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Anti-inflammatory properties of antidiabetic drugs: A “promised land” in the COVID-19 era?



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ABSTRACT

Inflammation is implicated in the development and severity of the coronavirus disease 2019 (COVID-19), as well as in the pathophysiology of diabetes. Diabetes, especially when uncontrolled, is also recognized as an important risk factor for COVID-19 morbidity and mortality. Furthermore, certain inflammatory markers [*i.e.* C-reactive protein (CRP), interleukin-6 (IL-6) and ferritin] were reported as strong predictors of worse outcomes in COVID-19 positive patients. The same biomarkers have been associated with poor glycemic control. Therefore, achieving euglycemia in patients with diabetes is even more important in the era of the COVID-19 pandemic. Based on the above, it is clinically interesting to elucidate whether antidiabetic drugs may reduce inflammation, thus possibly minimizing the risk for COVID-19 development and severity. The present narrative review discusses the potential anti-inflammatory properties of certain antidiabetic drugs (*i.e.* metformin, pioglitazone, sitagliptin, linagliptin, vildagliptin, alogliptin, saxagliptin, liraglutide, dulaglutide, exenatide, lixisenatide, semaglutide, empagliflozin, dapagliflozin, canagliflozin), with a focus on CRP, IL-6 and ferritin.

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1. Introduction

Inflammation plays a key role in the development and severity of the new coronavirus disease 2019 (COVID-19).¹ Indeed, severe COVID-19 pneumonia is related to systemic hyper-inflammation (or cytokine storm).² Serum C-reactive protein (CRP), interleukin-6 (IL-6) and ferritin have been recognized as strong predictors of the COVID-19 severity and mortality.^{3–5} Diabetes is also considered as a significant risk factor for COVID-19 morbidity and mortality.⁶ Indeed, a recent meta-analysis (83 studies, $n = 78,874$ hospitalized patients with confirmed COVID-19) reported that pre-existing diabetes almost doubled the risk for severe/critical COVID-19 [$n = 22$ studies; odds ratio (OR) 2.10, 95% confidence interval (95%CI) 1.71–2.57] and almost tripled in-hospital mortality (OR 2.68, 95%CI 2.09–3.44).⁷ Similar results were reported in another meta-analysis (33 studies, $n = 16,003$ patients) for both COVID-19 severity (OR 2.75, 95%CI 2.09–3.62) and mortality (OR 1.90, 95%CI 1.37–2.64).⁸ Furthermore, chronic, low-grade inflammation is associated with insulin resistance and hyperglycemia,^{9–11} and inflammatory markers, such as CRP, IL-6 and ferritin, have been quantitatively related to HbA_{1c}.^{12–14} This highlights the importance of achieving euglycemia in patients with diabetes, especially in the era of COVID-19.

Based on the above, it is relevant to establish whether antidiabetic therapies may reduce the inflammatory reaction, thus possibly minimizing the risk for COVID-19 development and severity. The present narrative review discusses the potential anti-inflammatory properties of certain antidiabetic drugs (*i.e.* metformin, pioglitazone, sitagliptin, linagliptin, vildagliptin, alogliptin, saxagliptin, liraglutide, dulaglutide, exenatide, lixisenatide, semaglutide, empagliflozin, dapagliflozin, canagliflozin), based mainly on available data from clinical studies and with a focus on CRP, IL-6 and ferritin.

1.1. Metformin

Metformin mechanism of action classically involves both AMP-activated protein kinase (AMPK)-independent and AMPK-dependent pathways.¹⁵ In many studies, this drug has been shown to inhibit mitochondrial respiration as well as mitochondrial glycerophosphate dehydrogenase, leading to suppression of ATP production and hepatic gluconeogenesis, whereas AMPK activation enhances catabolic pathways generating ATP and switches off cellular processes consuming ATP.^{15,16}

There is basic and clinical evidence for an anti-inflammatory action of metformin.¹⁷ Metformin was also shown to suppress the secretion of pro-inflammatory cytokines in hepatocytes and macrophages.¹⁸ Among 110 patients with type 2 diabetes mellitus (T2DM), those on metformin ($n = 65$) had significantly lower CRP levels compared with those on glibenclamide ($n = 45$) (5.6 vs 8.3 mg/dL, $p = 0.01$).¹⁹ In another study, 208 T2DM patients were randomly assigned to metformin or placebo for 24 weeks; serum CRP levels were significantly decreased from 14.4 ± 0.6 to 9.6 ± 0.2 mg/L ($p < 0.001$) in the metformin group, whereas they were unchanged in the placebo group (from 14.5 ± 0.6 to 15.8 ± 0.8 mg/L).²⁰ In the Diabetes Prevention Program (DPP), among metformin-treated T2DM men ($n = 363$) and women ($n = 710$), CRP was significantly reduced at 1 year (by 7%, $p = 0.006$ and by 14%, $p < 0.001$, respectively).²¹ However, others have reported no effects of metformin on CRP²² or high-sensitivity CRP (hsCRP)²³ in T2DM patients. Previous meta-analyses also reported that metformin significantly reduced CRP in middle-age and older adults with chronic low-grade inflammation [142 studies; 3247 patients; standardized mean difference (SMD): -0.16; 95%CI: -0.22 to -0.09, $p < 0.0001$; $I^2 = 79.9\%$],²⁴ as well as in women with polycystic ovary syndrome (17 studies; 403 women; SMD: -0.86; 95%CI: -1.24 to -0.48, $p < 0.0001$; $I^2 = 84.6\%$).²⁵

Data on the effects of metformin on IL-6 and ferritin are limited. Metformin was shown to inhibit IL-6 expression in mucosal cells of patients with inflammatory bowel disease.²⁶ Furthermore, metformin suppressed IL-1 β -induced release of IL-6 in human macrophages, vascular smooth muscle and endothelial cells.²⁷ Circulating IL-6 levels were

reduced in a duration- and dose-dependent manner (*i.e.*, at a dose of 1000 mg q.d. for 1 year) after 12 months of metformin therapy in T2DM patients ($n = 112$).²⁸ Similarly, metformin (titrated up to 1500 mg q.d.) significantly lowered IL-6 (from 133 ± 68 to 114 ± 57 pg/mL, $p < 0.05$) at 12 months in 36 T2DM patients.²⁹ In the same study, ferritin was also decreased (from 171 ± 23 to 164 ± 19 ng/mL, $p < 0.05$) following metformin treatment.²⁹

1.2. Pioglitazone

Pioglitazone is a peroxisome proliferator-activated receptor (PPAR)- γ agonist that reduces insulin resistance by stimulating lipogenesis and suppressing lipolysis in the adipose tissue, as well as by decreasing hepatic triglycerides, visceral fat mass and activity, thus promoting peripheral insulin sensitivity.^{30,31} Furthermore, pioglitazone enhances glucose uptake by the skeletal muscle and beta-cell function.³²

In animal studies, the expression of IL-6 was suppressed in human monocytes³³ as well as in white adipose tissue and cardiomyocytes.^{34,35} In 34 T2DM patients, pioglitazone therapy for 6 months significantly decreased circulating CRP levels (from 1.73 ± 1.30 to 1.23 ± 0.75 μ g/mL, $p < 0.05$); IL-6 levels were non-significantly reduced (from 1.78 ± 1.32 to 1.50 ± 0.97 pg/mL, $p = ns$).³⁶ Similarly, a previous meta-analysis reported that pioglitazone significantly lowered hsCRP levels (15 trials, $n = 1448$ T2DM patients; SMD = -0.54, 95%CI: -0.92 to -0.16, $p < 0.05$; $I^2 = 90\%$) but not IL-6 (4 trials, $n = 422$ T2DM patients; SMD = -1.5, 95%CI: -3.08 to 0.07, $p = 0.06$).³⁷ No data exist on the impact of pioglitazone on ferritin.

1.3. Dipeptidyl peptidase-4 inhibitors (DPP4-i)

DPP4-i increase the endogenous levels of bioactive incretins, including glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), by inhibiting their enzymatic degradation.³² As a consequence, insulin secretion is enhanced in a glucose-dependent way, whereas glucagon secretion is suppressed.³²

DPP4-i may exert immune regulatory functions, that are potentially beneficial in autoimmune and inflammatory diseases, as recently reviewed.³⁸ A recent meta-analysis ($n = 1607$ T2DM patients; 16 trials) reported a significant reduction in CRP levels following DPP4-i therapy compared with placebo (WMD: -0.86 mg/L; 95%CI: -1.36 to -0.36, $p = 0.001$; $I^2 = 84.4\%$).³⁹

1.4. Sitagliptin

itagliptin (either 50 or 100 mg/day) has been reported to significantly decrease CRP levels in 67 newly diagnosed T2DM patients at 12 weeks (from 6.1 ± 1.0 to 3.3 ± 0.5 mg/L, $p < 0.05$),⁴⁰ in 48 patients at 3 months (from 0.8 ± 0.1 to 0.5 ± 0.1 μ g/L, $p < 0.05$),⁴¹ in 22 patients at 12 weeks (by 24%, $p < 0.05$),⁴² in 36 patients at 6 weeks (by 44.9%, $p = 0.006$)⁴³ and in 20 T2DM patients at 6 months [from 1.60 (0.45–2.85) to 0.70 (0.35–1.25) mg/L, $p < 0.01$].⁴⁴ Furthermore, hsCRP was significantly reduced over 7 years of follow-up in T2DM patients treated with sitagliptin (100 mg/day) in combination with either metformin ($n = 201$; from 2.4 ± 0.9 to 1.8 ± 0.4 mg/L, $p < 0.05$), pioglitazone ($n = 196$; from 2.5 ± 1.0 to 2.0 ± 0.6 , $p < 0.05$) or sulfonylureas ($n = 194$; from 2.3 ± 0.8 to 1.8 ± 0.3 mg/L, $p < 0.05$).⁴⁵ Sitagliptin (100 mg/day)-induced CRP decrease was also reported elsewhere.^{46,47} In contrast, the Sitagliptin Investigation on Glycemic Effects in Yokohama (SINGLE-Y) study, involving 270 T2DM patients, found that 3 months of sitagliptin (50 mg/day) did not affect hsCRP (from 0.12 ± 0.78 to 0.09 ± 0.10 mg/dL, $p = ns$).⁴⁸ Furthermore, no significant change in hsCRP was observed in another study of 205 T2DM patients treated with sitagliptin (25, 50, or 100 mg/day) for 12 months.⁴⁹ Similar results were reported in other studies using sitagliptin 50 or 100 mg/day.^{50–52}

IL-6 levels were non-significantly decreased at 3 months among 24 sitagliptin-treated T2DM patients (from 3.5 ± 0.6 to 2.7 ± 0.3 pg/mL,

$p = ns$),⁴¹ whereas they were significantly lowered by sitagliptin in 22 T2DM patients at 12 weeks (by 24%, $p < 0.05$),⁴² as well as at 12 months (from 15.8 ± 6.2 to 12.8 ± 4.3 pg/mL, $p = 0.03$) in 31 T2DM patients.⁵³

The impact of sitagliptin on ferritin has not been investigated. There is only one study involving 5 T2DM patients with major beta-thalassemia treated with sitagliptin; there was a trend of ferritin reduction in 4/5 patients.⁵⁴

1.4.1. Linagliptin

Data on linagliptin and CRP are scarce. In one study, involving 21 T2DM patients on hemodialysis (HD), no change in CRP levels was found at 6 months after initiating linagliptin.⁵⁵ Similar results were reported among 35 T2DM patients undergoing HD receiving linagliptin for 3 months⁵⁶ and among 45 T2DM patients on linagliptin for 26 weeks.⁵⁷ Linagliptin was found to inhibit IL-6 production in human umbilical vein endothelial cells⁵⁸ and monocytes.⁵⁹ No relevant human studies are available. There is only one study investigating ferritin changes after 6 months of linagliptin therapy among 25 T2DM patients on HD, reporting no effect.⁶⁰

1.4.2. Vildagliptin

Among 60 T2DM patients with coronary artery disease (CAD), 12-week vildagliptin therapy reduced hsCRP by 60%.⁶¹ Similar effects were also reported in other studies.^{62–66} Neutral studies also exist.^{67,68}

In animal studies, vildagliptin was shown to attenuate the isoproterenol-induced increased mRNA expression of IL-6 in cardiomyocytes.⁶⁹ However, no change in IL-6 was observed following 12 weeks of vildagliptin therapy in 27 T2DM patients.⁷⁰ In contrast, another study found a significant decrease in IL-6 levels in vildagliptin-treated T2DM patients at 12 weeks (from 2.47 ± 0.52 to 1.54 ± 0.16 pg/mL, $p < 0.01$).⁷¹ No study has investigated the impact of vildagliptin on ferritin.

1.4.3. Alogliptin

Limited data exist on the effects of alogliptin on CRP or IL-6. No significant change in hsCRP levels were observed at 24 months following alogliptin treatment in the Study of Preventive Effects of Alogliptin on Diabetic Atherosclerosis (SPEAD-A) ($n = 172$ T2DM patients).⁷² In animal models, alogliptin decreased IL-6,^{73,74} as also shown in *in vitro* studies.⁷⁵ In humans, in the SPEAD-A study, IL-6 was significantly increased [baseline = 2.1 ($1.4, 2.7$) ng/dL; median change 0.1 ($-0.3, 0.7$), $p < 0.05$] in alogliptin-treated T2DM patients followed for 24 months.⁷² There are no data on ferritin and alogliptin.

1.4.4. Saxagliptin

In diabetic mice, saxagliptin was able to reduce serum CRP.⁷⁶ However, no impact on hsCRP was observed in saxagliptin-treated T2DM patients compared with placebo in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53 (SAVOR-TIMI 53) trial.⁷⁷ Similarly, saxagliptin did not affect the secretion of IL-6 from adipocytes in 40 non-diabetic overweight/obese patients followed for 6 weeks.⁷⁸ No data on ferritin and saxagliptin exist.

1.5. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs)

GLP-1 RAs promote insulin secretion by the beta-cells and inhibit glucagon secretion by the alpha-cells of the pancreas.⁷⁹ GLP-1 RAs also delay gastric emptying and suppress food intake.⁷⁹ GLP-1 RAs have been reported to exert anti-inflammatory properties *via* several molecular mechanisms, both *in vivo* and *in vitro*.⁸⁰

1.5.1. Liraglutide

Liraglutide has been reported to exert antioxidant and anti-inflammatory effects *in vitro*^{81,82} as well as in T2DM patients⁸³ and in patients with non-ST-segment elevation myocardial infarction.⁸⁴ In

this context, among 52 T2DM patients receiving liraglutide at a dose of 0.6–1.2 mg/day for 12 weeks, CRP was significantly decreased (by 0.89 ± 0.59 mg/L, $p = 0.018$).⁸⁵ Similar results were observed following liraglutide (1.2–1.8 mg/day) therapy for 24 weeks in T2DM patients.^{86–89} Of note, liraglutide-induced weight loss was related to improvements in circulating hsCRP levels in obese patients with prediabetes or T2DM.⁹⁰ In contrast, no significant changes in hsCRP were observed among 44 T2DM patients after 6 and 12 weeks of liraglutide (1.2 and 1.8 mg/day, respectively)⁹¹ as well as among 165 T2DM after 14 weeks of liraglutide (0.65–1.9 mg/day).⁹²

Liraglutide significantly reduced both circulating and hepatic levels of IL-6 in diabetic mice⁹³ as well as IL-6 expression in the hippocampus, suggesting protection against neuroinflammation.⁹⁴ In T2DM patients, a recent meta-analysis of 13 randomized controlled trials ($n = 1187$; follow-up ranged from 8 to 24 weeks), found that IL-6 concentrations were significantly lower [mean difference (MD): -3.90 ; 95%CI: -5.03 to -2.76 , $p < 0.00001$] in the liraglutide group (1.2 mg/day) compared with the controls in those with stage 3 diabetic nephropathy.⁹⁵ Similarly, liraglutide (1.2–1.8 mg/day) for 26 weeks led to a significant reduction in circulating IL-6 levels (-22.6% ; 95%CI: $-38.1, -3.2$, $p = 0.025$) among 19 type 1 DM patients.⁹⁶ One study, however, reported no changes in IL-6 concentrations after 14 weeks of liraglutide (0.65–1.9 mg/day).⁹²

Liraglutide (0.9 mg/day for 24 weeks) was shown to significantly decrease serum ferritin levels (from 158.9 ± 147.4 to 91.8 ± 69.9 ng/mL, $p < 0.01$) in 19 T2DM patients with NAFLD/NASH based on liver biopsy in the LEAN-J study.⁹⁷ No other relevant data exist.

1.5.2. Dulaglutide

There are limited data on dulaglutide, CRP and IL-6. In one study, 755 T2DM patients were randomized to receive either dulaglutide once weekly (0.75 or 1.5 mg) or placebo; changes from baseline in hsCRP levels at 16 weeks were $-0.98, -0.08$ and 0.62 mg/L for dulaglutide 1.5 mg ($p < 0.001$ compared with placebo), dulaglutide 0.75 mg, and placebo, respectively.⁹⁸ In another smaller study, once weekly dulaglutide (0.75 mg in 8 T2DM patients and 1.5 mg in 5 patients) led to a significant reduction in serum IL-6 levels (from 1.42 ± 0.84 to 0.31 ± 0.23 pg/mL, $p < 0.001$) at 26 weeks.⁹⁹ No study investigated the effects of dulaglutide on ferritin.

1.5.3. Exenatide

Exenatide reduced circulating markers of oxidative stress and inflammation in T2DM patients.^{100,101} In 61 T2DM patients on exenatide (5 or 10 μ g twice daily) for a mean of 1.4 years, circulating CRP levels decreased from 5.1 ± 1.7 to 2.7 ± 1.2 mg/L ($p < 0.001$).¹⁰² Similarly, serum hsCRP was lowered by 34% ($p = 0.05$) in 38 T2DM patients taking exenatide (5 μ g twice per day) for a mean of 26 weeks.¹⁰³ In another study involving 23 T2DM patients (11 patients on placebo and 12 patients on exenatide 5 μ g twice daily for 4 weeks, followed by 10 μ g twice daily for 12 weeks), hsCRP was significantly reduced in the exenatide group (-37%) compared with placebo ($+137\%$).¹⁰⁰ Exenatide therapy for 1 year also led to lower hsCRP levels (from 1.81 ± 0.25 to 1.30 ± 0.22 mg/L, $p = 0.008$) in 30 T2DM patients.¹⁰⁴

Circulating IL-6 levels fell from 3.01 ± 0.49 to 2.07 ± 0.57 pg/mL ($p < 0.05$) after 12 weeks of exenatide treatment (10 μ g twice daily) in 12 T2DM patients.¹⁰⁵ In another study, 18 T2DM patients received exenatide for 3 months (5 μ g twice daily for the first month, followed by 10 μ g for the next 2 months); serum IL-6 concentrations were reduced from 15.69 ± 10.86 ng/mL at baseline to 10.76 ± 5.15 ng/mL at 3 months ($p = 0.001$).¹⁰⁶ No data on the effects of exenatide on ferritin are currently available.

1.5.4. Lixisenatide

Lixisenatide was reported to downregulate the expression of proinflammatory cytokines, including IL-6, in human fibroblast-like

synoviocytes and in primary chondrocytes.^{107,108} No human study evaluated the impact of lixisenatide on CRP, IL-6 and ferritin.

1.5.5. Semaglutide

In a 52-week weight management trial ($n = 957$ non-diabetic obese patients randomized to oral semaglutide 0.05–0.4 mg/day or placebo), hsCRP was reduced by up to 43% vs placebo in all semaglutide groups at week 52; these reductions were either significant or close to significance.¹⁰⁹ However, statistical significance was lost after adjustment for change in body weight.¹⁰⁹ In another 52-week randomized, open-label trial involving 412 T2DM patients on oral semaglutide 14 mg and 410 T2DM patients on empagliflozin 25 mg, greater decreases in CRP levels were observed at 52 weeks in the semaglutide than in the empagliflozin group (estimated treatment ratio: 0.74, 95%CI: 0.65, 0.84, $p < 0.0001$).¹¹⁰ No data exist on semaglutide, IL-6 and ferritin.

1.6. Sodium Glucose Co-Transporter-2 inhibitors (SGLT2i)

SGLT2i inhibit the renal reabsorption of glucose, thus promoting renal glucose excretion and, subsequently, lowering plasma glucose levels.^{111,112} Potential anti-inflammatory effects have been reported for SGLT2i¹¹³.

1.6.1. Empagliflozin

Among 50 T2DM patients with CAD, empagliflozin 10 mg/day significantly lowered CRP at 6 months (from 0.11 to 0.07 mg/dL, $p = 0.003$).¹¹⁴ Empagliflozin 10 mg/day for 12 months also notably reduced hsCRP by 54% (from 1.33 to 0.59 mg/L, $p = 0.007$) in 51 T2DM patients.¹¹⁵ However, in another study with 58 T2DM patients receiving empagliflozin 25 mg/day for 6 weeks, no significant changes in hsCRP levels were found (2.10 ± 1.72 vs 1.99 ± 1.19 mg/L, baseline vs 6 weeks, respectively).¹¹⁶

Interestingly, empagliflozin was reported to decrease markers of oxidative stress and inflammation (including IL-6) in the lungs of mice, thus suggesting a role in preventing pulmonary fibrosis,¹¹⁷ as well as in rat cardiomyoblasts (including reduction of IL-6 expression), thus potentially minimizing infarct size.¹¹⁸ Similarly, in diabetic rats empagliflozin exhibited anti-oxidant and anti-inflammatory effects in the kidneys; urinary IL-6 levels were also lowered.¹¹⁹ Overall, experimental data strongly support a protective role of empagliflozin against cardiac and renal inflammation.^{120,121} However, clinical evidence is lacking. There is one study reporting that empagliflozin significantly reduced circulating IL-6 levels in 32 men T2DM patients; this IL-6-lowering effect of empagliflozin was greater than that of canagliflozin.¹²²

In a large-scale proteomics study, empagliflozin 25 mg/day led to significant decreases in circulating ferritin levels after 4 weeks of treatment.¹²³ Furthermore, a sub-study of the EMPA-HEART CardioLink-6 randomized clinical trial, involving 82 T2DM patients with CAD, showed that 6 months of empagliflozin treatment (10 mg/day) was associated with a significant reduction in ferritin levels (mean difference $-21.83 \mu\text{g/L}$, 95%CI: $-37.96, -5.7$; $p = 0.008$).¹²⁴

1.6.2. Dapagliflozin

In animal studies, dapagliflozin was shown to exert anti-oxidant and anti-inflammatory actions in the kidney, liver and lungs.^{125,126} There is also data supporting a CRP-lowering effect of dapagliflozin in humans.¹²⁷ In this context, dapagliflozin 10 mg/day combined with metformin significantly lowered CRP (from 6.2 ± 1.1 to 3.1 ± 0.7 mg/L, $p < 0.05$) in 59 T2DM patients at 12 weeks²⁶ as did dapagliflozin 5 mg/day after 12 weeks (from 2410 ± 2814 to 1607 ± 1960 ng/mL, $p < 0.01$) in 27 T2DM patients.¹²⁸ In contrast, among 11 T2DM patients with non-alcoholic steatohepatitis, treatment with dapagliflozin 5 mg/day for 24 weeks led to a non-significant reduction in hsCRP.¹²⁹ Furthermore, another study reported a significant increase in median hsCRP levels in 36 T2DM patients treated with dapagliflozin (10 mg/day) for 12 weeks (from 1.93 to 6.03 mg/L, $p = 0.009$).¹³⁰

In a randomized, placebo-controlled study ($n = 32$ T2DM patients), 8 weeks of dapagliflozin (10 mg/day) therapy led to a significant placebo-corrected reduction in IL-6 levels (by -1.87 pg/mL, $p < 0.05$).¹³¹ A *post-hoc* analysis of another randomized, double-blind, placebo-controlled trial involving 33 T2DM patients, found that urinary IL-6 excretion was significantly decreased by 23.5% ($p = 0.04$).¹³²

With regard to ferritin, there are studies reporting that dapagliflozin 5 mg/day significantly decreased ferritin levels in T2DM patients with either NASH or non-alcoholic fatty liver disease (NAFLD).^{129,133} Similarly, ferritin was significantly lowered after 12 weeks of dapagliflozin (10 mg/day) therapy in 26 obese T2DM patients.¹³⁴

1.6.3. Canagliflozin

Among 100 T2DM patients treated with canagliflozin 300 mg/day for 52 weeks, there was a non-significant trend for a decrease in serum CRP levels.¹³⁵ Furthermore, no change was observed in serum CRP after 12 weeks of canagliflozin 100 mg/day therapy in 12 T2DM patients.¹³⁶ In contrast, hsCRP was significantly reduced from baseline at 3, 6 and 12 months of treatment (from 0.39 ± 0.07 to 0.20 ± 0.05 , 0.20 ± 0.04 and 0.21 ± 0.04 ng/mL, respectively, $p < 0.05$) in 35 T2DM patients with chronic heart failure treated with canagliflozin 100 mg/day.¹³⁷

A proteomic model found that canagliflozin 300 mg/day significantly lowered plasma IL-6 concentrations (by 26.6%, $p = 0.010$).¹³⁸ Similar results were reported in animal studies.^{139,140} However, in human studies no significant changes in IL-6 levels have been found following treatment with canagliflozin (100 mg/day, 24 weeks).^{122,141} In contrast, canagliflozin 300 mg/day for 52 weeks was shown to significantly lower serum IL-6 (by 22%) in 100 T2DM patients.¹³⁵

In a small study (9 T2DM patients), canagliflozin 100 mg/day for 12 weeks led to a significant decrease in median ferritin levels (from 72 to 55 ng/mL, $p = 0.003$).¹⁴² Furthermore, serum ferritin concentrations were significantly and progressively lowered from baseline to 3 and 6 months (from 184.9 to 143.8 and 117.3 ng/mL, respectively, $p < 0.05$) in 35 canagliflozin (100 mg/day)-treated NAFLD patients.¹⁴³ Similar results were also reported in T2DM patients with biopsy-proven NASH.¹⁴⁴ Of note, SGLT2i have been suggested for NAFLD/NASH treatment^{145–147} as is the case for pioglitazone and GLP-1 Ras.^{148,149}

Overall, diabetes has been closely linked to inflammation.¹⁵⁰ Furthermore, HbA_{1c} has been positively related to hsCRP, IL-6 and ferritin levels,^{151–155} thus supporting also a role for euglycemia in reducing chronic inflammation in patients with diabetes. Apart from antidiabetic drugs, a healthy lifestyle (including diet, exercise and no smoking) can contribute to glucose and inflammation control.^{156,157} Interestingly, HbA_{1c} level was positively associated with inflammation and hypercoagulability, as well as negatively associated with SaO₂ in COVID-19 infected patients,¹⁵⁸ thus further highlighting the importance of achieving glucose control in the COVID-19 era.

1.7. Limitations of current evidence

Despite the multitude of reports, the data here analyzed (summarized in Table 1 for the human studies) fall short of providing good evidence for a clinically significant anti-inflammatory effect of the most common antidiabetic classes of medication for several reasons. Firstly, studies were frequently small in size or detecting small differences. Secondly, many studies involved patients of Asian origin, without appropriate control for other ethnicities. Thirdly, studies of similar design yielded contrasting results for one or the other biomarker, or inconsistent findings across biomarkers. Finally, and perhaps more importantly, most studies did not control, or were not equipped, for the anti-hyperglycemic effect, so that a *bona fide* pharmacologic effect of a given drug cannot be distinguished from a non-specific effect of improved glycemia.

Table 1
Summary of the effects of antidiabetic drugs on C-reactive protein, interleukin-6 and ferritin in human studies.

	C-reactive protein	Interleukin-6	Ferritin
Metformin	↓ —	↓	↓
Pioglitazone	↓	—	No data
Sitagliptin	↓ —	↓ —	No data
Linagliptin	—	No data	—
Vildagliptin	↓ —	↓ —	No data
Alogliptin	—	↑	No data
Saxagliptin	—	—	No data
Liraglutide	↓ —	↓ —	↓
Dulaglutide	↓	↓	No data
Exenatide	↓	↓	No data
Lixisenatide	No data	No data	No data
Semaglutide	↓	No data	No data
Empagliflozin	↓ —	↓	↓
Dapagliflozin	↑ ↓ —	↓	↓
Canagliflozin	↓ —	↓ —	↓

2. Conclusions

With all these limitations, perhaps the most suggestive data are those on ferritin for the SGLT2 inhibitors, which may be related to enhanced erythropoiesis rather than tissues inflammation. In any event, large, multiethnic, equipoised trials would be required to determine whether certain antidiabetic drugs exert inherent anti-inflammatory properties above and beyond their antihyperglycemic efficacy; the latter remains decidedly useful in COVID-19 disease.

Declaration of competing interest

NK has given talks, attended conferences and participated in trials sponsored by Astra Zeneca, Bausch Health, Boehringer Ingelheim, Elpen, Mylan, NovoNordisk, Sanofi and Servier. EF has received research support by Boehringer Ingelheim/Lilly&Co., AstraZeneca and Janssen and speaker's honoraria by Boehringer Ingelheim/Lilly&Co., Sanofi and AstraZeneca.

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