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Effects of rosiglitazone and metformin treatment on apelin, visfatin, and ghrelin levels in patients with type 2 diabetes mellitus

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Abstract

Visfatin, ghrelin, and apelin are the most recently identified adipocytokines; but their response to insulin-sensitizing agents is poorly clarified. We aimed to assess the differential effects of either rosiglitazone or metformin monotherapy on the aforementioned adipocytokines in patients with type 2 diabetes mellitus (T2DM). One hundred T2DM patients (30 men, 70 women), with poor glycemic control (glycosylated hemoglobin >6.5%) while taking 850 mg of metformin daily, were enrolled. All participants were randomized to receive either adjunctive therapy with rosiglitazone (8 mg/d, n = 50) or the maximum dose (2550 mg/d) of metformin (MET group, n = 50). Anthropometric parameters, glycemic and lipid profile, high-sensitivity CRP (hs-CRP), insulin resistance (homeostasis model assessment of insulin resistance index [HOMA-IR]), visfatin, ghrelin, and apelin were assessed at baseline and after 14 weeks of therapy. Both rosiglitazone and metformin led to similar, significant improvement in glycemic profile and apelin levels, whereas lipid parameters, fat mass, and visfatin remained almost unaffected ($P > .05$). Insulin resistance was significantly attenuated in both groups, but to a lesser degree in the MET group ($P = .045$). Rosiglitazone-treated patients experienced a significant decrease in hs-CRP and systolic blood pressure compared with baseline values and those of the MET group ($P < .05$). Besides, rosiglitazone treatment considerably increased plasma ghrelin (3.74 ± 1.52 ng/mL) in comparison with either baseline ($P = .034$) or metformin monotherapy values (−2.23 ± 1.87 ng/mL, $P = .008$). On the other hand, the MET group, rather than the rosiglitazone group, had decreased body mass index (−0.79 ± 0.47 vs 0.56 kg/m^2, $P = .009$). The aforementioned changes in apelin and ghrelin were independently associated with HOMA-IR changes. Both rosiglitazone and metformin favorably changed glycemic indexes and apelin levels. The addition of rosiglitazone seemed to confer greater benefits in ghrelin, hs-CRP, systolic blood pressure, and HOMA-IR regulation than metformin monotherapy. Although these results reflect improvement in cardiovascular risk profile, the overall clinical importance of insulin sensitizers must be further assessed.

1. Introduction

Insulin-sensitizing agents, such as thiazolidinediones and metformin, are widely used in type 2 diabetes mellitus (T2DM) because insulin resistance attenuation is a beneficial approach for treating diabetes and preventing cardiovascular diseases [1]. Both rosiglitazone, a thiazolidinedione derivative, and metformin improve glycemic control [2,3] and act on adipose tissue by improving dysregulated "adipocytokine" profile in the insulin-resistant state [4,5].

Apelin constitutes the most recently identified bioactive peptide in white adipose tissue [6]. Although experimental researches support the suppressive effects of this adipocytokine on insulin resistance [7], there are also limited opposite human data [8,9]. Notably, apelin also shows strong antiatherogenic actions in animal models, which render it a key factor in atherosclerosis treatment [10]. Therefore,

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studies on the effects of pharmaceutical interventions on apelin are warranted.

The gastric hormone ghrelin has been found to be a powerful orexigenic and adipogenic agent [11]. Low plasma ghrelin levels have been associated with elevated fasting insulin levels and insulin resistance in humans [12]. Besides this, limited evidence implicates ghrelin involvement in early atherosclerosis and diabetic-related vascular complications [13,14]. Thus, ghrelin could provide an important target of antidiabetic treatment of glucose regulation and atherosclerosis prevention.

Among novel adipocytokines, visfatin was originally identified as pre-B cell colony-enhancing factor and is also known as *nicotinamide phosphoribosyl transferase* (NAMPT) [15]. It is preferentially expressed in visceral adipose tissue and possesses insulin-mimetic bioactivity [16]. However, its relationship with insulin resistance is a subject of controversy [17]. Moreover, visfatin is produced by macrophages and exerts proinflammatory properties contributing to atherosclerosis progression [18]. It is still unknown whether antidiabetic regimens modulate visfatin.

An expanding body of data indicates the association between insulin resistance, adipocytokines, and consequent cardiovascular complications [19]. Unfortunately, clinical studies evaluating the differential effects of insulin-sensitizing regimens on plasma levels of visfatin, ghrelin, and apelin are lacking. Thus, we tested the hypothesis that combined treatment with metformin plus rosiglitazone might be superior to metformin monotherapy in terms of novel adipocytokines modification in patients with T2DM.

2. Methods

2.1. Subjects and study design

A total of 100 patients, aged 50 to 70 years, with T2DM (30 men, 70 women) were enrolled in this study. Study entrance criteria included already being treated with metformin (850 mg/d) alone for at least 4 months, but without adequate glycemic control (glycosylated hemoglobin [HbA_{1c}] >6.5%), and increased body mass index (BMI >25 kg/m^2). Absence of significant renal (creatinine >2 mg/dL) and hepatic dysfunction (alanine aminotransferase >3 times higher than the upper normal limit) or congestive heart failure (New York Heart Association II-IV) was also a prerequisite for participation. No patient had clinical evidence of either cardiovascular diseases (coronary, peripheral, carotid artery disease) or other major chronic diseases (autoimmune, life threatening). Patients with prior thiazolidinediones treatment or those with significant changes (>5%) in body weight for up to 4 months before study initiation were not included.

After initial evaluation, eligible patients were randomly assigned to the following groups for 14 weeks: (1) RSG (n = 50)—adjunctive therapy with a fixed dose of rosiglitazone (metformin 850 mg/d plus rosiglitazone 8 mg/d) or (2) MET (n = 50)—gradual titration of metformin to maximum dose (from 850 to 2550 mg/d). We used randomization software with password-protected database in computer. This programming scheme randomized 4 patients at a time in such a way as to ensure that equal numbers are allocated to each group.

A single operator measured waist-hip ratio (WHR), BMI, blood pressure (BP), and the percentage of body fat mass using the body composition analyzer (Bodystat 1500; Bodystat, Isle of Man, British Isles) at baseline and at the end of the study, as we have previously described [20]. All participants were instructed not to change their dietary habits or daily activities across the study period. Concomitant medications were maintained during the whole study period unless deemed medically appropriate. At the beginning, a written informed consent was obtained before randomization. The present study was approved by the local ethics committee and conducted in accordance with the Declaration of Helsinki.

2.2. Blood analyses

Blood samples were drawn between 8.00 and 10.00 AM after an overnight fast. Fasting plasma glucose (FPG) and lipid parameters were all measured in an automatic enzymatic analyzer (Olympus AU560, Hamburg, Germany). The glycosylated hemoglobin was determined by high-performance liquid chromatography (Menarini Diagnostics, Florence, Italy). We quantified plasma insulin using enzyme-linked immunosorbent assay method (DRG Diagnostics, Marburg, Germany). The inter- and intraassay coefficients of variance (CVs) were 3% and 3.4%, respectively. The homeostasis model of assessment insulin resistance index (HOMA-IR) was calculated [21]. Plasma levels of visfatin, ghrelin, and apelin (human apelin-12) were assayed using commercially available enzyme immunoassay kits according to the manufacturer's instructions (Phoenix Pharmaceuticals, Belmont, CA). The intraassay CVs were less than 5% for visfatin, less than 14% for ghrelin, and 5% for apelin, whereas the interassay CVs for the latter adipocytokines were 4%, 7.5%, and 14%, respectively. High-sensitivity CRP (hs-CRP) was assayed in serum by nephelometric procedure (BNII; Dade Behring, Marburg, Germany). Blood samples had been frozen and stored (−80°C).

2.3. Statistical analysis

Results are presented as mean ± SD. Normality of distribution was assessed with Kolmogorov-Smirnov test. Comparisons between and within groups were performed by Student t test and paired-samples t test, respectively. For nonparametric analysis between groups, we used χ^2 test. A Pearson correlation coefficient was used in univariate analysis, whereas standard multiple regression analysis explored the relationship between changes of adipocytokines and a number of independent variables. All tests were 2-tailed, and P value < .05 was considered to be

Table 1
Baseline characteristics of the patients

	RSG group (n = 49)	MET group (n = 48)	*P*
Sex (male/female)	13/36	16/32	.761
Age (y)	62 ± 8.3	62.7 ± 6.8	.760
Diabetes duration (y)	4.8 ± 1.7	3.7 ± 1.7	.355
Smokers	7 (14.3%)	14 (29.2%)	.071
Antihypertensive medications users	27 (55.1%)	29 (60.4%)	.340
Statins users	23 (47.1%)	20 (40.8%)	.771
hs-CRP (mg/L)	2.4 ± 1.39	2.36 ± 1.02	.912
Visfatin (ng/mL)	16.09 ± 5.39	18.13 ± 6.7	.851
Ghrelin (ng/mL)	10.37 ± 5.47	12.09 ± 4.03	.451
Apelin (ng/mL)	0.47 ± 0.18	0.48 ± 0.24	.909

Data are mean ± SD.

statistically significant. The computer software package SPSS (version 13.0; SPSS, Chicago, IL) was used for statistical analysis.

3. Results

In this open-label, randomized study, 100 patients with T2DM were initially recruited. Three patients were excluded from statistical analysis. One patient in the RSG group was prematurely withdrawn because of peripheral edema, whereas 2 patients in the MET group were lost to follow-up. Therefore, 49 patients in the RSG group and 48 patients in the MET group completed the study. The clinical and biochemical characteristics at study entry, shown in Tables 1 and 2, were similar between the 2 treatment groups. Other noteworthy adverse effects, such as cardiovascular events or heart failure symptoms, were not reported throughout the study period.

3.1. Clinical parameters

After 14 weeks of add-on rosiglitazone treatment, BMI (0.74 ± 1.17 kg/m^2) was significantly increased compared with baseline ($P < .05$) or MET group ($P < .001$). The latter rosiglitazone-related effects were not associated with significant alterations in body composition, expressed by WHR or percentage of fat-mass. In the MET group, BMI was significantly reduced; but body composition parameters remained unaltered.

Upon examining systolic BP, we noted a statistically significant down-regulation in the RSG group rather than in the MET group ($P = .036$). Diastolic BP was significantly decreased from baseline only in the RSG group ($P < .05$). Nevertheless, between-groups analysis showed a nonsignificant difference.

3.2. Biochemical parameters

As expected, both treatment arms caused significant decreases from baseline in FPG ($P < .010$). Glycosylated hemoglobin decreased by 11.08% in the RSG group and by 7.1% in the MET group, a significant and equal decrease ($P = .640$), whereas the proportion of patients achieving glycemic target (HbA_{1c} <6.5%) tended to be higher in the RSG group than in the MET group (56% vs 35%, $P = .055$) at the end of the study. Fasting insulin levels were reduced in both groups, but only rosiglitazone treatment achieved significant attenuation compared with baseline ($P = .035$). Furthermore, both treatment modalities led to considerable decreases in insulin resistance by the end of the study ($P < .05$). Of note, HOMA-IR reduction was almost 2-fold in the group of combined treatment (metformin plus rosiglitazone) than in the metformin monotherapy group ($P = .045$).

Adjunctive therapy with rosiglitazone conferred small and nonsignificant increases in total cholesterol, low-density

Table 2
Clinical and biochemical parameters at baseline and at the end of the study

	RSG group (n = 49)			MET group (n = 48)			
	Baseline	Wk 14	*P*1	Baseline	Wk 14	*P*1	*P*2
BMI (kg/m^2)	29.65 ± 2.58	30.49 ± 2.29	.032	29.75 ± 2.47	28.96 ± 2.57	.013	<.001
WHR	0.93 ± 0.1	0.93 ± 0.08	.854	0.93 ± 0.07	0.93 ± 0.08	.810	.794
Fat mass (%)	35.84 ± 4.14	35.59 ± 4.68	.540	41.02 ± 6.46	40.96 ± 7.9	.961	.842
Ht (%)	42.4 ± 3	40 ± 3.6	<.001	41.6 ± 4.4	41.7 ± 5.1	.852	.007
Systolic BP (mm Hg)	135.5 ± 13	130.6 ± 17.4	.012	134.3 ± 18.6	133 ± 15.6	.675	.036
Diastolic BP (mm Hg)	82.7 ± 9.2	77.5 ± 9.5	.007	81.3 ± 7.2	79.3 ± 5.6	.415	.311
HbA_{1c} (%)	7.85 ± 0.79	6.98 ± 1.32	<.001	7.61 ± 0.47	7.07 ± 1.04	.014	.291
FPG (mg/dL)	173.6 ± 41.1	145.5 ± 43.2	<.001	173.2 ± 22.1	152.6 ± 25.7	.009	.640
Insulin (mU/L)	11.63 ± 6.11	9.13 ± 4.15	.035	11.6 ± 3.35	10.02 ± 3.9	.058	.578
HOMA-IR	5.02 ± 2.64	3.28 ± 1.37	.002	4.96 ± 2.31	3.98 ± 1.34	.024	.045
TChol (mg/dL)	203.2 ± 45.1	213.3 ± 55.1	.232	211.4 ± 50.6	201.3 ± 56.4	.268	.157
Triglycerides (mg/dL)	148 ± 53.6	164.2 ± 114.6	.407	140.4 ± 69.8	115.2 ± 40.4	.064	.191
HDL-C (mg/dL)	44.2 ± 9.6	45.9 ± 8.9	.187	46.6 ± 13.2	47.3 ± 12.2	.500	.625
LDL-C (mg/dL)	129.4 ± 45.5	134.6 ± 46.9	.505	135.3 ± 39	132.8 ± 54.3	.784	.577
WBC (cells/μL)	7530 ± 1516	7212 ± 2038	.395	6607 ± 1782	6561 ± 1343	.937	.689

Data are mean ± SD. Ht indicates hematocrit; TChol, total cholesterol; HDL-C, high-density lipoprotein cholesterol; WBC, white blood cells count; *P*1, *P* values of changes of variables within groups; *P*2, *P* values of changes of variables between groups.

lipoprotein cholesterol (LDL-C), and triglycerides compared with values at baseline and in the MET group ($P > .05$). Negligible increases in high-density lipoprotein cholesterol were documented in both groups compared with baseline ($P > .05$). We did not detect any sex differences in the aforementioned variables.

3.3. Adipocytokines and hs-CRP

All data are presented in Fig. 1. Concerning apelin, we documented an equivalent and significant increase from baseline in both groups ($P < .05$). Finally, the rosiglitazone-induced decrease in hs-CRP levels (from 2.4 ± 1.39 to 1.45 ± 0.71 mg/L) was considerably greater ($P < .001$) than that caused by metformin (from 2.36 ± 1.02 to 2.15 ± 0.92 mg/L). Adjunctive therapy with rosiglitazone significantly up-regulated ghrelin levels (3.74 ± 1.52 ng/mL) as compared with values either at baseline ($P = .034$) or in MET group (−2.23 ± 1.87 ng/mL, $P = .008$). Plasma levels of visfatin were increased in both groups (RSG: by 4 ± 2.83 ng/mL, MET: by 5.48 ± 3.64 ng/mL), but none of these increments was statistically significant.

Looking for sex differences, we noted that both insulin-sensitizing modalities induced greater changes of all adipocytokines in the women subgroup compared with its male counterpart. Nevertheless, those sex differences did not reach statistically significance level and had no influence on between–treatment-groups comparison.

3.4. Correlations

At baseline, we assessed the relationship of adipocytokines and hs-CRP with the rest of variables. Pearson correlation showed significant associations of apelin with age ($r = 0.298$, $P = .015$), BMI ($r = -0.424$, $P = .005$), HOMA-IR ($r = -325$, $P = .036$), and FPG ($r = -0.566$, $P = .007$). Baseline values of ghrelin significantly correlated with visfatin ($r = 0.199$, $P = .023$), BMI ($r = 0.313$, $P = .012$), and HOMA-IR ($r = -0.293$, $P = .008$). Besides ghrelin, visfatin was significantly correlated with hs-CRP ($r = 0.604$, $P = .029$), BMI ($r = 0.245$, $P = .041$), and fat mass ($r = 0.382$, $P = .017$) at the beginning of the study. Finally, baseline hs-CRP showed significant relationships with visfatin, BMI ($r = 0.534$, $P = .019$), WHR ($r = 0.564$, $P = .010$), white blood cells count ($r = 0.362$, $P = .016$), and LDL-C ($r = 458$, $P = .042$).

Among novel adipocytokines, ghrelin and apelin were significantly altered in our study population. Thereby, we examined the changes of the latter adipocytokines in relation to the changes of the rest of the variables. We found apelin changes to be significantly associated with alterations in LDL ($r = -0.665$, $P = .021$) and HOMA-IR ($r = -0.571$, $P = .007$). The latter correlations remained significant in standard multiple regression analysis ($R^2 = 0.421$, $P = .033$). In parallel, we observed ghrelin alterations to be significantly correlated with changes in BMI ($r = 0.637$, $P = .002$), HOMA-IR ($r = -0.316$, $P = .005$), and hs-CRP ($r = -0.312$, $P = .008$). Standard multiple regression analysis revealed BMI and HOMA-IR changes to be independent predictors of ghrelin changes, explaining 29.2% of its variation ($P = .031$). No sex differences in the above correlations were found.

4. Discussion

In the presence of equivalent improvement in glycemic profile after combined treatment (metformin plus rosiglitazone) or metformin monotherapy, the main findings of this study were as follows: (1) We showed for the first time the positive effects of insulin-sensitizing medications on plasma apelin levels in patients with T2DM. (2) Adjunctive therapy

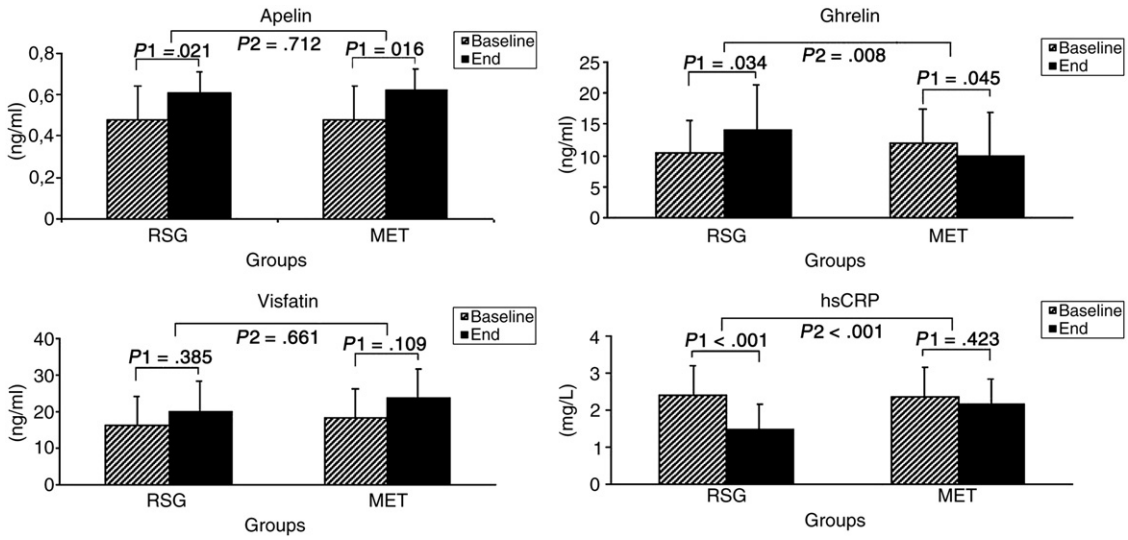

Fig. 1. Effects of 14 weeks of rosiglitazone (8 mg/d) (RSG) and maximum-dose metformin (2550 mg/d) (MET) treatment on apelin, ghrelin, visfatin, and hs-CRP concentrations. *P*1 indicates *P* values of changes of variables within groups; *P*2, *P* values of changes of variables between groups.

with rosiglitazone considerably increased ghrelin levels compared with maximum dose of metformin. (3) Visfatin levels were not affected by both antidiabetic regimens. (4) Treatment regimens significantly differed with regard to insulin sensitivity, hs-CRP, systolic BP, and BMI changes.

Up to now, there are only 2 cross-sectional studies [8,9] in diabetic patients about the relationship between apelin and insulin resistance, reporting controversial results. To our knowledge, this is the first study demonstrating a remarkable increase, from baseline, in apelin concentrations by either add-on rosiglitazone treatment or maximum dose of metformin. Recent in vitro and in vivo research approaches strongly suggest interplay between apelin and insulin resistance [7]. In our study, HOMA-IR reduction appeared to be an independent predictor of apelin increment. A plausible explanation is that insulin-sensitizers trigger apelin secretion through adenosine 5′ monophosphate–activated protein kinase (AMPK) activation, leading to insulin resistance alleviation. More data will prove whether adipose tissue–derived apelin constitutes a compensatory mechanism to insulin resistance, which could halt atherosclerosis progression [22].

One of the most important findings of the present study was the significant up-regulation of ghrelin levels in the RSG group compared with the MET group. This is the third study examining the effects of thiazolidinediones on plasma ghrelin levels. In the first trial, no ghrelin change was reported after rosiglitazone treatment [23]. However, that study was performed in women with polycystic ovary syndrome, but without T2DM. In contrast to our study, Kusaka et al [24] demonstrated that metformin decreased and pioglitazone, another member of thiazolidinediones, slightly increased fasting ghrelin in T2DM. The first explanation for this discrepancy derives from the use of pioglitazone, which has been shown to exert different metabolic effects than rosiglitazone [25]. Secondly, we hypothesized that baseline BMI might have influenced our results because BMI is well established to correlate with ghrelin concentrations [11]. Indeed, previous authors enrolled moderately overweight Japanese patients compared with our almost-obese white subjects. Moreover, we demonstrated a positive, independent association between ghrelin and BMI changes. Regarding the orexigenic effects of ghrelin, one could suggest that ghrelin may in part account for the opposite effects of rosiglitazone and metformin on body weight [14]. Unfortunately, we did not assess energy intake; so we cannot draw firm conclusions about the interaction between ghrelin and the consequent weight changes.

In line with earlier human studies, we also observed an inverse correlation between ghrelin and HOMA-IR [26,27]. Paradoxically, we noticed that metformin monotherapy reduced plasma ghrelin levels, despite the attenuation of insulin resistance. Ghrelin constitutes a significant regulator of AMPK, whose activation predominantly mediates hypoglycemic and insulin-sensitizing effects of thiazolidinediones and metformin [28,29]. Trying to explain the above paradox, we postulated that plasma ghrelin may not exclusively reflect AMPK stimulation because it derives from numerous sources (skeletal muscle, adipose tissue, liver) [30]. Most importantly, emerging, but extremely limited, evidence implicates the antiatherogenic and cardioprotective action of ghrelin [31,32]. Large, prospective studies are required to examine the potential effects of insulin sensitizers on cardiovascular end points through ghrelin modification.

Most, but not all, previous studies support the absence of association between visfatin and insulin sensitivity [33,34]. Both of our insulin-sensitizing modalities induced nonsignificant up-regulation of plasma visfatin. Despite the lower power (66.6%) of our study to detect significant changes in visfatin, this is in consistence with recent clinical trials [33,35-38]. Perhaps, the insulin-mimetic action of visfatin may be mediated by binding to the insulin receptor via a distinct binding site. In addition to this, visfatin gene expression has been recently found to be enhanced in macrophages of human unstable carotid and coronary atherosclerotic lesions, where insulin sensitizers' influence seems to be limited [18,39]. The above mechanisms could explain visfatin's actions dissociation from insulin sensitivity. Thereby, insulin sensitizers might have little effect on visfatin blood kinetics and its expanded role in atherosclerotic process.

As expected, insulin resistance was considerably suppressed in both treatment groups, but to a greater extent in the combined-treatment group. This clinical important finding may be attributed to the complementary modes of action of rosiglitazone and metformin [40]. Regarding hs-CRP and BP, rosiglitazone adjunctive therapy rather than metformin monotherapy induced a pronounced decline. These differential effects on hs-CRP, a well-validated cardiovascular biomarker, deserve further consideration in clinical process of selecting therapeutic strategy [41]. Conversely, add-on rosiglitazone slightly deteriorated lipid profile and significantly increased BMI, despite the maintenance of fat mass. Rosiglitazone-related weight gain is somewhat problematic for diabetic patients. It has been predominantly ascribed to fluid retention and may have detrimental effects on cardiac function [42]. Although none of our patients reported congestive heart failure, this risk should be always taken into consideration.

The main limitation of our study was the small sample. However, we used numerous selection criteria to create adequately homogeneous groups. Another limitation of our study was the use of HOMA-IR instead of euglycemic-hyperinsulinemic clamp method. The former is a less accurate manner, which mostly reflects hepatic insulin sensitivity. Furthermore, we did not include a healthy control group to compare the insulin-sensitizing effects. Finally, we measured total ghrelin, which cross-reacts with degraded fragment of active ghrelin. Perhaps, active ghrelin assays would have provided more precise results.

Nowadays, there is debate about the long-term cardiovascular outcomes of thiazolidinediones [43]. Given the known cardiovascular risk of insulin resistance, its improvement by thiazolidinediones appears theoretically promising in the early stage. Nevertheless, rosiglitazone should be used with great caution regarding the incidence of myocardial infarction and heart failure revealed in recent meta-analyses [44,45]. On the other hand, the apparent cardiovascular benefit of metformin is well established [46]. Therefore, patients' characteristics likely to benefit from insulin-sensitizing effects of rosiglitazone combined with a low heart-failure risk constitute a safe and effective therapeutic approach [47].

In conclusion, adjunctive therapy with rosiglitazone or metformin monotherapy favorably changed apelin levels together with improved glycemic control. For patients inadequately controlled on low dose of metformin, addition of rosiglitazone may be preferable to continued monotherapy with higher doses of metformin regarding its more favorable results on ghrelin, hs-CRP, BP, and HOMA-IR. The overall cardiovascular risk of each patient should be always balanced before antidiabetic strategy selection.

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