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Running Title: DPP-4 and plasma adiponectin

Word Count: Abstract 242, text 2960, references 73, tables 2, figures 5

Abstract

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

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

Results: Eight RCTs with nine treatment-arms were included. Meta-analysis did not suggest a significant pooled effect of DDP-4 inhibitors on adiponectin values (weighed-mean-difference [WMD]: 0.19 µg/mL, 95%CI: -0.50, 0.88). However, a significant elevation of plasma adiponectin concentrations was observed in the subset of trials with 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, 1.00, p=0.907). There was a significant elevation of plasma adiponectin levels in the subset of trials comparing DPP-4 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 hypoglycemic drugs as comparators), or using other hypoglycemic drugs (WMD: -0.18 µg/mL, 95%CI: -0.99, 0.62, p=0.654). No significant effect was found for treatment duration, confirmed by meta-regression analyses.

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

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

1. Introduction

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

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

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

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

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

2. Methods

2.1 Search Strategy

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

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

2.2 Study Selection

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

2.3 Data extraction

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

2.4 Quality assessment

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

2.5 Quantitative Data Synthesis

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

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

2.6 Meta-regression

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

2.7 Publication bias

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

3. Results

3.1 Flow and characteristics of included studies

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

3.2 Risk of bias assessment

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

3.3 Effect of DPP-4 inhibitors on plasma adiponectin concentrations

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

3.4 Meta-regression

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

3.5 Publication bias

The funnel plot of the study standard error by effect size (WMD) was slightly asymmetric, suggesting potential publication bias in the meta-analysis (**Figure 5**). Using "trim and fill" correction, one potentially missing RCT was 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 (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 correlation tests (Kendall's Tau with continuity correction = -0.31, z = 1.15, two-tailed p-value = 0.251) did not suggest any potential publication bias.

4. Discussion

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

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

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

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

Our subgroup analysis revealed a significant elevation of plasma adiponectin levels in the subset of trials with vildagliptin, but not sitagliptin, suggesting a specific effect rather than a class effect of DPP-4 inhibitors. The

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

4.1 Limitations

The present meta-analysis has potential limitations that should be mentioned. The included studies were heterogeneous, generally short-term (≤6 months), and with small population sizes. Only two types of DPP-4 inhibitors were assessed in the included trials, thus the impact of other members of this drug class on adiponectin status remains elusive. Furthermore, most of included studies were not primarily designed to assess the effects of DPP-4 inhibitors on adiponectin concentrations. Finally, the number of trials that were included was relatively few, which made it difficult to assess any dose-response relationship.

4.3 Conclusions

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

Abbreviations

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

Conflicts of interest: none.

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Figure captions

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

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

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

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

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

Table 1. Demographic characteristics of the included studies.

Study	Derosa[8], 2010	Derosa[10], 2012	Derosa[9], 2012	Forst[13], 2013	Hibuse[25], 2014	Shimoda[15],2014	Derosa[14], 2014	Mikada[30], 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

								Controls 59±7
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	Arm 1 11/3 Arm 2 7/6 Controls 11/3
BMI (kg/m^2)	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})	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 ± 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