Journal of Diabetes and Its Complications xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Effect of dipeptidyl peptidase-4 inhibitors on circulating tumor necrosis factor-α concentrations: A systematic review and meta-analysis of controlled trials

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ARTICLE INFO

Article history:
Received 1 May 2017
Received in revised form 25 May 2017
Accepted 30 May 2017
Available online xxxx

Keywords:
Tumor necrosis factor-α
Diabetes
Inflammation
DPP-iv
Meta-analysis

ABSTRACT

Objective: Dipeptidyl peptidase-4 (DPP-4) inhibitors improve glycemic control in patients with type 2 diabetes mellitus. There are also reports of an effect of these drugs in reducing inflammation through inhibition of tumor necrosis factor-α (TNF-α) that is an important mediator for several inflammatory processes. The present systematic review and meta-analysis were performed to evaluate the effect of DPP-4 inhibitors on circulating TNF-α levels in T2DM patients.

Methods: A systematic review and a meta-analysis were undertaken on all controlled trials of DPP-4 inhibitors that included measurement of TNF-α. The search included PubMed-Medline, Scopus, ISI Web of Knowledge and Google Scholar databases. Quantitative data synthesis was performed using a random-effects model, with standardized mean difference (SMD) and 95% confidence interval (CI) as summary statistics. Meta-regression and leave-one-out sensitivity analysis were performed to assess the modifiers of treatment response.

Results: Eight eligible articles (6 with sitagliptin and 2 with vildagliptin) comprising 9 treatment arms were selected for this meta-analysis. Meta-analysis suggested a significant reduction of circulating TNF-α concentrations following treatment with DPP-4 inhibitors (SMD: −1.84, 95% CI: −2.88, −0.80, $p = 0.001$). The effect size was robust in the sensitivity analysis and not mainly driven by a single study. A subgroup analysis did not suggest any significant difference between the TNF-α-lowering activity of sitagliptin (SMD: −1.49, 95% CI: −2.89, −0.10) and vildagliptin (SMD: −2.80, 95% CI: −4.98, −0.61) (p = 0.326).

Conclusion: This meta-analysis of the 8 available controlled trials showed that DPP-4 inhibition in patients with type 2 diabetes mellitus was associated with significant reductions in plasma TNF-α levels with no apparent difference between sitagliptin and vildagliptin.

1. Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors improve glycemic control in type 2 diabetes mellitus (T2DM) by inhibiting the enzyme DPP-4 that is present on the surface of most cells, and deactivates glucagon-like peptide-1 (GLP-1) secreted by the L-cells of the small intestine.[1] DPP-4 inhibitors increase the endogenous GLP-1 levels whose main action is to stimulate glucose-dependent insulin release from the pancreatic islets and is associated with delayed gastric emptying and decreased hepatic glucagon secretion, hence these agents are not associated with hypoglycemia (unless combined with insulin or sulphonylurea drugs) and have a weight neutral effect.[2,3]

Source of funding: No funding has been received for preparing this review.

Conflict of interests: MB has served on the speaker's bureau and as an advisory board member for Amgen, Sanofi, Aventis and Lilly. NK has given talks, attended conferences and participated in trials sponsored by Amgen, Angelini, Astra Zeneca, Boehringer Ingelheim, Galenica, MSD, Novartis, Novo Nordisk, Sanofi and WinMedica. DPM has given talks and attended conferences sponsored by MSD, Libytec and AstraZeneca. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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http://dx.doi.org/10.1016/j.jdiacomp.2017.05.016
1056-8727/

DPP-4 inhibitors are used mainly as add-on antidiabetic drugs to metformin, though monotherapy is considered in cases of metformin intolerance.[2] Licensed DPP-4 inhibitors (all are not available in every country) include alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin. Large clinical trials for the regulatory authorities have been undertaken to assess their cardiovascular effects that have suggested that there are no increased risks of adverse coronary heart disease outcomes in high-risk patients over 18 to 36 months apart from a potential increase in the risk of hospitalization for heart failure with saxagliptin and alogliptin.[4–6]

Tumor necrosis factor-α (TNF-α) is produced by activated macrophages and T cells, and is then secreted into the circulation and aggregates into a trimeric structure that binds to specific receptors i.e. TNF receptor R1 (TNFR1) and TNFR2.[7] This results in extensive immune effects including release of inflammatory cytokines, up-regulation of endothelial adhesion molecules and leukocyte migration, and is the target of biological antibody compounds (e.g. infliximab and adalimumab) used for chronic disease treatment.[8]

There are reports of the reduction of circulating TNF-α levels by DPP-4 inhibitors though the mechanism of this remains unclear.[9] This potential anti-inflammatory property of DPP-4 inhibitors could be an important pleiotropic effect given that low-grade inflammation is implicated in the atherosclerotic process[10] and may play an important role in the development of T2DM complications.[11,12] The present systematic review and meta-analysis were performed to evaluate the effect of DPP-4 inhibitors on circulating TNF-α levels in T2DM patients.

2. Methods

2.1. Search strategy

These systematic review and meta-analysis were designed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[13] PubMed-Medline, Scopus, ISI Web of Knowledge and Google Scholar databases were searched using the following terms in titles and abstracts: (alogliptin or camegliptin or dutogliptin or gemigliptin or linagliptin or saxagliptin or sitagliptin or teneligliptin or vildagliptin) AND ("tumor necrosis factor-α" OR "tumor necrosis factor α" OR "tumor necrosis factorα" OR TNF-α OR TNFα OR "TNF α"). All interchangeable formats of "α" including "alfa", "alpha" and "a" were also used during the search. The wild-card term "*" was used to increase the sensitivity of the search strategy. The search was limited to articles published in English language. The literature was searched from inception to April 02, 2017.

2.2. Study selection

Original studies were included if they met the following inclusion criteria: (i) controlled clinical trial with either parallel or cross-over design, (ii) investigating the impact of DPP-4 inhibitors versus control on circulating concentrations of TNF-α, and (iii) included sufficient information on TNF-α concentrations at baseline and at study end in both intervention and control groups or providing the net change values. Exclusion criteria were: (i) non-clinical studies, (ii) uncontrolled studies, (iii) observational studies with case–control,

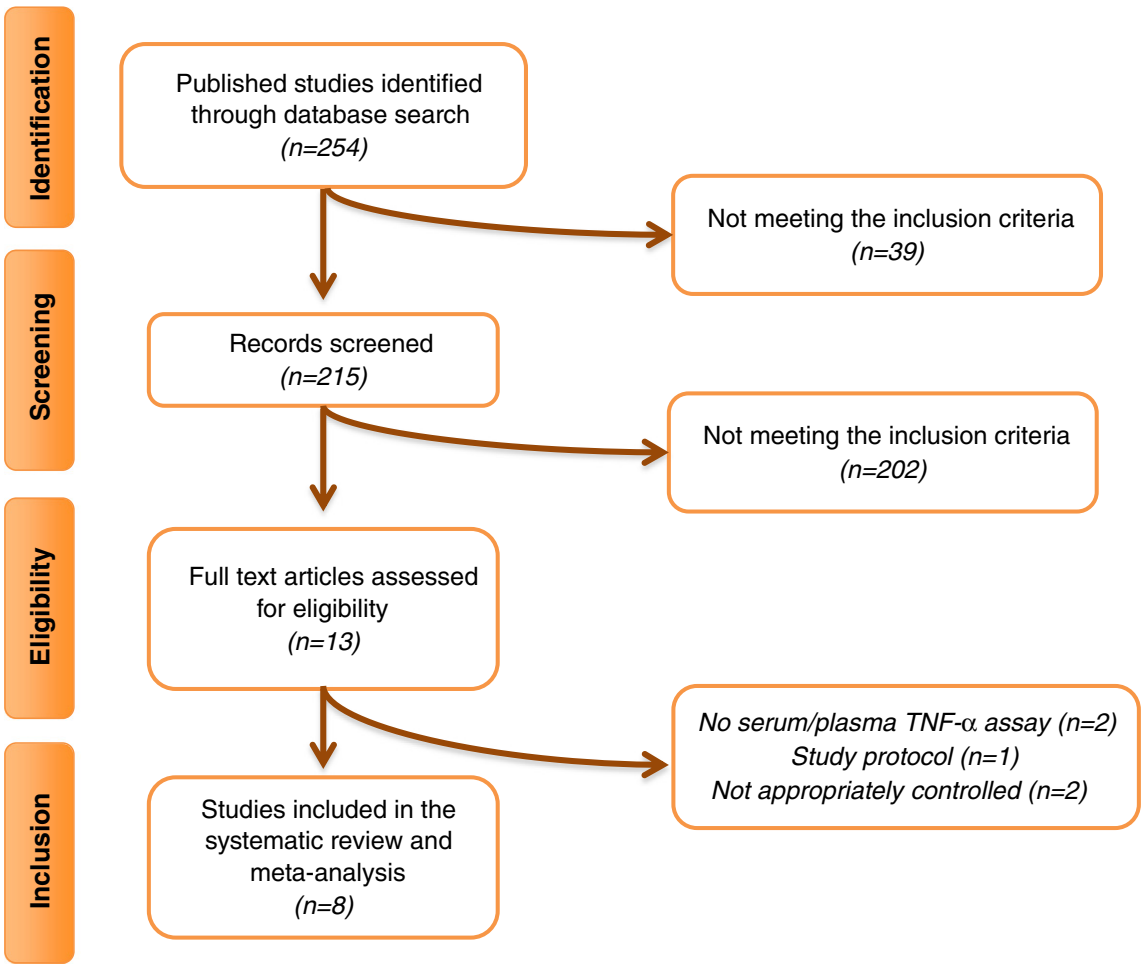

Fig. 1. Flow chart of the number of studies identified and included into the meta-analysis.

Please cite this article as: Atkin SL, et al. Effect of dipeptidyl peptidase-4 inhibitors on circulating tumor necrosis factor-α concentrations: A systematic review and meta-an.... *Journal of Diabetes and Its Complications* (2017), http://dx.doi.org/10.1016/j.jdiacomp.2017.05.016