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1 **Effect of Dipeptidyl Peptidase-4 Inhibitors on Plasma Adiponectin: A Systematic Review and Meta-Analysis of**
2 **Randomized Controlled Trials**

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17 **Running Title:** DPP-4 and plasma adiponectin

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21

22 **Abstract**

23 **Background/Objectives:** The effect of dipeptidyl peptidase-4 (DPP-4) inhibitors on plasma concentrations of
24 adiponectin, a fat-derived hormone with anti-atherogenic and anti-inflammatory properties, is uncertain. A systematic
25 review and meta-analysis of randomized controlled trials (RCTs) was conducted to investigate this association in
26 humans.

27 **Methods:** RCTs investigating the impact of DPP-4 inhibitors on plasma adiponectin concentrations were identified after
28 searching PubMed-Medline, SCOPUS, and Google Scholar databases (up to February 2015). As quantitative data
29 synthesis methods, the random-effects model and the generic inverse variance method were applied. Standard methods
30 of meta-regression, sensitivity analysis, and publication bias assessments were performed.

31 **Results:** Eight RCTs with nine treatment-arms were included. Meta-analysis did not suggest a significant pooled effect
32 of DPP-4 inhibitors on adiponectin values (weighed-mean-difference [WMD]: 0.19 µg/mL, 95%CI: -0.50, 0.88).
33 However, a significant elevation of plasma adiponectin concentrations was observed in the subset of trials with
34 vildagliptin (WMD: 0.55 µg/mL, 95%CI: 0.13, 0.98, $p=0.010$) but not sitagliptin (WMD: -0.06 µg/mL, 95%CI: -1.13,
35 1.00, $p=0.907$). There was a significant elevation of plasma adiponectin levels in the subset of trials comparing DPP-4
36 inhibitors versus placebo or no treatment (WMD: 0.74 µg/mL, 95%CI: 0.36, 1.12, $p <0.001$) but not in the subset using
37 hypoglycemic drugs as comparators), or using other hypoglycemic drugs (WMD: -0.18 µg/mL, 95%CI: -0.99, 0.62,
38 $p=0.654$). No significant effect was found for treatment duration, confirmed by meta-regression analyses.

39 **Conclusions:** DPP-4 inhibitors cause a significant increase in plasma adiponectin concentrations and this effect is
40 greater with vildagliptin than sitagliptin.

41

42

43 **Keywords:** Adiponectin; Cardiovascular diseases; Dipeptidyl peptidase-4 inhibitors; Meta-analysis; Systematic review;
44 Type 2 diabetes mellitus.

45

46 **1. Introduction**

47 Incretins are gastrointestinal hormones released in response to food intake to increase insulin secretion [1]. Glucagon-
48 like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are the two gut peptides accounting for
49 most of the incretin effects; both stimulate in a glucose-dependent manner the secretion of insulin, delay gastric
50 emptying, increase satiety, decrease adipogenesis, and enhance adipokine expression [1-3]. GLP-1 inhibits the secretion
51 of glucagon by α -cells, thus reducing hepatic glucose production [1]. The enzyme dipeptidyl peptidase-4 (DPP-4) is
52 responsible for the rapid proteolytic cleavage of GLP-1 and GIP to inactive metabolites [4]. DPP-4 inhibitors are a new
53 drug class that delay endogenous degradation of GLP-1 and GIP and produce approximately a 2-fold increase in the
54 concentrations of these gut peptides [1,5-6]. Currently available DPP-4 inhibitors include sitagliptin, vildagliptin,
55 saxagliptin, teneligliptin, anagliptin, **dutogliptin**, alogliptin, and linagliptin. Among these, sitagliptin and vildagliptin are
56 the most frequently used.

57 A large body of literature has shown that DPP-4 inhibitors exert beneficial effects in type 2 diabetes by improving β -
58 cell function, ameliorating both fasting and postprandial glucose values, reducing insulin resistance, decreasing body
59 weight, inflammatory markers, oxidative stress and LDL-cholesterol, and increasing HDL-cholesterol and vascular
60 endothelial function [7-15]. Therefore, cardioprotective effects have been proposed for this class of drugs [3,5,16-19],
61 however, findings from large trials and recent meta-analyses have not supported cardiovascular (CV) benefits for DPP-
62 4 inhibitors [20-22].

63 Among the supposed CV benefits of these drugs, many glucose-independent effects are included, such as the increased
64 circulating levels of incretins and activity of B-type natriuretic peptide, neuropeptide Y, stromal cell-derived factor 1-
65 alpha, and the effects on endothelial function and adipokine concentrations [12,17,23-25]. Adiponectin is a fat-derived
66 hormone with anti-atherogenic and anti-inflammatory properties; its concentrations decrease in obesity and are
67 inversely associated with visceral fat mass, insulin resistance, glucose intolerance, dyslipidemia, chronic subclinical
68 inflammation and oxidative stress [26-27]. Furthermore, decreased levels of adiponectin have been related with an
69 increased risk of CV diseases and vascular injury, while increased values are associated with lower risk of myocardial
70 infarction and significantly predicted a lower risk of future CV events in men [28-29].

71
72 The effects of DPP-4 inhibitors on circulating adiponectin levels are highly **uncertain**, since either an increase [9-10,13-
73 14,24-25] or no effects [8,15,26,30] have been reported.

74
75 The aim of this study was to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) in
76 order to investigate the effect of the treatment with DPP-4 inhibitors on the plasma concentrations of adiponectin in
77 humans.

78
79 **2. Methods**

80 *2.1 Search Strategy*

81 A similar research approach has been used and described in previous original articles [31-34]. Briefly, this study was
82 designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analysis
83 (PRISMA) statement [35], SCOPUS (<http://www.scopus.com>), Medline (<http://www.ncbi.nlm.nih.gov/pubmed>) and
84 Google Scholar (<http://www.scholar.google.com>) databases were searched using the following search terms in titles and
85 abstracts (also in combination with MESH terms): (“dipeptidyl peptidase 4” OR “dipeptidyl peptidase IV” OR DPP-4

86 OR DPP-IV OR sitagliptin OR saxagliptin OR vildagliptin OR linagliptin OR dutogliptin OR alogliptin OR
87 **teneligliptin OR anagliptin**) AND (adiponectin). The wild-card term “*” was used to increase the sensitivity of the
88 search strategy. No language restriction was used in the literature search. The search was limited to studies in humans.
89 The literature was searched from inception to February 21, 2015.

90

91 *2.2 Study Selection*

92 Original studies meeting the following inclusion criteria were selected: (i) randomized controlled clinical trials with
93 either parallel or cross-over design, (ii) investigating the impact of DPP-4 inhibitors, either as monotherapy or
94 combination therapy, on plasma/serum concentrations of adiponectin, (iii) treatment duration of at least two weeks, (iv)
95 providing sufficient information on adiponectin concentrations at baseline and end of trial in both treatment and control
96 groups or the net change values. Exclusion criteria were (i) lack of a control group in the study design, (ii) observational
97 studies with case-control, cross-sectional or cohort design, and (iii) lack of sufficient information on baseline or end of
98 trial adiponectin concentrations.

99

100 *2.3 Data extraction*

101 After reviewing eligible studies, the following data were abstracted: 1) first author's name; 2) publication date; 3) study
102 location; 4) study design; 5) number of participants in the DPP-4 and control groups; 5) dose and duration of treatment
103 in the treatment group; 6) drugs used in the control group; 7) age, gender, and body mass index (BMI) of study
104 participants; 8) prevalence of coronary heart disease and hypertension; and 9) baseline and end of trial plasma
105 concentrations of adiponectin.

106

107 *2.4 Quality assessment*

108 A systematic assessment of bias in the included studies was performed using the following Cochrane criteria [36]:
109 adequacy of sequence generation, allocation concealment, blinding, addressing of dropouts (incomplete outcome data),
110 selective outcome reporting, and other potential sources of bias. Based on the Cochrane Handbook recommendations, a
111 judgment of “yes” indicated low risk of bias, while “no” indicated high risk of bias. Labeling an item as “unclear”
112 indicated an unclear or unknown risk of bias.

113

114 *2.5 Quantitative Data Synthesis*

115 Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [37]. Net changes
116 in measurements (change scores) were calculated as follows: measure at end of follow-up – measure at baseline. For
117 cross-over trials, net change in plasma concentrations of adiponectin were calculated by subtracting the value after
118 control intervention from that reported after treatment. All values were calculated in percentage changes from baseline
119 levels. Standard deviations (SDs) of the mean difference were calculated using the following formula: $SD = \text{square root}$
120 $[(SD_{\text{pre-treatment}})^2 + (SD_{\text{post-treatment}})^2 - (2R \times SD_{\text{pre-treatment}} \times SD_{\text{post-treatment}})]$, assuming a correlation coefficient (R) = 0.5. If
121 the outcome measures were reported in median and inter-quartile range, mean and standard SD values were estimated
122 using the method described by Hozo et al. [38]. When standard error of the mean (SEM) was only reported, standard
123 deviation (SD) was estimated using the following formula: $SD = SEM \times \text{sqrt}(n)$, where n is the number of subjects.
124 When the results were presented in multiple time points, only data relating to the longest duration of treatment were
125 considered.

126 In order to compensate for the heterogeneity of studies in terms of demographic characteristics of the included
127 populations and also differences in study design, the random-effects model (using Der Simonian-Laird method) and the
128 generic inverse variance method were applied. Heterogeneity was quantitatively assessed using I^2 index. Effect sizes
129 were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). In order to evaluate the
130 influence of each study on the overall effect size, sensitivity analysis was conducted using leave-one-out method, i.e.
131 removing one study each time and repeating the analysis [39-40].

132

133 *2.6 Meta-regression*

134 Random-effects meta-regression was performed using unrestricted maximum likelihood method to evaluate the
135 association between calculated WMD and potential moderators including duration of treatment with DPP-4 inhibitors.

136

137 *2.7 Publication bias*

138 Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, fail-safe N test, and
139 Begg's rank correlation and Egger's weighted regression tests. Duval & Tweedie "trim and fill" method was used to
140 adjust the analysis for the effects of publication bias [41].

141

142 **3. Results**

143 *3.1 Flow and characteristics of included studies*

144 With the initial literature search, 189 articles were found (**Figure 1**). All these records were screened, and 132 did not
145 meet the inclusion criteria. The full text of the remaining 11 studies was carefully assessed for eligibility and 8 were
146 selected for the meta-analysis because they satisfied the inclusion criteria. Reasons for rejecting the other 3 articles
147 were: lack of comparison group, short treatment duration (< 2 weeks). A total number of 810 subjects were included in
148 the 8 eligible studies, comprising 423 individuals treated with DPP-4 inhibitors alone [15,30] or in combination with
149 metformin [9-10,13-14], pioglitazone [8], biguanides/sulfonylureas [25], miglitol [30], and 387 individuals treated with
150 placebo or other oral hypoglycemic drugs (**Table 1**). Overall, we have evaluated 8 eligible studies with 9 treatment
151 arms. The largest study had a population size of 178 subjects [10], while the smallest study recruited only 26 subjects
152 [25]. Included studies were published between 2010-2014 and were conducted in Italy [8-10,14], Japan [15,25,30], and
153 Germany [13]. The following DPP-4 inhibitors were used: sitagliptin [8,10,15,25,30] and vildagliptin [9,13-14]. The
154 duration of DPP-4 inhibitors therapy was variable, ranging from 3 months [25] to 12 months [8-10,15]. All these
155 randomized trials had a parallel design; only two were placebo-controlled [9-10], the others compared DPP-4 inhibitors
156 with other oral hypoglycemic drugs [8,13-15,25,30]. The inclusion criteria were quite homogeneous: most patients were
157 affected by poorly controlled type 2 diabetes [8-10,14,25]. The demographic and baseline biochemical parameters of
158 the included studies are shown in Table 1.

159

160 *3.2 Risk of bias assessment*

161 Some of the analyzed studies provided insufficient information about randomization procedures (**Table 2**). Similarly,
162 blinding of participants or researchers was often inadequate or absent [13,15,25,30]. Furthermore, most study designs
163 did not include a placebo arm [8,13-15,25,30] and two studies had baseline imbalance in the patient characteristics
164 [25,30]. However, all studies appeared to be free of selective outcome reporting.

165

166 3.3 Effect of DPP-4 inhibitors on plasma adiponectin concentrations

167 Meta-analysis did not suggest a significant pooled effect (WMD: 0.19 $\mu\text{g/mL}$, 95% CI: -0.50, 0.88, $p=0.597$).
168 However, this result was sensitive to one study [8]. After excluding the referred trial from the analysis, a significant
169 increase in plasma adiponectin levels was found (WMD: 0.58 $\mu\text{g/mL}$, 95% CI: 0.27, 0.89, $p<0.001$) (**Figure 2**). When
170 the studies were categorized according to the type of DPP-4 inhibitor used, there was a significant elevation of plasma
171 adiponectin levels in the subset of trials with vildagliptin (WMD: 0.55 $\mu\text{g/mL}$, 95% CI: 0.13, 0.98, $p=0.010$) but not
172 sitagliptin (WMD: -0.06 $\mu\text{g/mL}$, 95% CI: -1.13, 1.00, $p=0.907$) (**Figure 3 A and B**). With respect to treatment duration,
173 there was no significant treatment effect in either subgroup of trials lasting <48 (WMD: 0.27 $\mu\text{g/mL}$, 95% CI: -0.26,
174 0.81, $p=0.313$) or ≥ 48 weeks (WMD: 0.16 $\mu\text{g/mL}$, 95% CI: -1.06, 1.38, $p=0.802$) (**Figure 3 C and D**). Finally, there
175 was a significantly greater effect of DPP-4 inhibitors on plasma adiponectin concentrations when compared against
176 placebo (or no treatment) (WMD: 0.74 $\mu\text{g/mL}$, 95% CI: 0.36, 1.12, $p<0.001$) rather than active control (WMD: -0.18
177 $\mu\text{g/mL}$, 95% CI: -0.99, 0.62, $p=0.654$) (**Figure 3 E and F**).
178

179 3.4 Meta-regression

180 Random-effects meta-regression was performed to assess if the adiponectin response to DPP-4 inhibitors is associated
181 with duration of treatment. The results did not suggest any significant association between the changes in plasma
182 concentrations of adiponectin and duration of treatment (slope: -0.003; 95% CI: -0.04, 0.04; $p=0.883$) (**Figure 4**).
183

184 3.5 Publication bias

185 The funnel plot of the study standard error by effect size (WMD) was slightly asymmetric, suggesting potential
186 publication bias in the meta-analysis (**Figure 5**). Using “trim and fill” correction, one potentially missing RCT was
187 imputed on the left side of funnel plot, yielding an effect size of 0.06 (95% CI: -0.56, 0.67). Egger’s linear regression
188 (intercept = 0.58, standard error = 1.29; 95% CI = -2.49, 3.64, $t=0.45$, $df=7$, two-tailed $p=0.670$) and Begg’s rank
189 correlation tests (Kendall’s Tau with continuity correction = -0.31, $z=1.15$, two-tailed $p\text{-value}=0.251$) did not suggest
190 any potential publication bias.
191

192 4. Discussion

193 Findings from the current meta-analysis of randomized controlled trials suggested that treatment with DPP-4 inhibitors
194 was associated with a modest increase in plasma adiponectin levels in patients with type 2 diabetes. This effect was
195 evident for vildagliptin but not sitagliptin, and also in trials comparing DPP-4 inhibitors versus placebo but not other
196 hypoglycemic drugs. The duration of treatment did not affect the results.

197 **In most [24,42-45], but not all [46-47] experimental animal models, treatment with DPP-4 inhibitors has been shown to
198 increase plasma adiponectin concentrations. Similarly, most open-label human studies [12,48-49] but not all [11,50]
199 have suggested an improvement in vascular endothelial function and circulating adiponectin levels after the use of
200 DPP-4 inhibitors.**

201 Many potential mechanisms have been hypothesized to explain this effect. There is evidence indicating that treatment
202 with DPP-4 inhibitors improves weight loss and decreases inflammation and oxidative stress in type 2 diabetic patients
203 [11]. Nevertheless, the increase in adiponectin concentrations after therapy with DPP-4 inhibitors has been reported
204 without change in body weight [13,25], and DPP-4 inhibitors do not usually promote weight loss [1]. In rats, DPP-4
205 inhibitors were found to increase the mRNA expression of adiponectin receptor 1, the receptor of adiponectin more

206 abundantly expressed in muscles [45]. DPP-4 is considered as a new adipokine released by fully differentiated
207 adipocytes, above all by visceral fat, and its levels are inversely correlated with adiponectin concentrations [51].
208 Therefore, inhibiting DPP-4 by DPP-4 inhibitors may potentially increase adiponectin levels. Furthermore, adiponectin
209 levels are inversely associated with insulin resistance [28], and the insulin sensitizing effects of the DPP-4 inhibitors
210 [42], as well as other pharmacologic and non-pharmacologic insulin sensitizing approaches [52-53], might beneficially
211 impact on adiponectin concentrations. Reduction of oxidative stress by DPP-4 inhibitors [11,25] is another possible
212 mechanism, since increase in systemic and/or local oxidative stress reduce adiponectin production [25]. Finally, the
213 effects of DPP-4 inhibitors on adiponectin values could be mediated by the increased concentrations of GLP-1.
214 Exendin-4, a GLP-1 receptor agonist, has been shown to promote adiponectin secretion by increasing adiponectin
215 mRNA expression in high fat-fed rats and, via the protein kinase-A pathway, in 3T3-L1 adipocytes [54-55].
216 DPP-4 inhibitors have been reported to improve vascular endothelial dysfunction, a marker of the very early stage of
217 atherosclerosis, both in experimental and human studies. In animals, these drugs enhance nitric oxide (NO)
218 bioavailability [56-57], attenuate intimal hyperplasia in response to vascular injury, reduce atherosclerotic lesions
219 [44,58-59], and augment neovascularization by increasing circulating endothelial progenitor cells [60]. In humans,
220 DPP-4 inhibitors stimulate ischemia-induced revascularization through endothelial NO synthase (eNOS) signaling [24],
221 and reverse vascular endothelial dysfunction by increasing flow-mediated dilatation [12,48,61]. In many of these
222 studies, the increase in adiponectin concentrations is the relevant factor responsible for the protective action of DPP-4
223 inhibitors on endothelial dysfunction [12,24,44,48]. Adiponectin stimulates NO production by eNOS, plays anti-
224 inflammatory roles, and favorably impacts on lipid and glucose metabolism. Consistent with all these effects,
225 hypoadiponectinemia has been proposed as a risk factor for the development of cardiovascular diseases [26-29,62].
226 Therefore, increased adiponectin levels might be one of the mechanisms of the pleiotropic effects of DPP-4 inhibitors.
227 Other beneficial effects include reduction of glucose values, insulin resistance, oxidative stress, LDL-cholesterol, and
228 increase of HDL-cholesterol and vascular endothelial function [7-15]. **Furthermore, DPP-4 inhibitors exert strong anti-**
229 **inflammatory actions both in animals and in humans, by decreasing the activity and concentrations of interleukin-1 β ,**
230 **interleukin-6, tumor necrosis factor- α , C-reactive protein, and by the inhibition of T cell migration [14,46,55,63-68].**
231 Cardio-protective benefits have therefore been proposed for this class of drugs.
232 Human studies in type 2 diabetic patients treated with DPP-4 inhibitors have reported decreased atherosclerosis
233 progression [69], mitigation of myocardial dysfunction during dobutamine stress echocardiography [70-71], while the
234 administration of stromal cell-derived factor 1-alpha, whose biological activity is augmented by DPP-4 inhibitors,
235 resulted in clinical improvements in patients with ischemic cardiomyopathy [72]. These results have been confirmed in
236 many experimental and animal studies, and human long-term CV outcome trials in patients with type 2 diabetes are
237 ongoing [4-5,16-17,19,23].
238 In contrast to the favorable results observed in experimental and short-term clinical studies, data from longer clinical
239 trials are, however, disappointing, since two large RCTs in patients with type 2 diabetes and CV diseases or at high risk
240 of adverse CV events showed that DPP-4 inhibitors neither increased nor decreased CV outcomes [20-21]; furthermore,
241 the rate of hospitalization for heart failure was increased with saxagliptin [20]. Therefore, the CV efficacy of DPP-4
242 inhibitor **isn't yet fully known** and warrants further investigation.
243
244 Our subgroup analysis revealed a significant elevation of plasma adiponectin levels in the subset of trials with
245 vildagliptin, but not sitagliptin, suggesting a specific effect rather than a class effect of DPP-4 inhibitors. The

246 pharmacodynamic profile of all DPP-4 inhibitors is similar across the drug class, with minor pharmacokinetic
247 differences [6,18,22]. However, reduced daily glucose fluctuations have been reported with vildagliptin compared with
248 sitagliptin [11,73], and this led to a greater increase in GLP-1 and β -cell response, and reduction of plasma levels of
249 glucagon, nitrotyrosine, and inflammatory markers [11]. Differences in the binding properties of these drugs (sitagliptin
250 binds non-covalently to the enzyme, while vildagliptin forms a covalent adduct, with a stable and longer inhibition), and
251 a hypothesized better bioavailability might justify the differential effects of these two DPP-4 inhibitors on plasma
252 adiponectin levels [11]. Indeed, a significant benefit of vildagliptin, but not of other DPP-4 inhibitors, has been found in
253 the reduction of stroke risk [22], and intima-media thickness [69]. Longer follow-up studies, comparing the effects of
254 specific DPP-4 inhibitors are needed to better characterize the effects of these drugs on the risk of CV endpoints;
255 adiponectin concentrations should be evaluated too, since this adipokine might play a role on the differential CV
256 benefits of the DPP-4 inhibitors.

257

258 *4.1 Limitations*

259 The present meta-analysis has potential limitations that should be mentioned. The included studies were heterogeneous,
260 generally short-term (≤ 6 months), and with small population sizes. Only two types of DPP-4 inhibitors were assessed in
261 the included trials, thus the impact of other members of this drug class on adiponectin status remains elusive.

262 Furthermore, most of included studies were not primarily designed to assess the effects of DPP-4 inhibitors on
263 adiponectin concentrations. Finally, the number of trials that were included was relatively few, which made it difficult
264 to assess any dose-response relationship.

265

266 *4.3 Conclusions*

267 Findings from the present meta-analysis of RCTs showed a significant increase in the values of plasma adiponectin
268 concentrations following treatment with vildagliptin, thus suggesting another aspect of the pleiotropic properties of
269 DPP-4 inhibitors. While waiting the results from ongoing long-term trials on CV outcomes, this meta-analysis adds a
270 small piece of evidence to the existing knowledge about the efficacy of DPP-4 inhibitors in type 2 diabetic patients.

271

272 **Abbreviations**

273 CI= confidence interval, CMA= Comprehensive Meta-Analysis, CV= cardiovascular, DPP-4= dipeptidyl peptidase-4,
274 GIP= glucose-dependent insulinotropic polypeptide, GLP-1= Glucagon-like peptide-1, SD= standard deviation, RCTs=
275 randomized controlled trials, SEM= standard error of the mean, WMD= weighted mean difference.

276

277 **Conflicts of interest:** none.

278

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492

493 **Figure captions**

494

495 **Figure 1.** Flow chart of the number of studies identified and included into the meta-analysis.

496 **Figure 2.** Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of DPP-4
497 inhibitors on plasma adiponectin concentrations. Lower plot shows leave-one-out sensitivity analysis.

498 **Figure 3.** Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of DPP-4
499 inhibitors on plasma adiponectin concentrations in trials with vildagliptin (A), trials with sitagliptin (B), trials lasting <
500 48 weeks (C), trials lasting \geq 48 weeks (D), placebo-controlled trials (E) and active-controlled trials (F).

501 **Figure 4.** Meta-regression plots of the association between mean changes in plasma adiponectin concentrations and
502 duration of treatment with DPP-4 inhibitors. The size of each circle is inversely proportional to the variance of change.

503 **Figure 5.** Funnel plot detailing publication bias in the studies reporting the impact of DPP-4 inhibitors on plasma
504 adiponectin concentrations. Open diamond represents observed effect size; closed diamond represents imputed effect
505 size.

506

Table 1. Demographic characteristics of the included studies.

Study	Derosa⁸, 2010	Derosa¹⁰, 2012	Derosa⁹, 2012	Forst¹³, 2013	Hibuse²⁵, 2014	Shimoda¹⁵,2014	Derosa¹⁴, 2014	Mikada³⁰, 2014
Location	Italy	Italy	Italy	Germany	Japan	Japan	Italy	Japan
Design	Randomized double-blind trial	Randomized double-blind placebo-controlled trial	Randomized double-blind placebo-controlled trial	Randomized open-label trial	Randomized controlled trial	Randomized open-label trial	Randomized double-blind controlled trial	Randomized open-label trial
Duration	12 months	12 months	12 months	24 weeks	3 months	12 weeks	6 months	24 weeks
Inclusion criteria	Poorly controlled T2DM patients	Poorly controlled T2DM patients	Poorly controlled T2DM patients	T2DM patients	Poorly controlled T2DM patients	T2DM patients	Poorly controlled T2DM patients	Overweight T2DM patients
Intervention	Treatment pioglitazone + sitagliptin 100 mg Controls pioglitazone + metformin	Treatment metformin+ sitagliptin 100 mg Controls metformin+ placebo	Treatment metformin+ vildagliptin 100mg Controls metformin+ placebo	Treatment metformin+ vildagliptin 100mg Controls metformin+ glimepiride	Treatment sitagliptin 25/100 mg ± biguanides/sulfonylureas Controls biguanides and/or sulfonylureas	Treatment sitagliptin 50/100 mg Controls glimepiride	Treatment metformin+ vildagliptin 100 mg Controls metformin+ glimepiride	Arm 1° Sitagliptin 50 mg Arm 2* Sitagliptin 50 mg+miglitol Controls# miglitol
Participants	Treatment 75 Controls 76	Treatment 91 Controls 87	Treatment 84 Controls 83	Treatment 22 Controls 22	Treatment 16 Controls 10	Treatment 25 Controls 25	Treatment 83 Controls 70	Arm 1 14 Arm 2 13 Controls 14
Age (years)	Treatment 57±5 Controls 58±6	Treatment 56±9 Controls 55±8	Treatment 54±8 Controls 52±7	NS	Treatment 63 (2) Controls 56 (5)	Treatment 64±10 Controls 62±14	Treatment 60±10 Controls 57±9	Arm 1 59±12 Arm 2 61±12

Gender (M/F)	Treatment 37/38 Controls 39/37	Treatment 42/49 Controls 44/43	Treatment 42/42 Controls 43/40	NS	Treatment 9/7 Controls 6/4	Treatment 16/9 Controls 15/10	Treatment 42/44 Controls 36/34	Controls 59±7 Arm 1 11/3 Arm 2 7/6 Controls 11/3
BMI (kg/m²)	Treatment 27.9±1.5 Controls 27.7±1.3	Treatment 28.1±1.2 Controls 28.9±2.0	Treatment 27.9±1.5 Controls 27.8±1.4	NS	Treatment 24.9 (1.2) Controls 28.1 (1.4)	Treatment 24.9±4.1 Controls 25.3±3.6	Treatment 27.9±1.6 Controls 27.7±1.3	Arm 1 28.8±2.5 Arm 2 28.3±2.5 Controls 29.5±5.5
Smokers (%)	Treatment 36 Controls 39	Treatment 24 Controls 26	Treatment 23 Controls 25	NS	NS	NS	Treatment 30 Controls 30	NS
Glucose (mg/dL)	Treatment 143±19 Controls 142±18	Treatment 143±16 Controls 141±13	Treatment 141±15 Controls 139±14	Treatment 151±27 Controls 148±34	Treatment 142 (6) Controls 156 (10)	Treatment 142±32 Controls 145±33	Treatment 140±18 Controls 139±16	Arm 1 135±23 Arm 2 144±29 Controls 133±22
Insulin (μU/mL)	Treatment 18.4±3.6 Controls 18.2±3.4	Treatment 18.1±4.2 Controls 18.4±4.5	Treatment 17.9±4.2 Controls 17.3±3.9	Treatment 12.9±6.7 Controls 12.9±7.2	NS	Treatment 8.0±4.6 Controls 8.3±5.0	Treatment 19.1±4.4 Controls 18.3±3.8	Arm 1 9.5±4.7 Arm 2 9.5±11.0 Controls 7.0±5.4
HOMA-IR (mmol/L×μU/mL)	Treatment 6.7±2.5 Controls 6.4±2.3	Treatment 6.4±2.3 Controls 6.4±2.2	Treatment 6.3±2.1 Controls 6.0±2.0	NS	Treatment 2.0 (0.3) Controls 5.0 (2.1)	NS	Treatment 6.6±2.4 Controls 6.3±2.2	NS
HOMA-β (μU×mL⁻¹/mmol×L⁻¹)¹⁾	Treatment 54.6±49.9 Controls	Treatment 80.3±65.7 Controls	Treatment 81.9±65.1 Controls	NS	Treatment 29.7 (5.7) Controls 45.6 (12.1)	NS	NS	NS

	52.1±47.8	83.7±69.3	80.8±64.2						
HbA1c (%)	Treatment 8.5±0.9 Controls 8.4±0.8	Treatment 8.1±0.8 Controls 8.0±0.7	Treatment 8.1±0.6 Controls 8.2±0.7	Treatment 7.4±0.7 Controls 7.3±0.6	Treatment 7.5 (0.2) Controls 7.8 (0.4)	Treatment 7.3±0.5 Controls 7.5±0.6	Treatment 7.9±0.9 Controls 7.8±0.8	Arm 1 7.5±0.9 Arm 2 7.1±0.8 Controls 6.9±0.5	
Total cholesterol (mg/dL)	NS	NS	NS	NS	NS	Treatment 185±29 Controls 178±23	Treatment 194±23 Controls 189±19	NS	
HDL-cholesterol (mg/dL)	NS	NS	NS	NS	Treatment 58 (2) Controls 51 (4)	Treatment 55±15 Controls 47±10	Treatment 43±8 Controls 39±4	Arm 1 50±13 Arm 2 55±10 Controls 54±16	
LDL- cholesterol (mg/dL)	NS	NS	NS	NS	Treatment 119 (7) Controls 130 (12)	Treatment 104±27 Controls 99±18	Treatment 139±15 Controls 139±15	Arm 1 125±22 Arm 2 133±24 Controls 123±22	
Triglycerides (mg/dL)	NS	NS	NS	NS	Treatment 157 (26) Controls 228 (39)	Treatment 133±71 Controls 157±68	Treatment 133±44 Controls 142±53	Arm 1 227±135 Arm 2 190±172 Controls 180±110	
Hs-CRP (mg/L)	Treatment 2.1±1.0 Controls 2.0±0.9	Treatment 1.8±0.7 Controls 2.0±0.9	Treatment 1.9±2.0 Controls 1.7±0.8	NS	NS	NS	Treatment 2.2±1.3 Controls 2.2±1.3	NS	
Adiponectin (µg/mL)	Treatment 5.4±0.9 Controls 5.3±0.8	Treatment 5.0±0.8 Controls 5.2±1.1	Treatment 5.2±1.0 Controls 5.4±1.2	Treatment 5.0±3.5 Controls 5.6±3.1	Treatment 6.7±0.8 Controls 4.6±0.3	Treatment 7.0±3.6 Controls 7.6±3.5	Treatment 4.8±1.6 Controls 4.5±1.3	Arm 1 6.5±3 Arm 2 7.5±4 Controls 7.4±2.3	

° Arm1: 50 mg of sitagliptin once a day; *Arm 2: 50 mg of sitagliptin once a day+50 mg of miglitol three times a day; # Controls: 50 mg of sitagliptin once a day

Data are expressed as mean \pm SD or mean (SEM)

Abbreviations: BMI = body mass index; HOMA-IR = homeostasis model assessment – insulin resistance; HbA1c= glycosylated hemoglobin; Hs-CRP = high sensitive C reactive protein; NS = non stated; T2DM = type 2 diabetes mellitus

Table 2. Risk of bias assessment in the studies included in this meta-analysis.

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Free of other bias
Derosa ⁸ , 2010	L	L	L	L	L	L
Derosa ⁹ , 2012	L	L	L	L	L	L
Derosa ¹⁰ , 2012	L	L	L	L	L	L
Forst ¹³ , 2013	U	U	H	U	L	L
Derosa ¹⁴ , 2014	L	L	L	L	L	L
Shimoda ¹⁵ , 2014	L	H	H	L	L	L
Hibuse ²⁵ , 2014	U	U	H	L	L	H
Mikada ³⁰ , 2014	U	U	H	L	L	H

Criteria defined for quality assessment are based on the Cochrane guidelines.

Abbreviations: H, high risk of bias; L low risk of bias; U unclear or unrevealed risk of bias