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Effect of phosphodiesterase-5 inhibitors on glycemic control in person with type 2 diabetes mellitus: A systematic review and meta-analysis

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ABSTRACT

Chronic use of phosphodiesterase-5 inhibitors (PDE-5i) has been shown to improve insulin action on muscle glucose uptake by the prolongation of nitric oxide (NO)/cyclic guanosine monophosphate (cGMP)/protein kinase (PKG) signalling.

Aims: As the effects of PDE-5i on glycemic control in person with type 2 diabetes mellitus (T2DM) have not been systematically explored, we conducted a meta-analysis of available randomized controlled trials (RCTs).

Methods: A literature search was performed through electronic databases including MEDLINE (Pubmed), The Cochrane Library, SCOPUS, Web of Science, CINAHL, www.clinicaltrials.gov and www.clinicaltrialresults.org until April 2016 without language restriction. Studies were included if they met the following criteria: (i) RCTs of the chronic use of PDE-5i compared with placebo or no active treatment in T2DM patients (ii) reporting of HbA1c or glycated haemoglobin or fasting plasma glucose (FPG).

Results: Four studies involving a total of 198 patients fit into the inclusion criteria. All included studies used the same PDE-5i, sildenafil. Reports of HbA1c were analysed as only one study reported FPG. PDE-5i had no beneficial effect on HbA1c with weighted mean difference (WMD) of 0.17% (95% CI, –0.64 to 0.97).

Conclusion: This meta-analysis suggests that large and well-controlled studies are warranted to shed light on the effect of PDE-5i on glycemic control in people with type 2 diabetes mellitus.

Introduction

The incidence of type 2 diabetes mellitus (T2DM) is progressing worldwide [1]. Due to low capacity of insulin secretion or action, persons with T2DM have a dysfunction in the intermediate metabolism of carbohydrates, proteins and lipids causing sustained hyperglycemia [2]. Consequently, insulin resistance develops in target organs and peripheral sites, which is associated with endothelial dysfunction by a number of mechanisms including interruption of the subcellular signalling pathways of both insulin and nitric oxide (NO) production [3]. In human vascular smooth muscle cells, reduced NO bioavailability contributes to impaired insulin utilization in insulin resistant conditions [4]. The increase in glucose transport is stimulated by insulin via the endothelium-derived NO/cyclic guanosine monophosphate (cGMP) pathway. Importantly, insulin mediated NO/cGMP signalling on glucose uptake, requires protein kinase G (PKG) activation by promoting the translocation of glucose transporter 4 (GLUT4) to the cell membrane [5]. Then PKG activation is essential for the final downstream effects of RhoA/Rho-associated kinases (ROCKs) in the control of adipogenesis [6]. In rat pancreatic β-cells, acute cGMP enhancement has an insulinotropic effect despite the fact that prolonged increases in cGMP may reduce insulin secretion [7,8].

Phosphodiesterase-5 inhibitors (PDE-5i) have been used for the treatment of erectile dysfunction by enhancing NO/cGMP-mediated signalling in cavernous smooth muscle. The prevention of cGMP breakdown by selective PDE-5i evokes an amplified NO signal and concomitantly, enhanced vascular function of glucose delivery to muscle cells in postmenopausal women with type 2 diabetes [9,10]. Chronic use of PDE-5i, particularly sildenafil, increases NO formation via the endothelial nitric oxide synthase (eNOS) pathway, as shown in an *in vitro* study [11]. Since PDE-5 protein is detected in preadipocytes, it seems likely that PDE-5 has a potential role in adipocyte differentiation and mitochondrial biogenesis [6]. In the high-fat induced insulin resistant mouse model, chronic PDE-5 inhibition improved insulin sensitivity with the resultant increased energy balance and weight loss due to enhanced energy expenditure

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[4]. In a recent study in patients at risk of diabetes, 3-month treatment, with a PDE-5i, caused an enhancement in insulin sensitivity and a reduction in albuminuria, whilst maintaining a balance in fibrinolysis [12]. In a recent meta-analysis, chronic use of PDE-5i in type 2 diabetes showed an improved endothelial function in 6 RCTs of 476 patients [2]. Nevertheless, the effects of PDE-5 inhibitors on glycated haemoglobin and fasting plasma glucose are still inconclusive. Therefore, we conducted this meta-analysis to explore the chronic effects of PDE-5i on glycemic control in person with type 2 diabetes.

Methods

Literature searches

Reports of randomized controlled trials of the chronic use of PDE-5i in persons with type 2 diabetes were searched through electronic databases including MEDLINE, The Cochrane Library, Scopus, Web of Science, CINAHL, www.clinicaltrials.gov and www.clinicaltrialresults.org. The databases were searched from inception to the end of April 2016 without language restriction. A hand search of articles and reference lists of potentially relevant articles was also performed. The MeSH terms used were "phosphodiesterase-5 inhibitors", "type 2 diabetes mellitus" and "insulin resistance". The keyword search was used by combining haemoglobin A_{1c}, glycosylated haemoglobin, fasting plasma glucose and postprandial plasma glucose with specific PDE-5i (sildenafil, vardenafil, tadalafil, avanafil, udenafil and mirodenafil).

Study selection

Eligible studies were selected by three independent reviewers. Inclusion criteria for study selection included: (i) randomized controlled trials of the chronic use of PDE-5i (daily or weekly or alternate day or on-demand) compared with placebo or no active treatment in patients with type 2 diabetes (ii) reports of HbA_{1c} or fasting plasma glucose as outcome measures. Studies that included acute dosing of PDE-5i or in people with type 1 diabetes or gestational diabetes were not considered to be eligible. Abstract presentations were excluded.

Data extraction and quality assessment

Data extraction and quality assessment were performed independently by two authors. The data extracted included: year of publication, country of origin, study design, duration of study, sample size, duration of diabetes, age of participants, intervention, outcome measures and results. The methodological quality of included studies was assessed using the Jadad scale, scale to evaluate the general quality of medical research, with three dimensions of internal validity including randomization, double-blinding and patient attrition [13]. Studies that scored three or more, out of the possible maximum of five points, were regarded as high quality.

Statistical analysis

Glycated haemoglobin or HbA1c was analysed since only one of the included studies reported FPG [14]. Treatment effect was then estimated, with a mean difference in the change of values from baseline, between the PDE-5i group and the control group. When the variances of the change values were not provided or the calculation based on the data reported was not possible, the pooled inter-study variance was imputed from the studies reporting variances. The inverse variance-weighted method was used for the pooling of mean differences and the estimation of a 95% confidence interval (95% CI). Random effects model was applied to accommodate for the variations in study characteristics. Heterogeneity across studies was quantified using the I^2 statistic, with $I^2 > 50\%$ representing significant heterogeneity [16]. Sensitivity analysis was performed by excluding low quality studies. The meta-analysis was conducted using Review Manager (RevMan) program version 5.3.5 (Cochrane Collaboration, Oxford, UK).

Results

Study selection

One hundred and eighty-one reports were initially identified. Of these, 19 studies were finally retrieved after screening of titles and abstracts. Amongst them, 14 studies were further excluded from the analysis since they did not fulfill the inclusion criteria with the following reasons: acute doses of PDE-5i, no glycemic outcome and active-controlled trial. The remaining five randomized controlled trials [14,15–18] were included in the qualitative synthesis but one study [18] had to be excluded in the final meta-analysis due to no quantitative data of glycemic parameters. Finally, four studies fit the inclusion criteria and were included in this meta-analysis [14,15–17]. Study selection process is shown in Fig. 1.

Study characteristics

Total sample size of the selected studies were 198 type 2 diabetes men; 100 randomized to PDE-5i and 98 to placebo. The number of subjects in individual studies varied from 8 to 42 patients in each arms. All studies were published in English and used the same PDE-5i, namely sildenafil. Additionally, all trials were double-blind and placebo-controlled in design except one [17], which compared sildenafil plus lifestyle modification (diet and exercise) and medical treatment for intensive glycemic control versus lifestyle modification (diet and exercise) and medical treatment for intensive glycemic control. One report [14] described the following two comparisons: (i) propionyl L-carnitine (PLC) alone versus PLC combined with PDE-5i (ii) PDE-5i monotherapy versus placebo. However, only the results of glycemic control comparing PDE-5i monotherapy versus placebo were focused on in this analysis [13].

The dosages of PDE-5i varied amongst the included studies, ranging from once daily, in two of the studies [15,16] to twice weekly or 2–3 times weekly in other two studies [14,17]. Even in the daily basis treatment of two studies, the strength of PDE-5i dose also varied by 50% (50 mg/day [15] and 100 mg/day [16]). Inconsistent dosages and frequency of administration could represent the main source of heterogeneity. The duration of diabetes in the four included studies also differed. One study lasted 4 weeks [15] whilst three studies [14,16,17] were of a 12 week duration. Of the four studies, two [15,17] assessed the direct effect of PDE-5i on glycemic control, whilst the remaining two studies [14,16] evaluated HbA1c level as a co-primary outcome measure. Although three studies [14–16] were of high quality, one study [17] was rated as low quality, due to an absence of blinding and no description of patient attrition for each groups. Characteristics of the included studies and their outcome assessment are presented in Table 1.

Efficacy: HbA1c

A single comprehensive analysis was performed. The results were substantially heterogeneous (I^2 for heterogeneity = 53%, $p = 0.10$). This may indicate that the results of combined studies were not undertaken in the same way. Nevertheless, the random effect model was applied in combining the results to accommodate the variations in study characteristics. PDE-5 inhibitors had no beneficial effect on

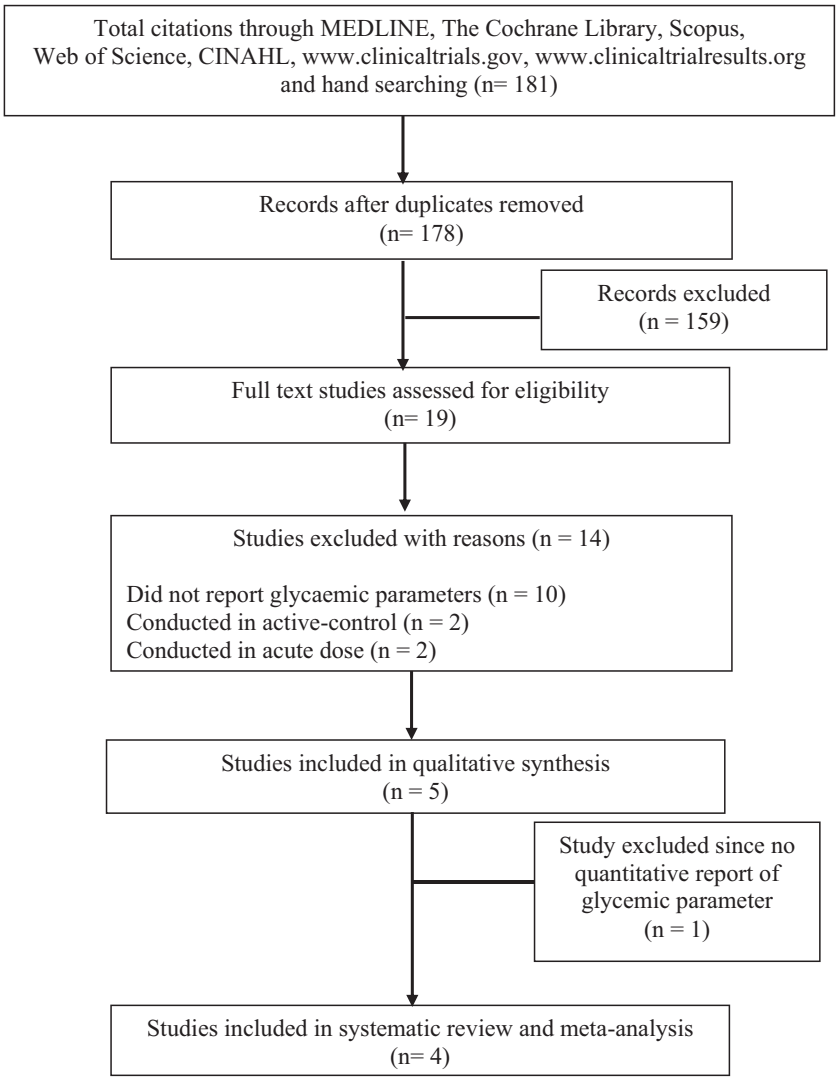

Fig. 1. Study selection process (PRISMA flow chart).

HbA1c. The pooled mean difference in the changes of HbA1c was 0.17% (95% CI, –0.64% to 0.97%), (Fig. 2).

Sensitivity analysis

Sensitivity analysis was conducted in regards to the methodological quality of studies. Of the four studies, one study [17] was of low quality graded 2 out of 5 points, due to a non-blinded design and no description of patient attrition for either group. When this study was excluded, the pooled results remained unchanged with moderate heterogeneity ($I^2 = 38\%$). Again, PDE-5 inhibitors did not improve glycemic control in person with type 2 diabetes (mean difference –0.13%; 95% CI, –1.02% to 0.75%).

Discussion

Restoration of cGMP levels by inhibiting phosphodiesterase-5 could be a prophylactic measure against the development of insulin resistance via improving endothelial dysfunction. Prolongation of NO/cGMP/PKG signalling by PDE-5i could favor stimulation of blood flow and improve insulin action on muscle glucose uptake, thereby decreasing the plasma glucose level. A study also found that nitric oxide/cGMP can stimulate glucose transport to skeletal muscle [19]. Additionally, PDE-5i induces NO production in basal and insulin resistant conditions by activation of eNOS through a PI3K dependent pathway without involvement of Akt-1 phosphorylation [11]. It has been reported that tadalafil administration promotes improvement in beta cell function in metabolic syndrome patient both men and women, which is independent of insulin sensitivity. However, as women are more sensitive to decreased cGMP degradation, improved beta cell function was not found in men in this study [20]. In rat liver cells, the effect of sildenafil seemed to decrease liver glycogenolysis and gluconeogenesis, evident by the reduction in hepatic glycogen phosphorylase (GP), without affecting the phosphoenol pyruvate carboxykinase enzyme. But this effect was only seen in high dose of PDE-5i [21].

In vascular smooth muscle cells, cGMP dependent PKG activation stimulates GLUT-4 translocation to the plasma membrane [5]. Furthermore, PKG affects insulin signalling in brown adipose tissue by reducing inhibitory phosphorylation of insulin receptor substrate (IRS-1) by Rho-associated kinase (ROCK) [6,22]. Amplified NO-cGMP signalling by PDE-5 inhibition is associated with increased insulin sensitivity which is evident by a greater insulin-mediated blood glucose lowering effect [23]. In addition to regulation of

Table 1
Characteristics of the included studies.

Author (Year)	Country	Study Design	Sample size (PDE5i:Ctr)	Duration (weeks)	Intervention	Primary Outcomes	Other Outcomes	Quality Score
Morano S (2007) [14]	Italy	DB, P	16 (8:8)	12	Sildenafil 50 mg twice weekly vs. placebo	SI, ROS, ICAM-1, P-selectin, AGE, T, PSV, EDV, RI, SWT	HbA_{1c}, FPG, TC, HDL, LDL, TG, IIEF score	4
Grover PF (2007) [15]	Mexico	DB, P	40 (20:20)	4	Sildenafil citrate 50 mg/day vs. placebo	hs-CRP, Micro-albuminuria, HbA1c, homocysteine	Total IIEF score	4
Giannetta E (2012) [16]	Italy	DB, P	59 (30:29)	12	Sildenafil 100 mg/day vs. placebo	Kinetic, geometric and performance parameters at CMR assessment	TGF-β, MCP1, PINP, NT-proBNP, ET-1, VEGF, BMI, HOMA Index, HbA_{1c}, HDL, TG, SBP, DBP	5
Kirilmaz U (2015) [17]	Turkey	Non-blinded, P	83 (42: 41)	12	Sildenafil 100 mg for 2–3 times per week + LM and intense GC vs. LM and intense GC	IIEF-5 score, BMI, HbA_{1c}	Total testosterone, free testosterone	2

Author (Year)	Mean Age (Years)[a]	Duration of diabetes (years)[a]	Baseline HbA1c (%) , (mmol/mol)[b]	Drug Therapy and other managements	Notes
Morano S (2007) [14]	PDE-5i: 54.0 ± 7.4 Ctr: 57.6 ± 4.3	PDE-5i: 8.1 ± 5.8 Ctr: 9.0 ± 6.1	PDE-5i: 7.8 (62) Ctr: 7.3 (56)	Diet and oral hypoglycemic agents but no use of TZD and insulin	Current diabetes treatment was continued
Grover PF (2007) [15]	PDE-5i: 48.30 ± 4.52 Ctr: 46.60 ± 8.73	PDE-5i: 4.52 ± 2.59 Ctr: 7.5 ± 3.24	PDE-5i: 8.1 (65) Ctr: 7.2 (55)	Glibenclamide, metformin or both but no insulin use	Antidiabetes treatment was given to all patients before and during the study period
Giannetta E (2012) [16]	PDE-5i: 60.7 ± 7.6 Ctr: 60.2 ± 8.3	PDE-5i: 6.7 ± 5.5 Ctr: 6.2 ± 5.7	PDE-5i: 7.9 (63) Ctr: 7.3 (56)	Metformin, secretagogues, statins, antihypertensive agents, but no use of insulin, TZD	Current medications could not be changed during the study period and 1 month after its completion
Kirilmaz U (2015) [17]	PDE-5i: 54.3 ± 10.1 Ctr: 55.5 ± 8.1	PDE-5i: 7.41 ± 8.05 Ctr: 8.38 ± 8.9	PDE-5i: 8.8 (73) Ctr: 9.3 (78)	Mediterranean diet, exercise and medical treatment for intensive glycemic control	Current medical treatment for glycemic control was continued

AGE = Advanced Glycation End Product; BMI = Body Mass Index; CMR = Cardiac Magnetic Resonance; Ctr = Control; DB = Double-Blind; DBP = Diastolic Blood Pressure; EDV = End Diastolic Velocity; FPG = Fasting Plasma Glucose; HbA1c = Glycosylated Haemoglobin; HDL = High Density Lipoprotein; HOMA = Homeostasis Model Assessment; hs-CRP = High sensitivity C Reactive Protein; ICAM-1 = Intercellular Adhesion Molecule-1; IIEF = International Index of Erectile Function; LM and intense GC = Lifestyle Modifications and intensive Glycemic Control; LSC = Life Satisfaction Checklist; MCP-1 = Monocyte Chemotactic Protein-1; NT-proBNP = N-terminal pro-B-type Natriuretic Peptide; P = Parallel; PDE-5i = Phosphodiesterase-5 Inhibitors; PEQ = Personal Experiences Questionnaire; PI = Pulsatility Index; PINP = Procollagen Amino Terminal Propeptide; PLB = Placebo; PSV = Peak Systolic Velocity; RI = Resistive Index; SBP = Systolic Blood Pressure; SI = Stimulation Index; SWT = Systolic Wave Time; T = Testosterone; TC = Total Cholesterol; TG = Triglycerides; TZD = Thiazolidinediones; VEGF = Vascular Endothelial Growth Factor.

[a] Data = mean ± SD.

[b] Data = International Federation of Clinical Chemistry (IFCC).

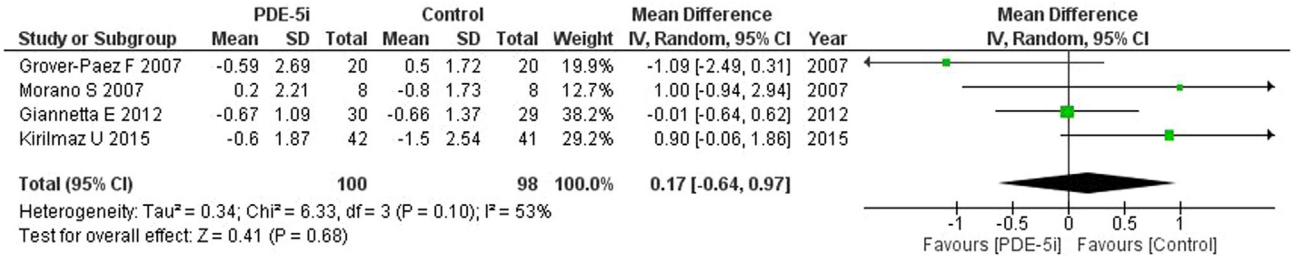

Fig. 2. Mean difference (95% CI) in the change of HbA1c for PDE-5i.

vascular tone and insulin action, NO-cGMP signalling regulates energy homeostasis and decreases body mass, as illustrated by long term sildenafil treating high-fat fed mice [4]. Likewise, short term sildenafil treatment augmented browning of white adipose tissue by increasing uncoupling protein-1 and PPAR-γ coactivator-1α protein expression, thereby leading to an improvement in energy balance and weight loss [24]. However, cGMP is barely detectable in human adipocytes although cAMP can be found abundantly [25]. It might be necessary to consider the abundance of PDE-5 in the vascular smooth muscle cells and the magnitude of the increase in cGMP levels by PDE-5i might be insufficient to activate PKG and to induce lipolysis and thermogenesis in adipocytes especially in the complicated pathophysiological processes of insulin resistant patients like type 2 diabetes [6]. In person with diabetes and hyperinsulinemia and advanced insulin resistance, insulin can up-regulate the expression of PDE-5 mRNA seen in human umbilical vein endothelial cells (HUVECs). Therefore, insulin induced PDE-5 up-regulation may be a possible reduced response of PDE-5i therapy [11]. This may explain why PDE-5 inhibitors had no effect on glycemic outcome in hyperinsulinemic insulin resistance conditions especially in person with type 2 diabetes. Thus, the up-regulation of PDE-5 expression induced by insulin appears to be one of the reasons of our negative findings.

NO causes a desensitization of the cGMP response reported in aortic smooth muscles. Moreover, PDE-5 is phosphorylated at a conserved serine residue by the cGMP-dependent PKG, leading to increased PDE-5 activity and limiting cGMP increase, which represents a negative feedback mechanism that lowers PKG activity again [26]. The regulatory domain of PDE-5, particularly GAF-A, reveals a major conformational change upon cGMP binding which apparently modifies the entire PDE-5 holoenzyme [27]. Since classic PDE-5 inhibitors interact with and block only the catalytic site of PDE-5, the impact of inhibition on the up-regulated PDE-5 activity could be too small for the person with type 2 diabetes. It has been reported that the levels of PDE-5 were increased and cGMP levels were reduced in the high-fat fed induced T2DM mice with ED, due to the increased ROS-mediated reduction of NO, when compared with type 1 diabetes mice, therefore PDE5 inhibitors may have reduced the efficacy in diabetes [28]. This might be an indicative of the negative results of our meta-analysis. Potential inhibitors acting at a regulatory GAF-A domain specific are expected to inhibit the pathophysiologically up-regulated PDE-5 activity without affecting basal PDE-5 activity [29].

To our knowledge, there is no systematic review which explores glycemic control in people with diabetes after chronic use of PDE-5i. A number of small randomized controlled trials were identified. The results of our analysis suggest that PDE-5 inhibition has no positive effect on glycemic control in patients with type 2 diabetes. As only published trials were included in our meta-analysis, there is a possibility of missing relevant data through publication bias. However, the number of studies included is too small to permit the use of funnel plot to assess the publication bias. There may be some methodological limitations across the included studies. Firstly, a small number of people with diabetes were enrolled, which may render the study to lack statistical power. Secondly, although most of studies used antidiabetic agents as primary treatment, they did not present full details of drug regimens and the diabetes management given to the patients, which could affect glycemic control. This made it difficult to evaluate the effect of PDE-5i. Lastly, most of the studies included were largely focused on erectile dysfunction and not primarily designed to examine the effect of glycemic outcomes.

Owing to significant heterogeneity across the studies ($I^2 = 53\%$), the clinical relevance of our meta-analysis may be weakened by variations in study population such as age, gender (men were included only) and race, dosages, level of glycemic control, duration of treatment and the patients' duration of diabetes diagnoses. More studies on clinical outcome are needed to better establish the effect of phosphodiesterase-5 inhibitors on glycemic control in person with type 2 diabetes mellitus. In one study, treatment duration was only 4 weeks [15], whereas others were of 12 weeks [14,16,17]. As the average lifespan of red blood cells is 120 days and their average half-life is about 8 weeks or 60 days, the appropriate treatment duration should be at least 8 weeks. The duration less than 120 days will usually give rise to low HbA1c results and may not accurately reflect glycemic control. It is believed that approximately 50% of glycation occur in 90–120 days and the remaining amount occurs before this [30]. Neither HbA1c reduction from PDE-5i treatment nor traditional antihyperglycemic treatments would be evident within 4 weeks. In addition, the dosages of PDE-5i used ranging from once daily [15,16] to twice weekly [14] or 2–3 times weekly [17], may be inadequate to achieve a possible improvement in glycemic outcome. The effect of dose was not explored as there were too small a number of studies to allow a subgroup analysis. Therefore, this inconsistency in sildenafil dosages is burdensome to draw conclusion from these studies. Due to chronic nature of diabetes and its complications, a wider range of daily dosing schedules may be required. Additionally, evidence from animal study suggested that hyperglycemia substantially evoked the up-regulation of PDE-5 in the sciatic nerve tissue of diabetic mice, rather than non-diabetes mice [31]. Indeed, the therapeutic response rate of PDE-5i is only 50–56% in the diabetes men with ED, whereas the reported efficacy of PDE-5i in the general population of men with ED is 74–97% [32]. Therefore, the homogenous daily dosing of PDE-5 inhibitors with longer treatment duration in patients with adult-onset T2DM, which is correlated with obesity, hyperglycemia and hyperinsulinemia, should be further explored.

In conclusion, the available evidence suggests inconclusive benefit of PDE-5 inhibitors, particularly sildenafil, on glycemic control as measured by HbA1c in type 2 diabetes. However, preserving cGMP levels by inhibiting phosphodiesterase-5 could be a prophylactic measure against the development of insulin resistance via improved endothelial dysfunction. With the correction of the lipid profile and the regulation of energy homeostasis, PDE-5i plays a role

in metabolic syndrome. Owing to variability in treatment duration and dosages of PDE-5i, large, and well-controlled studies are warranted. The long-term benefits of PDE-5 inhibitors on glycemic control remains to be determined. In addition, the emerging novel allosteric PDE-5 inhibitors targeting cGMP binding GAF-A domain is expected to represent efficient strategies for the chronic treatment of metaboglycemic disorders. Given the limitations of the currently available evidence based, larger and well-controlled studies with more consistent dosing of PDE-5 inhibitors and longer duration of trials with primary outcomes of the HbA1c or other measures of glycemic control are warranted to shed light on the effects of PDE-5 inhibitors on glycemic control in people with type 2 diabetes mellitus.

Conflict of interest

No conflicting relationship exists for any author.

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