

# The association between omentin and diabetes: a systematic review and meta-analysis of observational studies

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**Aims:** A number of studies have examined the association between the serum levels of omentin and diabetes, but the findings have been inconclusive. Herein, we systematically reviewed available observational studies to elucidate the overall relationship between omentin and diabetes, including type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and impaired glucose tolerance (IGT) among adolescent and adult population.

**Methods:** PubMed, Cochrane's Library, Science Direct, Scopus, Google Scholar, and ISI Web of Science databases were searched for all available literature until January 2019 for studies assessing the association between omentin and diabetes. The Newcastle–Ottawa Quality Assessment Scale was used to assess the quality of each study.

**Results:** A total of 28 articles met the inclusion criteria and were included in our systematic review and meta-analysis. There was a significant association between serum omentin and diabetes (WMD–1.68; 95% CI, –2.17 to –1.19;  $P<0.001$ ). The result of our sub-group analysis based on participants' health status revealed that omentin was significantly lower in T2DM and IGT subjects but not in T1DM ones compared to healthy controls.

**Conclusion:** We found that serum omentin level is significantly lower in T2DM and IGT patients but not in T1DM ones. These data could be used by clinicians for early diagnosis and management of diabetes. Furthermore, we need more clinical trials to investigate new agents which could influence omentin levels.

**Keywords:** omentin, diabetes, impaired glucose tolerance, systematic review, meta-analysis

## Introduction

It is expected for diabetes prevalence to increase from 171 million individuals in 2000 to 366 million by 2030.<sup>1</sup> Diabetes mellitus could be explained best as a complex, multifactorial, chronic metabolic, and endocrine disorder. It has been traditionally defined by the existence of hyperglycemia that can be produced by flaws in insulin secretion, insulin action, or both.<sup>2</sup> Individuals with diabetes have increased risk of other co-existing complications including myocardial infarction or stroke.<sup>3</sup> Accordingly, sufficient attention to diabetes is needed to be early diagnosed and treated to decrease its undesirable effects.

Recently, adipose tissue has attracted a lot of attention because of its crucial role in human metabolic pathways. Like an endocrine organ, adipose tissue releases a variety of adipokines including leptin, adiponectin, visfatin, TNF- $\alpha$ , and IL-6 [1,2]. These adipokines could control carbohydrate and lipid metabolism and appear to play a vital role in the pathogenesis of insulin resistance, diabetes, inflammation,

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atherosclerosis, and vascular endothelial dysfunction.<sup>4–10</sup> Identification of a novel adipokine associated with diabetes might provide new opportunities for clinicians for early diagnosis and better management of diabetes and its related complications. Omentin (intelectin, intestinal lactoferrin receptor, endothelin lectin HL-1, galactofuranose-binding lectin) is a novel fat depot-specific adipokine identified by Yang et al, in 2003 from a visceral omental adipose tissue cDNA library.<sup>11</sup> There are mainly two isoforms of omentin, omentin-1 and omentin-2, with omentin-1 being the major circulating form in human plasma.<sup>12</sup> Omentin is an anti-inflammatory adipokine and plays a crucial role in regulating insulin sensitivity through paracrine and endocrine factors where it could enhance insulin sensitivity and glucose metabolism.<sup>13</sup> Omentin could only hasten insulin-mediated glucose transport and has no modulating effect on the basal glucose transport which designates that it has no inherent insulin-like activity.<sup>14</sup> Based upon previous reports, plasma omentin levels inversely correlate with body mass index (BMI), fat mass, and fasting plasma insulin, and positively with insulin sensitivity, adiponectin, high-density lipoprotein cholesterol, and endothelial function.<sup>15–18</sup>

However, increasing body of literature has shown paradoxical relationships between serum omentin and diabetes with some studies suggesting a significant association between serum omentin level and diabetes<sup>19–23</sup> while others do not support such an association.<sup>18,24–27</sup> Currently, there is insufficient evidence showing whether serum omentin is related to diabetes, and determination of this relationship has rarely been conducted. To address these issues, we carried out this systematic review and meta-analysis by pooling the results from observational studies to examine the association between serum omentin and different types of diabetes including type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and impaired glucose tolerance (IGT) among adolescent and adult population.

## Methods and materials

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.<sup>28</sup>

## Data source and search strategy

We searched databases including PubMed, Scopus, Cochrane Library, Science direct, and ISI web of sciences up to January 2019 to identify relevant studies. The reference lists of the

included articles were also reviewed to identify additional eligible studies. In order to increase the power of our search strategy and minimize the chance of missing relevant articles, we also contacted expert scientists in the field of diabetes and omentin. The following search strategy was run in PubMed and tailored to each database when necessary: “Diabetes” OR “T2DM” OR “T1DM” OR “glucose tolerance” OR “NIDDM” OR “impaired glucose” OR “impaired fasting glucose” OR “prediabetes” OR “dysglycemia” OR “Diabetes Mellitus” OR “type 2 Diabetes Mellitus” OR “Hyperglycemia” OR “Glucose Tolerance Test” OR “Glucose Intolerance” OR “hyperglycemia” AND “omentin”.

## Inclusion criteria

To be included in the study, publications investigating the association between omentin and diabetes had to meet the following criteria: (1) original articles which examined the association between omentin and glucose metabolism dysfunction including T1DM, T2DM, and IGT; (2) human studies with no restrictions on study parameters (study duration, design, or sample size); (3) adequate data to calculate a relevant measure of association [mean difference, median (Range), and median (interquartile range)]; (4) articles published in English.

## Data extraction

Pairs of independent reviewers screened the titles and abstracts of each study prior to full-text screening of candidate studies. Any discrepancies in terms of decision on a given study were dealt with via discussion and if necessary, arbitration by a third reviewer. For all included studies, two reviewers independently extracted information including first author's name, year of publication, country, sample size, participants' age, gender, BMI, health status, study design, and omentin assay method.

## Study quality

The Newcastle–Ottawa Quality Assessment Scale (NOS) was used to assess the quality of included studies.<sup>29</sup> The scale consists of the assessment of three domains: selection, comparability, and outcome for a total score of 10 points for cross sectional and 9 points for case-control studies. Studies scoring 7–10, 3–6, and 0–3 points were identified as high, moderate, and low quality, respectively.<sup>30</sup>

## Statistical analysis

Statistical analyses were carried out using the STATA software (version 11.0; Stata Corporation). All data were

collected as means  $\pm$  standard deviation (SD) to estimate the pooled effects. Meta-analysis was performed using hedges'g with 95% confidence intervals (CIs) for assessing the association between serum omentin levels and diabetes. All analyses were done using the random effects model which takes the between-study variability into account.<sup>31</sup> The sensitivity analyses were also performed to assess the influence of each individual study on the stability of the meta-analysis results. Each time, one study was excluded to show the impact of that study on the combined effect estimate. We also conducted subgroup analyses based on different factors, including BMI, co-existing disease, participants' health status, and studies location.

### Assessment of heterogeneity

Heterogeneity of the study results was estimated by the chi-squared ( $\chi^2$ ) test and quantified using the  $I^2$  statistic, which represents the percentage of total variation across studies attributable to heterogeneity rather than to chance.  $I^2$  was calculated using the formula:  $I^2 = 100\% \times (Q - df) / Q$  (where  $Q$  is the chi-squared statistic, and  $df$  is the degree of freedom), and an  $I^2$  value of 75% or greater was deemed to indicate a high level of inconsistency. Significant heterogeneity was defined as a  $P$ -value of  $<0.05$ .<sup>30</sup>

### Assessment of publication bias

Publication bias was assessed by visual inspection of the funnel plots, and Egger's and Begg's tests were conducted to determine the degree of funnel plot asymmetry with  $p < 0.05$  representing significant publication bias.<sup>30</sup> When publication bias was found, trim & fill analysis performed to find out the effects of missed study on overall effects.

## Results

### Search results

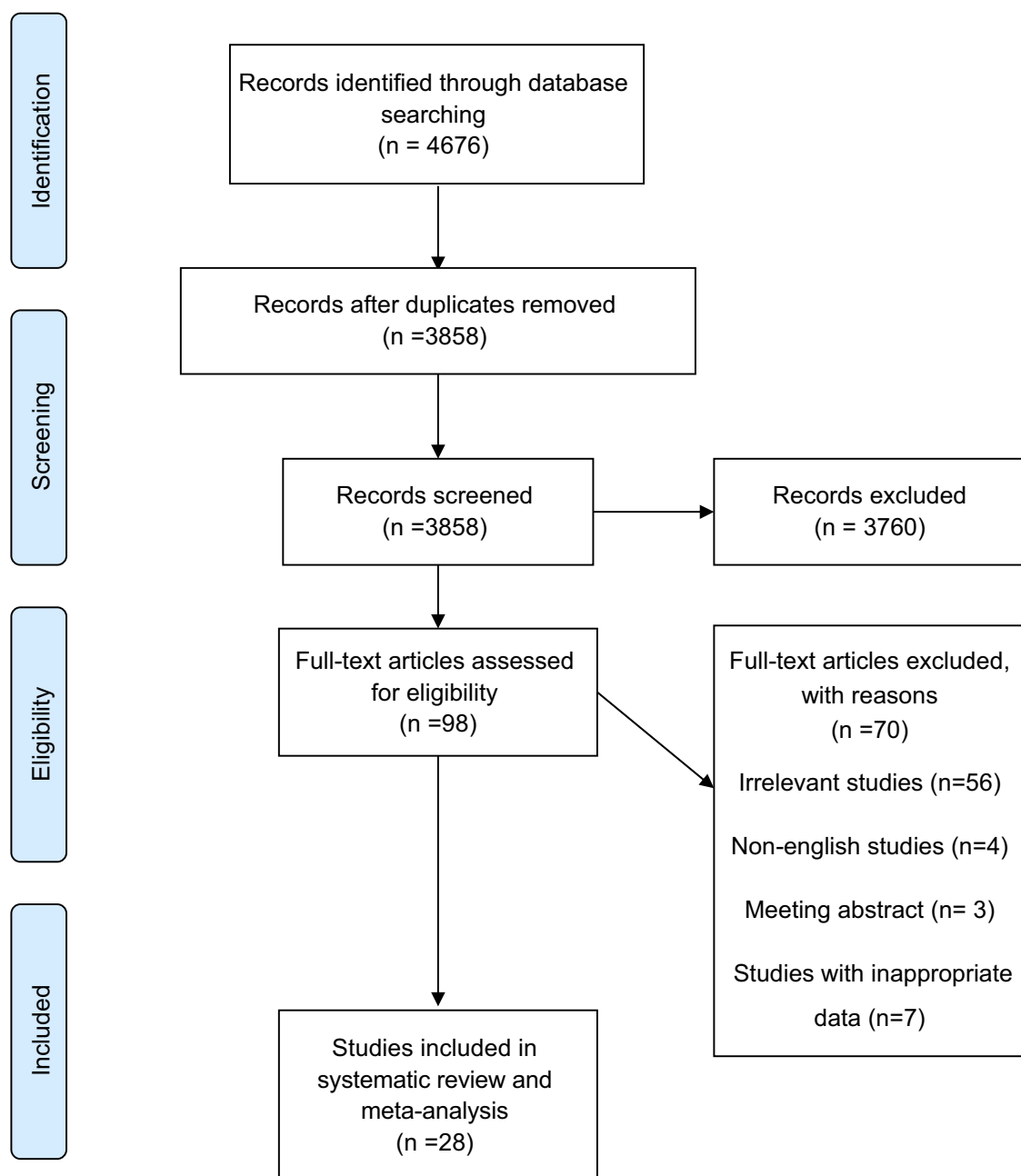
Our initial search through databases identified a total of 4675 articles. Removing duplicates yielded 3857 articles which were reviewed based on the title and abstract by two independent reviewers and 3039 irrelevant studies were excluded at this stage. Ninety-seven papers were retrieved and reviewed based on full text, and 28 articles met the inclusion criteria and were included in our systematic review and meta-analysis. The PRISMA flow diagram summarizes the results of the study selection process for this systematic review and meta-analysis (Figure 1).

## Overview of included studies

The general characteristics of the included studies are shown in Table 1. A total of 28 studies involving 3354 participants were included in our systematic review and meta-analysis with their sample size ranging from 37 to 496 subjects. Selected studies were published between 2008 and 2018. Mean age of the participants ranged between 11 and 67 years. Twenty-one studies recruited both gender,<sup>17,19,22–24,27,32–46</sup> four were conducted only in men,<sup>18,21,25,47</sup> and three used female subjects.<sup>20,26,48</sup> Included studies were conducted in participants with T1DM,<sup>17,32,40</sup> T2DM<sup>22,23,26,27,38,39,41,43–47</sup>, and patients with IGT.<sup>18,21,24,42</sup> Seven studies enrolled normal weight (BMI  $< 24.9$ ) subjects,<sup>23,32,33,36,44–46</sup> 13 recruited overweight participants (24.9  $\leq$  BMI  $\leq$  29.9)<sup>17,18,21,22,25,27,34,38,39,41,43,47,48</sup> and 6 were conducted on obese subjects<sup>20,24,26,35,37,42</sup> but 2 studies did not mention baseline BMI.<sup>19,40</sup> Two studies were cross sectional<sup>35,37</sup> and the others were case-control.<sup>17–27,32–34,36,38–48</sup> Based on the NOS, 10 studies ranked as high-quality<sup>23,27,32,35,37,40,41,43,44,47</sup> and the others as were classified as moderate in quality assessment.

## The association between serum omentin level and diabetes

Twenty-eight studies with 2941 participants examined serum omentin level among patients with diabetes (T1DM, T2DM, and IGT) and healthy subjects.<sup>17–27,32–48</sup> There was a significant association between serum omentin and diabetes (WMD = 1.68; 95% CI,  $-2.17$  to  $-1.19$ ;  $P < 0.001$ ). There was evidence of heterogeneity between the effect sizes of the included studies ( $I^2 = 96.9\%$   $p < 0.001$ ). So, we did sub-group analysis based on the BMI category (normal/overweight/obese), participants' health status (T1DM/T2DM/IGT), co-existing disease (diabetes/diabetes plus other complications), and location (Asia/Europe/Africa). None of these sub-group analyses could reduce heterogeneity. The result of our sub-group analysis based on participants' health status revealed that omentin was significantly lower in T2DM and IGT subjects but not in T1DM ones compared to healthy controls. The results of the sub-group analysis are shown in Table 2. There was evidence of publication bias (Begg's test:  $P < 0.001$ , Egger's test:  $P < 0.001$ ), therefore, we did trim & fill analysis to find out probable missed studies but this method could not add any studies to our included ones



**Figure 1** The flow diagram of study selection.

(Figure 2). The sensitivity analysis showed that removing any of the studies could not substantially change the association between omentin and diabetes.

## Discussion

In order to identify new biomarkers for early diagnosis of diabetes and better management of its progress and complications, various studies have been conducted. However, interpreting the literature to wrap up a final conclusion is such a difficult process for clinicians, comprehensive

systematic review and meta-analysis of available literature can represent the most reliable evidence.<sup>49</sup>

The present study included 28 observational studies which involved a total of 3354 individuals. Present study showed that serum level of omentin was significantly lower in T2DM and IGT subjects but not in T1DM ones compared to healthy controls. Furthermore, sub-group analysis could not reduce heterogeneity or change the overall results. Although overall results revealed a significant association between omentin with T2DM and IGT, there

**Table I** Characteristics of included studies

Author, year	Location	Sample size (F/M)	Age range	BMI	Study design	Assay method	Health status	Quality score
Abd-Elbaky et al., 2016 <sup>47</sup>	Egypt	160 M	40.3±3.6	26.7±0.55	Case-control	ELISA	T2DM	7/9
Zhang et al., 2014 <sup>27</sup>	China	58/62	66.53±10.68	26.07±2.20	Case-control	ELISA	T2DM	7/9
Yoo et al., 2011 <sup>46</sup>	Korea	53/37	54.54±6.99	24.02±2.42	Case-control	ELISA	T2DM	6/9
Yan et al., 2011 <sup>23</sup>	China	51/54	53.8±1.6	24.07±0.49	Case-control	ELISA	T2DM	6/9
Yan et al., 2011 <sup>45</sup>	China	35/25	51.6±8.45	24.05±3.75	Case-control	ELISA	T2DM	7/9
Wan et al., 2015 <sup>44</sup>	China	68/57	58.26±7.95	23.8±2.29	Case-control	ELISA	T2DM + Retinopathy	7/9
Urbanova et al., 2014 <sup>26</sup>	Czech	37 F	49.85±2.5	37.55±1.47	Case-control	ELISA	T2DM	4/9
Tekce et al., 2014 <sup>43</sup>	Turkey	39/52	54.9±10.8	25.7±3.55	Case-control	ELISA	T2DM + CKD	8/9
Tan et al., 2008 <sup>17</sup>	UK	39 M&F	30.2±4.5	25.5±3.1	Case-control	ELISA	T1DM	4/9
Sperling et al., 2016 <sup>42</sup>	Poland	33/31	30–60	38.95±6.05	Case-control	ELISA	IGT	4/9
Pan et al., 2010 <sup>41</sup>	China	68/83	37.99±6.02	25.7±3.74	Case-control	ELISA	T2DM	7/9
Nurten et al., 2018 <sup>40</sup>	Germany	213/283	11.35±4.17	–	Case-control	ELISA	T1DM	7/9
Motawi et al., 2018 <sup>22</sup>	Egypt	72/48	54.95±4.55	27.15±1.55	Case-control	ELISA	T2DM + CAS	6/9
Moreno-Navarrete et al., 2011 <sup>18</sup>	Spain	248 M	53.35±10.85	27.75±3.5	Case-control	ELISA	IGT	6/9
Matloch et al., 2018 <sup>39</sup>	Czech	8/30	67.45±8.76	29.05±4.34	Case-control	ELISA	T2DM + CAD	4/9
Kocijancic et al., 2015 <sup>38</sup>	Croatia	84/36	64.37±13.62	25.25±4	Case-control	ELISA	T2DM + HD	5/9
Gursoy et al., 2010 <sup>48</sup>	Turkey	120 F	53.75±9.45	29.3±5.25	Case-control	ELISA	T2DM	6/9
Kahwaji et al., 2017 <sup>37</sup>	Jordan	131/64	51.26±10.45	33.32±5.47	Cross sectional	–	T2DM + MetS	7/10
Nassif et al., 2013 <sup>36</sup>	Egypt	15/65	43.15±1.77	23.9±0.37	Case-control	ELISA	T2DM + HCV	4/9
Greulich et al., 2013 <sup>25</sup>	Germany	92 M	55.5±6.35	27.85±3	Case-control	ELISA	T2DM	5/9
Gateva et al., 2018 <sup>24</sup>	Bulgaria	68/12	50.4±10.6	37.15±5.65	Case-control	ELISA	IGT	4/9
Flehmig et al., 2014 <sup>35</sup>	Germany	74/67	48±14	46.1±10.1	Cross sectional	ELISA	T2DM	7/10
Elsaid et al., 2018 <sup>20</sup>	Egypt	90 F	46.6±6.7	30.45±4.55	Case-control	ELISA	T2DM	5/9
Dogan et al., 2016 <sup>33</sup>	Turkey	32/28	48.51±5.45	22.69±1.54	Case-control	ELISA	T2DM + CP	5/9
Ahmed et al., 2018 <sup>19</sup>	Egypt	100 M&F	–	–	Case-control	ELISA	T2DM + CVD	4/9
Abd El Dayem et al., 2015 <sup>32</sup>	Egypt	46/46	16.22±2.07	24.83±4.93	Case-control	ELISA	T1DM	7/9
El-Mesallamy et al., 2011 <sup>34</sup>	Egypt	23/67	56.53±2	28.33±0.53	Case-control	ELISA	T2DM + IHD	6/9
Kaushik et al., 2018 <sup>21</sup>	India	150 M	41.1±8.03	26.71±3.09	Case-control	ELISA	IGT	5/9

**Abbreviations:** BMI, body mass index; ELISA, enzyme-linked immunosorbent assay; T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; IGT, impaired glucose tolerance; CKD, chronic kidney disease; CAS, coronary artery stenosis; CAD, coronary artery disease; HD, hemodialysis; MetS, metabolic syndrome; CAN, cardiac autonomic neuropathy; HCV, hepatitis C virus; CP, chronic periodontitis; LAD, latent autoimmune diabetes; CVD, cardiovascular disease; IHD, ischemic heart disease.

are inconsistencies among included studies which should be taken into account when interpreting the results. We found significant heterogeneity in our study, which might be contributed to different population, sample size, omentin assay kit, participants' BMI, and age, presence of other co-existing diseases, subjects' health status and location of studies.

Our analysis failed to show any significant association between omentin and T1DM. The results of previous studies in this sub-group are inconsistent. In other words, some

evidence proved lower level of omentin in T1DM subjects<sup>17,22,32</sup> but Nurten et al, revealed higher levels of this adipokine in these populations.<sup>40</sup> The included studies of this sub-group had high<sup>32,40</sup> and moderate quality.<sup>17,22</sup> Another sub-group of our study included T2DM patients. The analysis proved lower levels of omentin in these populations which is consistent with previous reports,<sup>19,20,33,45</sup> but was not confirmed by some other evidence.<sup>35,39</sup> The quality of included studies was high<sup>23,27,35,37,41,43,44,47,50–52</sup> or moderate.<sup>12,19,20,25,26,33,34,36,38,39,45,46,48,53,54</sup> The last

**Table 2** Result of sub-group analysis of included studies in meta-analysis

Sub-grouped by	No. of trials	Effect size <sup>a</sup>	95% CI	I <sup>2</sup> (%)	P for heterogeneity	P for between sub-group heterogeneity
BMI category						
Normal weight (≤24.9 kg/m <sup>2</sup> )	12	−1.63	−2.45, −0.81	96.9	<0.001	<0.001
Overweight (24.9<BMI≤29.9)	13	−2.09	−2.92, −1.26	97.1	<0.001	
Obese (BMI ≥30)	6	−0.91	−1.8, −0.03	95.5	<0.001	
Health status						
T1DM	5	−1.35	−2.94, 0.23	98.3	<0.001	<0.001
T2DM	22	−1.98	−2.59, −1.36	96.4	<0.001	
IGT	4	−0.60	−1.11, −0.08	83.4	<0.001	
Co-existing disease						
Diabetes	23	−1.44	−1.99, −0.88	97	<0.001	<0.001
Diabetes plus other complications	8	−2.51	−3.68, −1.34	96.5	<0.001	
Location						
Asia	8	−1.19	−1.75, −0.63	92.2	<0.001	<0.001
Europe	15	−0.92	−1.45, −0.38	95.2	<0.001	
Africa	8	−3.32	−4.49, −2.15	95.2	<0.001	

**Note:** <sup>a</sup>Calculated by Random-effects model.

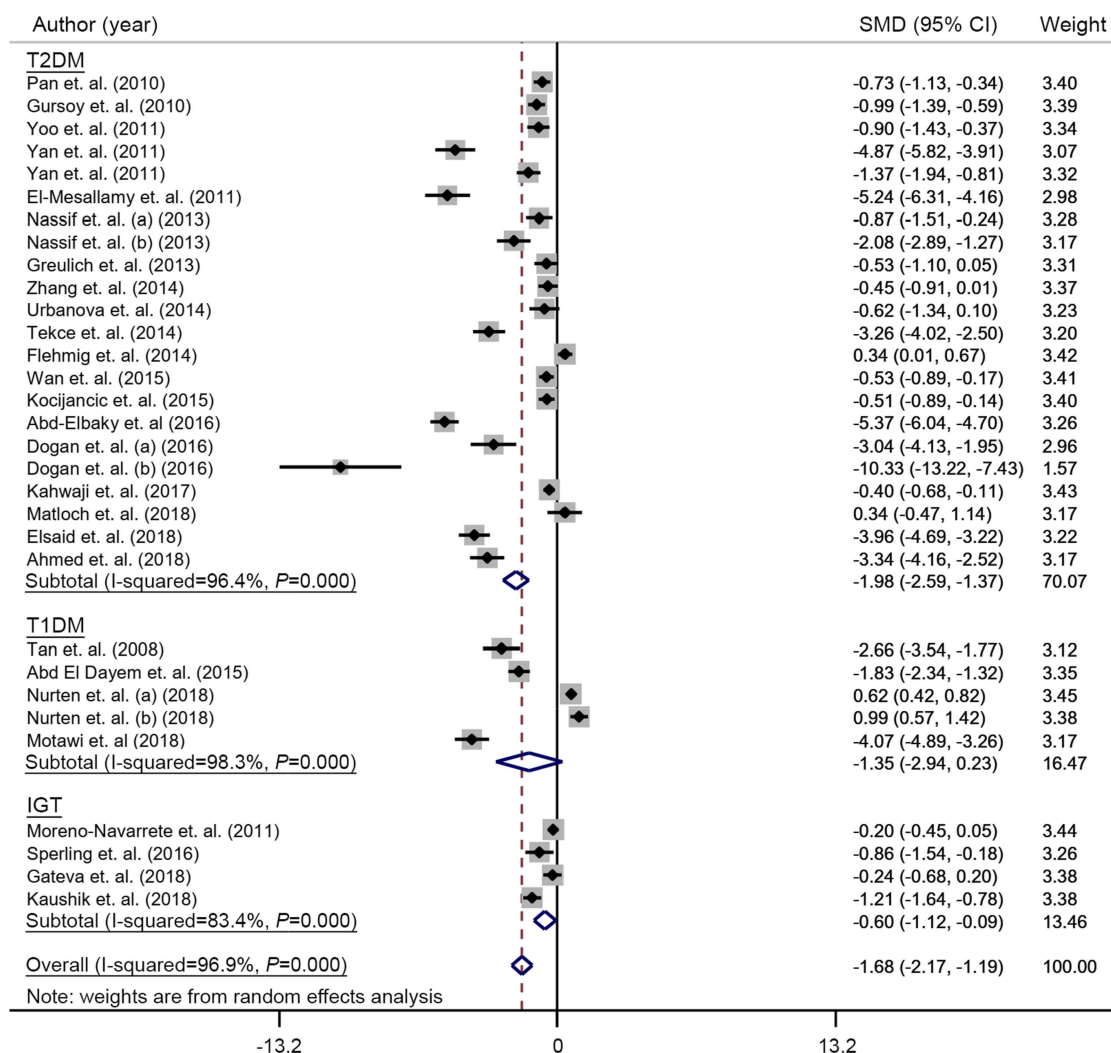
**Abbreviations:** BMI, body mass index; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; IGT, impaired glucose tolerance.

sub-group consisted of patients diagnosed with IGT. Our result revealed that omentin level was significantly lower in these subjects and was consistent with previous evidence,<sup>21</sup> although was not approved by other ones.<sup>18,24</sup> It should be stated that all the included studies in this sub-group ranked as moderate quality.<sup>18,21,24,42</sup> The possible explanation for discrepancies among available literature in each sub-group may be contributed to small sample size, different ethnicity, gender, and stages of diabetes. Insignificant association between omentin and T1DM could be attributed to primary absolute insulin deficiency seen in T1DM patients compared with T2DM patients which is due to lower omentin-1 levels<sup>55</sup> and higher BMI levels in T2DM subjects compared to T1DM patients.<sup>56</sup>

In recent years, visceral adipose tissue and adipokines have attracted lots of attention. Omentin, a novel adipokine, is mainly expressed in visceral adipose tissue and has been suggested as a biomarker of metabolic disease.<sup>57</sup> Based on previous evidence, serum omentin levels were negatively associated with metabolic risk factors. Also, it has been proved that omentin may play a role as an anti-inflammatory and insulin-sensitizing agent.<sup>18,58</sup> Recently, it has been documented that omentin may be associated

with vascular function modulation by endothelium-dependent vasodilation. Recent mechanism may explain the cardioprotective effects of omentin.<sup>18,59</sup> Omentin exerts its anti-atherosclerotic properties by supersession of cytokine-stimulated expression of adhesion molecules in endothelial cells.<sup>60</sup> In vitro studies illustrated that Omentin as a polypeptide hormone increases insulin-stimulated glucose uptake and also Akt phosphorylation in human adipocytes.<sup>14</sup> The Akt pathway is a signal transduction pathway which enhances survival and growth in reaction to extracellular signals. The dysfunction of Akt pathway regulation results in increased signaling activity which could lead to cancer and T2DM.<sup>61</sup> By activating protein kinase B, omentin boosts insulin signal transduction and enhances insulin-mediated glucose transport in adipocytes.<sup>14</sup> Decreased serum omentin level, observed in T2DM patients, could cause a reduction in insulin-stimulated glucose uptake in insulin-sensitive tissues. This may explain the state of insulin resistance present in T2DM.<sup>27,41</sup> It has been reported that glucose and insulin could decrease mRNA expression of omentin and omentin protein production in adipose tissue. This mechanism may indicate that plasma glucose and insulin levels directly or





**Figure 2** Forest plot of the association between the serum omentin levels and diabetes sub-grouped by types of diabetes.

**Abbreviations:** T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; IGT, impaired glucose tolerance.

indirectly modulate omentin synthesis.<sup>17</sup> On the other hand, serum omentin may influence the glucose or insulin levels. So we speculate that the association between omentin, insulin, and glucose might be a mutual relationship.<sup>27</sup>

The present study has some limitations that warrant consideration. First, significant heterogeneity was present in our analysis that would limit the generalization of our findings. Heterogeneity between studies may be explained by different population, sample size, omentin assay kit, participants' BMI and age, presence of other co-existing disease, subjects' health status and location of studies. Moreover, five of the included studies used a cross-sectional design.<sup>35,37,50–52</sup> The nature of cross-sectional studies makes it impossible to draw a causal link between variables. Since, it is a snapshot of the population, it could be altered overtime and included

Neyman's bias (prevalence-incidence bias), which is another form of selection bias and highlighted in longer-lasting disorders.<sup>62</sup> Other studies used case-control design which is prone to selection bias.<sup>63</sup>

There is no previous systematic review and meta-analysis assessing the link between serum omentin level and diabetes including T1DM, T2DM, and IGT in observational studies which could be considered as our study strength.

## Conclusion

According to what was discussed, we found that serum omentin level is significantly lower in T2DM and IGT patients but not in T1DM ones. These data could be used by clinicians for early diagnosis and management of

diabetes. Furthermore, we need more clinical trials to investigate new agents with possible influence on omentin levels.

## Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare no conflicts of interest in this work.

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