gene rs1137101.
**: AA genotype frequency of LepR gene rs1137101; $^{\#\#}$: AG+GG genotype frequency of LepR gene rs1137101.
*^{EA}: A allele frequency of LepR gene rs1137101 in European American subgroup; $^{\#EA}$: G allele frequency of LepR gene rs1137101 in European American subgroup.
*^{AA}: A allele frequency of LepR gene rs1137101 in African American subgroup; $^{\#AA}$: G allele frequency of LepR gene rs1137101 in African American subgroup.

between the active SLE group and the inactive SLE group, with the combined results showing no significant difference (SMD=-0.528, 95%CI (-1.197–0.140), p=0.121) (Fig. 3b).

The polymorphism of leptin gene (*e.g.* rs11761556, rs12706832, rs2071045 and rs2167270) and LepR gene (*e.g.* rs1137100, rs1137101, rs13306519, rs8179183, rs1805096, rs3790434, rs3806318 and rs7518632) has ever been reported the potential association with SLE (42). But we just retrieved three studies that evaluate the association between leptin/LepR gene polymorphism and SLE. We would include the entire leptin/LepR gene; however, one study (19) only reported LepR gene rs1137101 polymorphism, another study (42) only reported genotype frequency of several leptin/LepR gene and a third study (45) only reported allele frequency of several leptin/LepR gene in different ethnicities. Thus, we only analyse genotype frequency and allele frequency of LepR gene (rs1137101). Our pooled results showed that the AA genotype of rs1137101 was borderline significantly associated with the decreased risk of SLE in two com-

Table III. Meta-analysis of the association between circulating leptin level and SLE.

Groups	Population	No. of studies	Test of association			Test of heterogeneity		
			SMD	95%CI	*p*-value	Model	*p*-value	I^2
All	Overall	29	0.772	0.477, 1.066	<0.001	random	<0.001	91.8%
Ethnicity	Asian	15	0.863	0.504, 1.223	<0.001	random	<0.001	89.4%
	African	3	1.674	1.066, 2.282	<0.001	random	0.101	56.3%
	South American	2	-0.750	-4.031, 2.531	0.654	random	<0.001	99.0%
	North American	3	0.494	0.328, 0.661	<0.001	fixed	0.450	0.0%
	European	6	0.679	0.459, 0.899	<0.001	fixed	0.115	43.6%
Sample size	n≤30	8	0.948	0.523, 1.374	<0.001	random	0.001	70.3%
	n>30	21	0.706	0.351, 1.061	<0.001	random	<0.001	93.6%
Source	Serum	27	0.778	0.447, 1.109	<0.001	random	<0.001	92.2%
	Plasma	2	0.721	0.105, 1.337	0.022	random	0.008	85.7%
Sex	female	16	0.861	0.418, 1.305	<0.001	random	<0.001	92.3%
	male	2	1.574	-0.563, 3.711	0.149	random	<0.001	95.0%
Assay method	ELISA	21	0.642	0.303, 0.980	<0.001	random	<0.001	92.1%
	Radioimmunoassay	7	1.095	0.461, 1.729	0.001	random	<0.001	91.2%

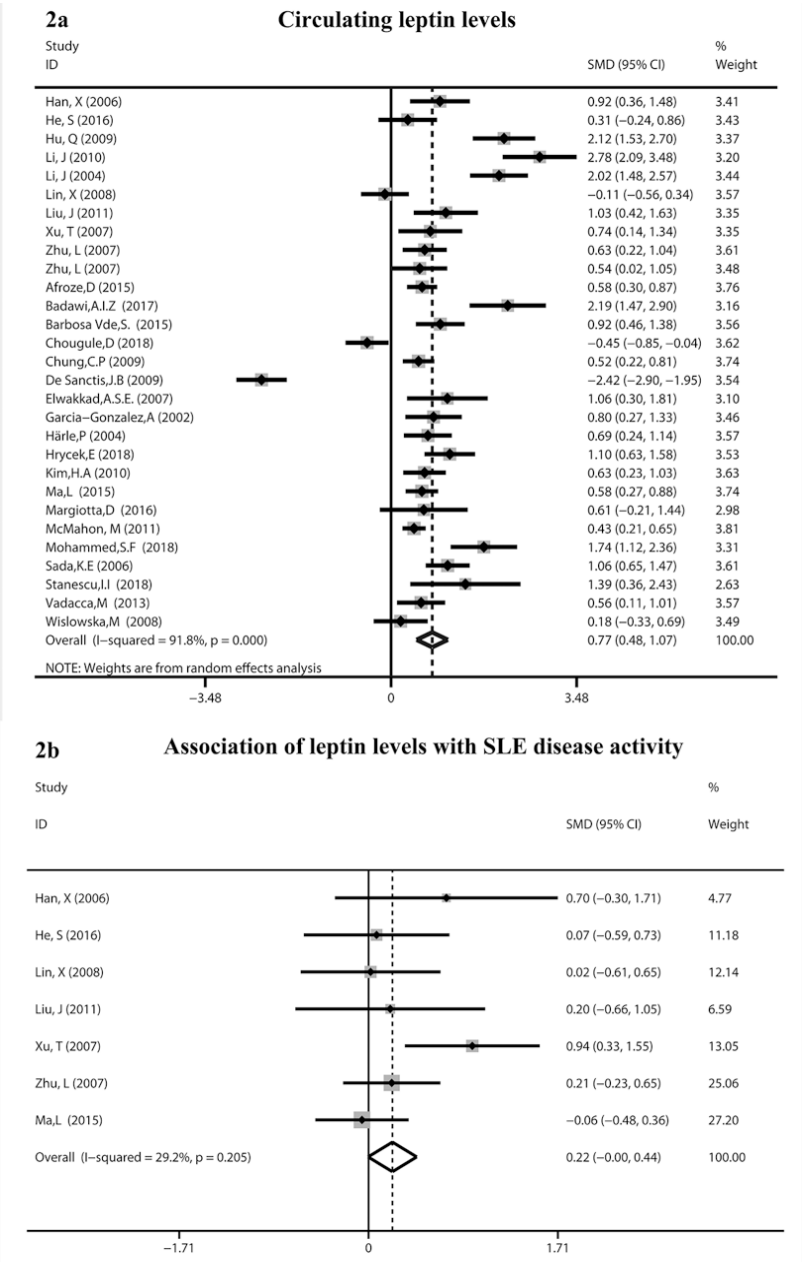

Fig. 2.

paratives (OR=0.622, 95%CI (0.366, 1.056), *p*=0.079); however, the GG genotype and AG genotype were not (OR=1.015, 95%CI (0.792, 1.300), *p*=0.908; OR=1.093, 95%CI (0.855, 1.396), *p*=0.478) (Fig. 4a). The LepR gene rs1137101 variant (AG+GG) was borderline significantly associated with the increased risk of SLE, and the pooled OR (95%CI) was 1.609 (0.947, 2.733) (p=0.079), with evidence of acceptable heterogeneity (I^2=32.3%, *p*=0.224) (Fig. 4b). No significant difference was detected in the variant G allele frequency of LepR gene rs1137101 between two groups (OR=1.002 95%CI (0.951–1.055), *p*=0.942, I^2=49.8%) (Fig. 4c).

– Heterogeneity, sensitivity test, and publication bias

Between-study heterogeneity was identified during the meta-analyses of leptin level in SLE patients compared to the healthy controls (Table III). It is a pity that we failed to determine the source of heterogeneity. Meta-regression analysis showed that ethnicity (*p*=0.438), sample size (*p*=0.516), source (*p*=0.952), sex (*p*=0.444) and assay method (0.470) did not have significant impacts on heterogeneity in the meta-analysis of leptin levels. As to the heterogeneity of LepR level, we conducted sensitivity analysis with leave-one-out method instead of meta-regression as a consequence of the small number of included studies; however, the heterogeneity did not decrease.

In addition, we carried out sensitivity analysis using the metan-based influ-

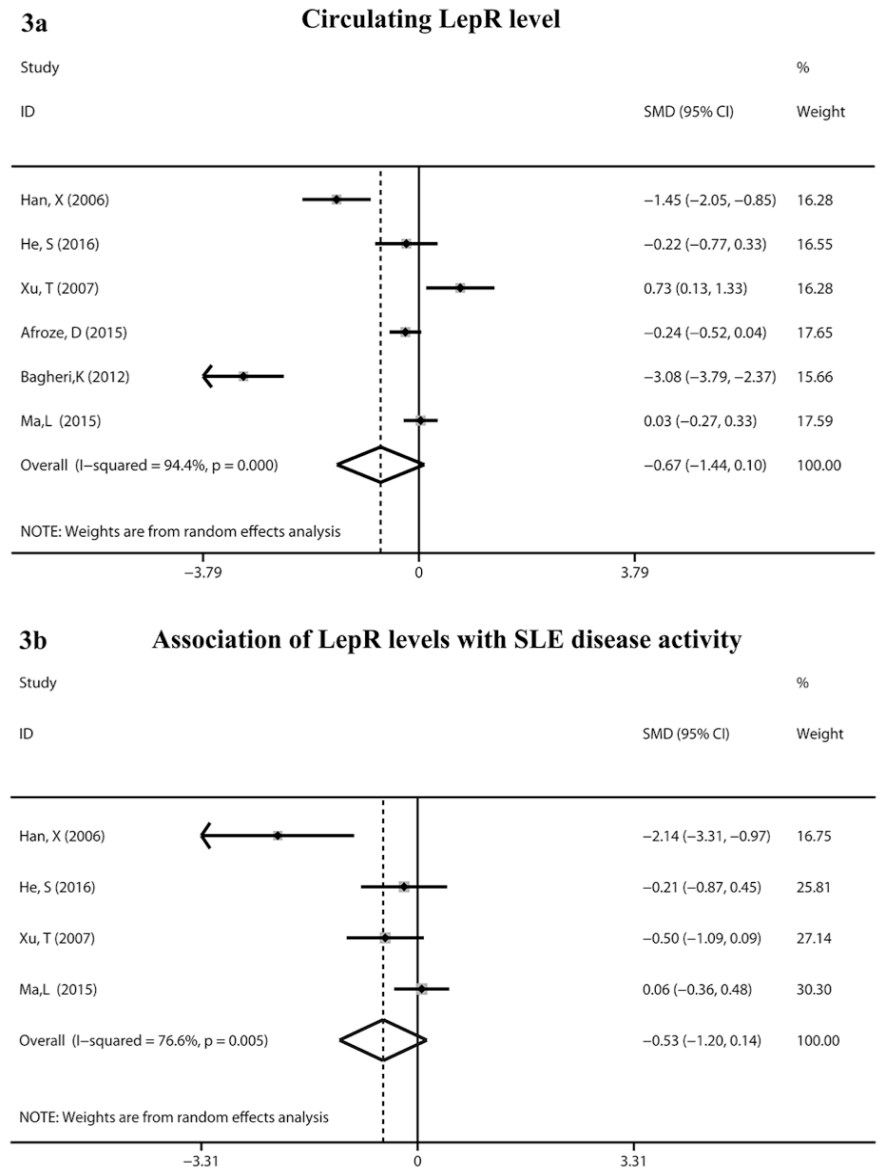

Fig. 3.

ence analysis and the result showed that no individual study significantly affected the pooled SMD of leptin levels (Supplementary Fig. S2) and LepR levels (Suppl. Fig. S3), indicating that the results of this meta-analysis are robust. Funnel plots representing SMD of the leptin level in SLE cases compared to healthy controls was used to evaluate publication bias. Through the visual inspection of the funnel plot, there was obvious asymmetry that indicated a possibility of publication bias, which was supported by the Egger and Begg test (p=0.093, p=0.003) (Suppl. Fig. S4). However, further verification by trim and fill funnel plot showed that this publication bias did not impact the pooled estimates. The pooled data that had been significant before the adjustment with "trim and fill" method remained significant after the adjustment (SMD=0.347, 95%CI (0.048–0.646), p=0.023) (Suppl. Fig. S5).

Discussion

Over the last two decades, leptin has been discovered to play a key role in regulating energy expenditure and neuroendocrine function. In addition to the metabolic role, leptin is increasingly being reported to act as an intricate switch connecting the body's energy stores to high-energy expenditure processes, including tumour, inflammation and autoimmunity (4). The abnormal expression of leptin has been found to correlate with various diseases; however, the exact association between leptin and SLE remains unclear. In 2018, a study by Mohammed *et al*. (17) reported that circulating leptin levels in SLE patients were significantly higher than healthy controls. Meanwhile, Chougule *et al*. (11) reported a contradictory finding that circulating leptin levels were significantly lower in SLE patients. Therefore, it is necessary to perform a comprehensive meta-analysis to clarify the correlation between leptin and SLE by increasing the statistical power. Although in 2015, Li *et al*. carried out a meta-analysis of 11 studies and in 2017, Lee *et al*. performed a meta-analysis of 18 studies, they only reported the association between leptin level and SLE (13, 14).

In this meta-analysis, we combined 34 studies, including 1844 SLE patients and 1511 healthy controls, to evaluate the association between circulating leptin level, LepR level as well as LepR gene (rs1137101) polymorphism and SLE. We found SLE patients showed a significantly higher leptin level and a trend toward a lower LepR level that did not reach statistical significance. However, the heterogeneity of the pooled analysis data was high and the findings should be interpreted with caution. We conducted meta-regression and subgroup analysis by sex, ethnicity, sample size, source and assay method and carried out leave-one-out method to determine the source of heterogeneity. Although the heterogeneity of partial subgroup analysis decreases, it was worth noting that majority of the heterogeneity remained unacceptable. The remained heterogeneity may be attributable to the difference in demographic characteristics (*e.g*. age and BMI), clinical features (*e.g*. lupus nephritis) and drugs used (*e.g*. immunosuppressive agents and antimalarial) in involved SLE patients. In addition, we also found SLE patients with SLEDAI≥10 showed a trend toward a higher leptin level that did not reach significant difference compared to those patients with SLEDAI<10, while the LepR level was no difference between active and inactive SLE patients.

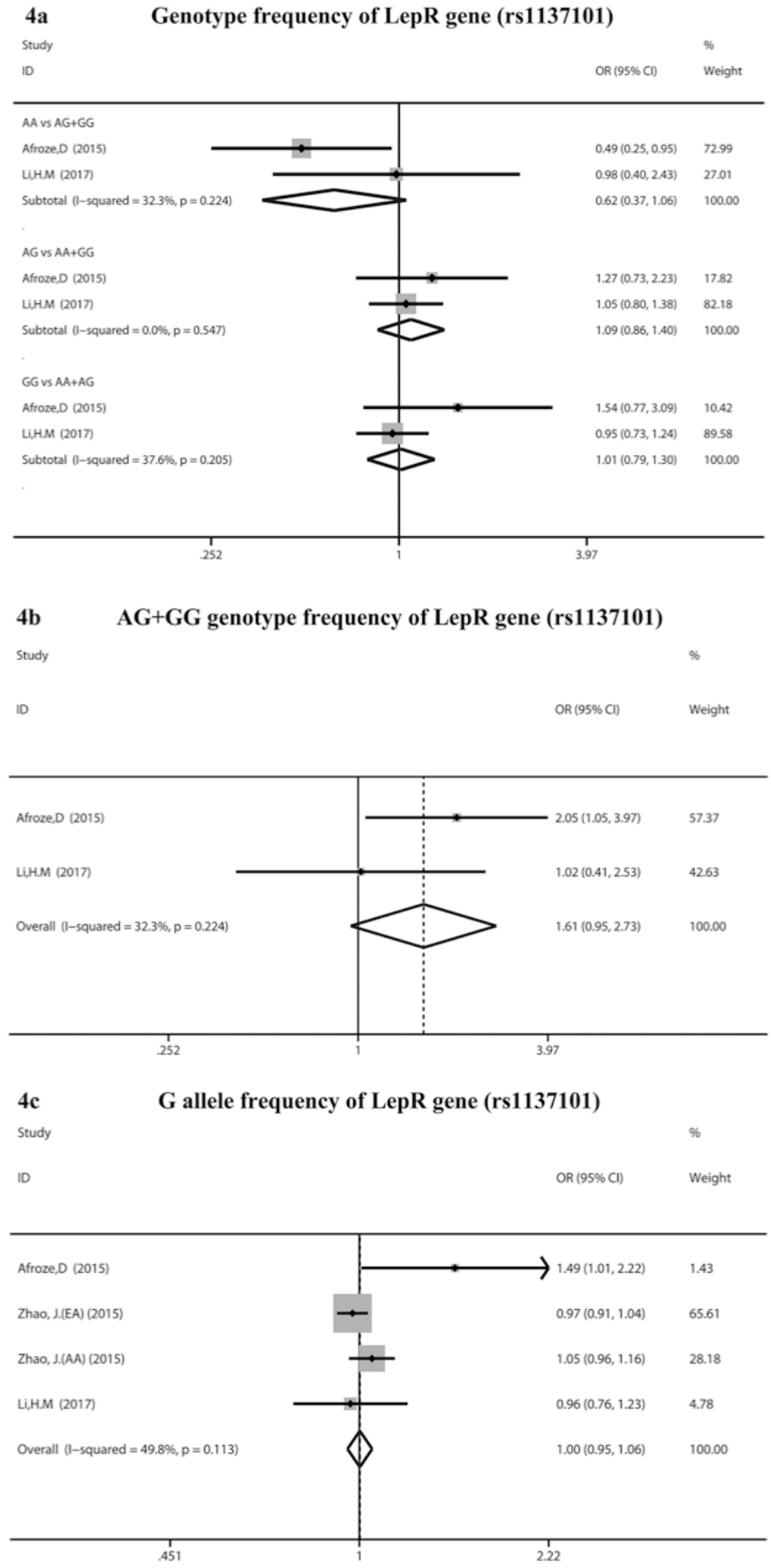

Fig. 4.

The findings regarding the association between elevated leptin level, decreased soluble LepR level as well as reduced frequency of AA genotype of rs1137101 and SLE can be explained by the following. It has been well-established that mononuclear macrophage, neutrophilic granulocytes, T helper cell (Th), regulatory T cell (Treg) and B cell all participate in the onset and/or progression of SLE. Leptin plays the regulatory roles on these immune effector cells in SLE. Leptin acts to promote macrophages secretion of pro-inflammatory cytokines (IL-6, TNF-α and IFN-γ) by upregulating the expression of the macrophage migration inhibitory factor and adhesion factors (*e.g.* CD25, CD39, CD69 and CD71) (46, 47). In addition to this, leptin acts to enhance the phagocytosis of apoptotic cells by macrophages via the downregulation of cAMP levels and the subsequent increase in apoptotic antigens has the potential to enhance the responsiveness of autoreactive T cells, resulting in severe damage to multiple tissues (48, 49). Leptin plays an indirect role in the neutrophils dysfunction in SLE as a consequence of only the short isoform of LepR expressed on the surface of neutrophils (50). Leptin promotes the production of TNF-α by resident mononuclear macrophages and the subsequent increase in TNF-α acts to promote neutrophils production of inflammatory markers (*e.g.* CD11b) via the TNFR1 receptor on the surface of neutrophils (51). CD11b acts as an early marker of neutrophil activation to enhance the release of neutrophil extracellular traps, further exacerbating the exposure of nuclear material to local immune cells and the inflammatory autoimmune environment (52, 53). Leptin also acts to delay T cell apoptosis via the increased expression of BCL-2 (14). It has been reported that leptin promotes Th1 secretion of pro-inflammatory cytokines (*e.g.* IL-2/IL-6/IFN-γ/TNF-α) and inhibits Th2 production of anti-inflammatory cytokines (*e.g.* IL-4/IL-10) (54). In addition to the well-characterised Th1 and Th2 lymphocyte imbalances, leptin acts to promote Th17 differentiation via the activation of IL-6/STAT3/RORγt signalling and inhibit Treg function via the activa-

tion of 5' AMP-activated protein kinase signalling (1). Th17 differentiation and deficiencies of Treg function act as a pivotal role in the pathogenesis of SLE. Leptin also promotes B cell production of autoantibodies and secretion of pro-inflammatory cytokines, further exacerbating tissue damage (55). Thus, leptin may influence the pathogenesis of SLE through above various mechanisms.

Few studies have investigated the underlying correlation between soluble LepR and the pathogenic mechanisms of SLE. LepR gene rs1137101 polymorphism is caused by substitution of A to G at nucleotide number 668 in exon 6 from the start codon 223 (56). The mutation leads to an amino acid change within the region encoding the extracellular domain of the leptin receptor and the subsequent abnormality of protein structure and receptor function. Unsal *et al*. (57) stated that the variant of rs1137101 was associated with varieties in the binding capacity of leptin and increased binding capacity was detected in subjects carrying GG genotype than for carriers of the A allele. Similarly, Abdu Allah *et al*. (56) reported that rs1137101 GG genotype with highly efficient binding capacity to leptin might activate cellular JAK2 / STAT3 signalling, which suggested GG genotype might enhance the role of leptin in the pathogenesis of SLE. However, our results indicated that rs1137101 AG genotype and GG genotype were not associated with the susceptibility to SLE, and AA genotype may be associated with a decreased risk of SLE. Carriers of the variant G allele (*i.e*. AG+GG) have the potential to increase the risk of SLE. In 2018, a study by Khaki-Khatibi *et al*. (58) reported the positive correlation between soluble LepR levels and G allele frequency in non-ST-segment elevation myocardial infarction; however, this association in SLE condition remained to be explored. Numerous studies in various populations indicated that carrying variant G allele of rs1137101 conferred a greater risk of obesity (59), suggesting the potential role of rs1137101 polymorphism in SLE may be attributable to the intricate interplay between G allele frequency, soluble LepR expression and abnormal lipid metabolism. Our pooled results demonstrated that no significant difference as regards the variant G allele frequency of rs1137101 was detected between SLE cases and healthy controls.

The present study has some limitations that should be considered. First, although we have conducted subgroup analysis and sensitivity analysis with leave-one-out method and meta-regression, partial results should be interpreted with caution as a consequence of high heterogeneity. Second, few studies have investigated the correlation between leptin gene polymorphism and SLE. Thus, the limited number of the included studies might be a possible explanation of the non-significant association between AG/GG genotype, variant G allele and SLE risk. More studies are necessary to confirm that AG+GG genotype of rs1137101 may be associated with an increased risk of SLE and mutation of A to G may increase the susceptibility to SLE. Nevertheless, this meta-analysis also has its strengths. Our study included 11 more studies than the 2 previously published meta-analysis as regards the leptin level. In addition, we are the first one to report the relationship between the soluble LepR level, LepR gene polymorphism and SLE by conducting meta-analysis.

In conclusion, elevated leptin levels were found in SLE patients, in particular for active SLE patients, regardless of sample size, source, or assay method. Circulating leptin levels were significantly higher in the SLE group in Asian, African, North American and European instead of South American. Circulating leptin levels were also significantly higher in female SLE group, but not in male SLE group. SLE patients showed decreased trend of LepR levels and increased trend of AG+GG genotype frequencies of LepR (rs1137101). Mutation of A to G at nucleotide number 668 in exon 6 of chromosome 1 may be associated with the increased susceptibility to SLE. A collection of preclinical and clinical studies are still needed to explore the underlying connection and explain these controversial results. In the coming years, leptin and LepR levels are expected to be developed as a novel biomarker of SLE severity. For those people with a family history of SLE, genetic screening of leptin/LepR may aid in assessing susceptibility to SLE and reinforce the need for prevention ahead of time.

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