



Anti-inflammatory Agents in the Treatment of Diabetes and Its Vascular Complications

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The association between hyperglycemia and inflammation and vascular complications in diabetes is now well established. Antidiabetes drugs may alleviate inflammation by reducing hyperglycemia; however, the anti-inflammatory effects of these medications are inconsistent and it is unknown whether their beneficial metabolic effects are mediated via modulation of chronic inflammation. Recent data suggest that immunomodulatory treatments may have beneficial effects on glycemia, β -cell function, and insulin resistance. However, the mechanisms underlying their beneficial metabolic effects are not always clear, and there are concerns regarding the specificity, safety, and efficacy of immune-based therapies. Herein, we review the anti-inflammatory and metabolic effects of current antidiabetes drugs and of anti-inflammatory therapies that were studied in patients with type 2 diabetes. We discuss the potential benefit of using anti-inflammatory treatments in diabetes and important issues that should be addressed prior to implementation of such therapeutic approaches.

The prevalence of diabetes is on the rise, with 415 million people affected worldwide according to recent data from the International Diabetes Federation (1). This number is predicted to increase further, with 642 million people expected to develop diabetes by 2040. While many factors are known to contribute to the development of diabetes and its complications, the involvement of the immune system in the pathogenesis of metabolic diseases has been gaining interest. It has long been appreciated that inflammation is central to the pathology of the pancreatic islet in type 1 diabetes. However, growing evidence suggests that inflammation also plays an important role in the pathogenesis of type 2 diabetes, including obesity-related insulin resistance, impaired insulin secretion, and diabetes-related vascular complications. Pioneering studies suggest that immunomodulatory treatments may improve glycemia, β -cell function, and/or insulin resistance in patients with type 2 diabetes (2,3). These studies constitute a proof of concept that chronic inflammation is implicated in the pathophysiology of type 2 diabetes, and therefore targeting inflammation may ameliorate diabetes, preventing its progression and vascular complications. However, the effects of immunomodulatory treatments are not limited to tissues involved in disease pathophysiology and thus might have unwarranted side effects. Moreover, current antidiabetes drugs may alleviate systemic and tissue-specific inflammation (4–12), and therefore the added value of using specific immunomodulatory treatments needs to be confirmed. Herein, we review the anti-inflammatory and metabolic effects of standard antidiabetes medications and of novel anti-inflammatory treatments. We further discuss issues that should be addressed prior to implementation of immune-based therapy in the treatment of diabetes.

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Role of Inflammation in Metabolic Disorders

Multiple mechanisms are thought to contribute to β -cell dysfunction, insulin resistance, and vascular complications of diabetes. They have previously been extensively reviewed and are beyond the scope of the current review (13). We briefly refer to several key mechanisms regulating inflammation in diabetes and their translational implications. In diabetes, hyperglycemia and elevated free fatty acids may promote inflammation by stimulating glucose utilization along with alterations in oxidative phosphorylation (3,4,14). Such metabolic dysregulation has been shown to induce a proinflammatory trait in macrophages residing or invading the adipose tissue and other tissues including the islets and vasculature (15–19). Glucotoxicity and lipotoxicity might also exert oxidative and endoplasmic reticulum stress, which in turn elicits an inflammatory response by activating thioredoxin-interacting protein (TXNIP) and the NLR family, pyrin domain containing 3 (NLRP3) inflammasome, which increase the release of active interleukin (IL)-1 β (3,4,14,18,20). IL-1 β further amplifies inflammation by inducing the expression of various cytokines and chemokines, resulting in the recruitment of immune cells including macrophages (“auto-stimulation”) (21). Similar mechanisms have been reported in diabetic β -cells, adipose tissue, and blood vessels (18,20,22,23). In type 2 diabetes, oligomers of islet amyloid polypeptide deposit in the pancreas and may trigger inflammation by stimulating the NLRP3 inflammasome and the generation of mature IL-1 β (24). Stress and inflammation may eventually lead to apoptosis and contribute to β -cell dysfunction, insulin resistance, and atherosclerosis.

In addition, obesity is associated with alterations in the gut microbiome along with increased gut leakiness of bacterial wall lipopolysaccharides (endotoxins) that may further promote tissue inflammation (25,26). Endotoxins, free fatty acids (probably in conjunction with fetuin), and cholesterol induce inflammation by activating Toll-like receptor (TLR) pathways and, subsequently, nuclear factor- κ B (NF- κ B)-mediated release of a broad range of cytokines and chemokines including tumor necrosis factor (TNF), IL-1 β , IL-8, and MCP-1 that promote the accumulation of various

immune cells in different tissues (17,18). It has recently been reported that in obesity, alterations of the gut microbiome might stimulate not only the innate immune system but also the adaptive immune system, which might contribute to insulin resistance (27). Adipose tissue inflammation can also be triggered by local hypoxia caused by rapid expansion of adipose tissue with insufficient vascular adaptation (28).

The renin-angiotensin system may also play a role in inflammation, insulin resistance, and vascular damage (29–32). Recent data suggest that this system may have a role in islet inflammation and β -cell dysfunction, independent of its effects on glucose metabolism. Angiotensin II has been shown to induce expression of chemokine MCP-1 and IL-6, leading to impaired mitochondrial function and insulin secretion, as well as increased β -cell apoptosis (33).

These findings shed new light on the mechanisms of inflammation in obesity and diabetes and open new venues for prevention of inflammation by modifying the proinflammatory microbiota or by using inhibitors of the renin-angiotensin system. Alternatively, it is possible to use treatments that target key molecules that regulate the inflammatory response.

Anti-inflammatory Properties of Antidiabetes Drugs

The link between nutrient metabolism and inflammation raises the hypothesis that correction of metabolic abnormalities by lifestyle modifications and/or antidiabetes medications may reduce inflammation, thereby improving β -cell function and insulin resistance while protecting against vascular complications, hence modifying the natural history of type 2 diabetes. The current available treatments for type 2 diabetes act through diverse mechanisms to improve glycemia. Many of these treatments also exert anti-inflammatory effects that might be mediated via their metabolic effects on hyperglycemia and hyperlipidemia or by directly modulating the immune system. Part of the findings as to the effects of different medications on systemic and tissue-specific inflammation was obtained in vitro or in animal models. Notably, in preclinical studies testing the anti-inflammatory effects of antidiabetes

drugs, the drug concentrations used were much higher than those used in clinical practice; therefore, the findings should be interpreted with caution. Below, we summarize the current data on the anti-inflammatory properties of antidiabetes medications (Table 1).

Metformin

Currently the first-line treatment of type 2 diabetes, metformin improves diabetes control primarily by suppressing hepatic glucose production and by improving insulin sensitivity. Its effects are thought to be mediated in part through activation of AMPK, a key regulator of cellular energy homeostasis known to exert both anti-inflammatory and antioxidant effects (34). Metformin has also been shown to directly inhibit production of reactive oxygen species from complex I (NADH:ubiquinone oxidoreductase) of the mitochondrial electron transport chain. In lipopolysaccharide-activated macrophages, metformin inhibited production of the proform of IL-1 β , while it boosted induction of the anti-inflammatory cytokine, IL-10 (35). Metformin has been shown to inhibit proinflammatory responses in vascular endothelial and smooth muscle cells (5,36). Recent reports have demonstrated that metformin may attenuate oxidized LDL-induced proinflammatory responses in monocytes and macrophages and inhibit monocyte-to-macrophage differentiation (37). In rodents, it decreased the expression of the proinflammatory and proapoptotic protein TXNIP in β -cells and hepatocytes (38). In human studies, however, the effects of metformin on inflammation are not well established. In the U.S. Diabetes Prevention Program, metformin modestly reduced C-reactive protein (CRP) levels in patients with impaired glucose tolerance (39). Others found that metformin decreased the levels of several markers of endothelial dysfunction and coagulation but did not affect TNF- α or CRP (40). In the LANCET Trial: A Trial of Long-acting Insulin Injection to Reduce C-reactive Protein in Patients With Type 2 Diabetes, metformin did not modify the levels of inflammatory biomarkers in patients with recent-onset type 2 diabetes, despite improved glycemia (41). Of note, recent studies suggest that metformin may have beneficial effects in chronic inflammatory diseases and cancers and may extend life

Table 1—Anti-inflammatory effects of glucose-lowering agents used in the treatment of type 2 diabetes

Drug	Mechanism of action	Main findings	Remarks and limitations	References
Biguanides	Activate AMPK	↓ or ↔ CRP; ↔ inflammatory biomarkers; ↓ markers of endothelial dysfunction and coagulation	May have beneficial effects in chronic inflammatory diseases and cancer	39–43
SUs	Close K_{ATP} channels on β -cell plasma membranes	↓ or ↔ inflammatory markers and markers of endothelial dysfunction; ↓ or ↔ CRP	Conflicting data; modest effect, if any	45–49
TZDs	Activate the nuclear transcription factor PPAR γ	↓↓ CRP; ↓ inflammatory markers; ↑ adiponectin	Consistent anti-inflammatory effect	46,48,49,57–61
DPP-4 inhibitors	Inhibit DPP-4 activity, increasing postprandial active incretin concentrations	↓ Inflammatory cytokines and biomarkers; ↓ CRP	Moderate effect; requires further study	10,62–64,66–70
GLP-1 RAs	Activate GLP-1 receptors	↓ Inflammatory cytokines and biomarkers; ↓ markers of endothelial dysfunction; ↓ CRP	Moderate effect; requires further study	47,74,75
SGLT2 inhibitors	Inhibit SGLT2 in the proximal nephron	Unknown	Future studies needed	—
Insulins	Activate insulin receptors	↓ or ↔ inflammatory cytokines and immune mediators; ↓ or ↔ CRP	Moderate effect, although data conflicting	41,78,79
ROS, reactive oxygen species.				

span independent of its effects on glucose metabolism (42,43). Several clinical studies are currently assessing the effects of metformin in this context and whether these are mediated via modulation of the inflammatory state.

Sulfonylureas

While these agents directly stimulate insulin secretion by the β -cell, they have also been shown to have anti-inflammatory effects. As an example, glyburide has been shown to inhibit the NLRP3 inflammasome and subsequent IL-1 β activation in macrophages (24,44). Similarly, gliclazide also decreased the expression of inflammatory markers and endothelial dysfunction in patients with type 2 diabetes (45). By contrast, in various comparative clinical trials, no significant changes in CRP were observed with sulfonylurea (SU) therapy, whereas significant reductions were found with the thiazolidinedione (TZD) pioglitazone and the glucagon-like peptide 1 (GLP-1) receptor agonist (GLP-1 RA) exenatide (46–48). In a recent 52-week comparative study examining the effects of metformin, gliclazide, and pioglitazone on markers of inflammation, coagulation, and endothelial function, no improvements were seen in inflammatory markers (IL-1, IL-6, and TNF- α) with SU therapy compared with the other treatments, while similar glycemic control was attained (49).

TZDs

Extensive data support the direct role of peroxisome proliferator-activated receptor (PPAR) γ in the negative regulation of inflammation. TZDs are PPAR γ agonists that improve metabolism by increasing insulin sensitivity primarily by increasing glucose utilization and decreasing hepatic glucose production. In rodents, they may have direct protective effects on the β -cell against oxidative stress and apoptosis, which may contribute to preservation of β -cell mass (50). Despite extensive research, the precise mechanism(s) underlying the beneficial metabolic effects of TZDs are still not well understood and may involve stimulation of AMPK; both PPAR γ and AMPK are important regulators of inflammation (51). Indeed, TZDs have anti-inflammatory effects, which may affect both insulin resistance and cardiovascular risk. TZDs have been shown to decrease inflammatory markers in visceral adipose tissue, liver, atherosclerotic

plaques, and circulating plasma (52). Pioglitazone treatment decreased invasion of adipose tissue by proinflammatory macrophages and increased hepatic and peripheral insulin sensitivity (53). Treatment with TZDs also decreased inflammation in nonalcoholic steatohepatitis and in atherosclerotic lesions (54,55).

Various clinical studies have examined the anti-inflammatory and antiatherogenic properties of TZDs. A meta-analysis showed that pioglitazone and rosiglitazone significantly decreased serum CRP levels in both people with and people without diabetes, irrespective of effects on glycemia (56). Treatment with TZDs improved endothelial function, decreased hs-CRP and inflammatory markers, and increased adiponectin levels (46,48,49,57–59). In a study using ^{18}F -fluorodeoxyglucose positron emission tomography imaging in subjects with impaired glucose tolerance or type 2 diabetes, pioglitazone treatment attenuated inflammation in atherosclerotic plaques (60). This was associated with increased HDL cholesterol level and decreased hs-CRP. This may explain the finding that treatment of subjects with type 2 diabetes with pioglitazone was associated with reduced cardiovascular morbidity (61).

Dipeptidyl Peptidase-4 Inhibitors

There is substantial evidence that dipeptidyl peptidase (DPP)-4 inhibitors can improve a variety of cardiovascular risk factors and inflammation (62–64). DPP-4 inhibitors were found to suppress NLRP3, TLR4, and IL-1 β expression in human macrophages (65). High-fat diet-fed obese rodents of advanced age treated with vildagliptin for 11 months had improved glucose tolerance, enhanced insulin secretion, and higher survival rate (9). Furthermore, treatment with the DPP-4 inhibitor prevented peri-insulinitis, typically observed in rodents fed a high-fat diet. In clinical studies, a potent anti-inflammatory effect has been reported with sitagliptin in patients with type 2 diabetes. Treatment with sitagliptin for 12 weeks reduced mRNA expression of CD26, TNF- α , TLR2, TLR4, proinflammatory kinases c-Jun N-terminal kinase-1 and inhibitory κB kinase, and inhibitor of chemokine receptor CCR-2 in mononuclear cells, as well as of plasma CRP, IL-6, and free fatty acids (10). In a cohort of Japanese patients with uncontrolled diabetes and coronary artery

disease, sitagliptin improved the inflammatory state and endothelial function (66). Furthermore, sitagliptin added to the antidiabetes regimen of patients with type 2 diabetes already treated with metformin, and pioglitazone reduced hs-CRP and other inflammatory markers (67,68). Studies examining the effects of the DPP-4 inhibitors vildagliptin and linagliptin showed that they also reduce inflammation (69,70). However, large randomized controlled prospective studies analyzing the cardiovascular safety of different DPP-4 inhibitors, including Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction (SAVOR-TIMI 53), Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE), and Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), have not demonstrated cardiovascular benefit with DPP-4 inhibitors (71–73). Of note, in these studies follow-up was relatively short, the patients already had established cardiovascular disease, and the studies were designed to show noninferiority rather than superiority. The findings should therefore be interpreted with caution.

GLP-1 RAs

GLP-1 RAs induce weight loss and improve glycemia and cardiovascular risk factors, which may be partially mediated by their anti-inflammatory effects. In patients with type 2 diabetes, treatment with GLP-1 analogs may modulate the proinflammatory activity of the innate immune system, leading to reduced proinflammatory activation of macrophages and consequently the expression and secretion of proinflammatory cytokines, such as TNF- α , IL-1 β , and IL-6 and increased adiponectin (74). With regard to the effects of GLP-1 analogs on CRP, a small placebo-controlled study demonstrated a significant reduction in CRP levels with exenatide (75). In a 12-month comparative study, exenatide demonstrated a significant decrease in hs-CRP compared with SU (47). However, the effects of GLP-1 RAs on cardiovascular morbidity and mortality are currently unknown.

Insulin

Several studies have suggested that insulin may exert an anti-inflammatory response, independent of its effects on

glycemia (76,77). Insulin has been shown to alleviate inflammation through several mechanisms, including increased endothelial nitric oxide release and decreased expression of proinflammatory cytokines and immune mediators, such as NF- κB , intracellular adhesion molecule-1, and MCP-1, as well as several TLRs (76). In a randomized parallel-group study in patients with type 2 diabetes, serum concentrations of hs-CRP and IL-6 were markedly reduced in insulin-treated patients compared with metformin, despite similar glycemic control (78). This may suggest that insulin reduces inflammation, irrespective of its effects on glycemia. In contrast, in LANCET, treatment with insulin compared with placebo or metformin did not provide an anti-inflammatory benefit, despite improved glycemia (41). Similarly, in Outcome Reduction with an Initial Glargine Intervention (ORIGIN), insulin treatment did not affect cardiovascular mortality (79). Overall, the findings as to the anti-inflammatory effects of insulin are controversial and inconclusive.

Sodium–Glucose Cotransporter 2 Inhibitors

Sodium–glucose cotransporter (SGLT) 2 inhibitors improve glycemia by inhibiting reabsorption of glucose in the proximal tubule of the kidney, inducing glucosuria and lowering plasma glucose levels. Currently, there are limited data available with regard to the anti-inflammatory properties of SGLT2 inhibitors. Treatment with the SGLT inhibitor phlorizin in *Psammomys obesus* gerbils was shown to decrease islet inflammation, possibly related to the improvement in glucotoxicity (3). In type 2 diabetic mice, the SGLT2 inhibitor ipragliflozin was shown to improve hyperglycemia, insulin secretion, hyperlipidemia, and liver levels of oxidative stress biomarkers and reduce markers of inflammation including IL-6, TNF- α , MCP-1, and CRP levels (80). While no clinical trial has reported the effects of SGLT2 inhibitors on inflammatory markers, the recent EMPA-REG OUTCOME [BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients] demonstrated a 38% reduction in cardiovascular death in patients with type 2 diabetes and cardiovascular disease after treatment with empagliflozin (81). It is of interest whether this effect is in part mediated by anti-inflammatory properties.

Table 2—Metabolic effects of anti-inflammatory drugs

Drug	Mechanism of action	Main findings	Remarks and limitations	References
Anti-TNF- α antibody, soluble TNF receptor:Fc fusion protein	TNF- α antagonism	No effect on insulin sensitivity; \uparrow insulin secretion; \downarrow CRP	Studies underpowered and of short duration	83–87
IL-1 receptor antagonist, IL-1 β -specific antibody	IL-1 β antagonism	\downarrow HbA _{1c} ; \uparrow insulin sensitivity; \uparrow insulin secretion; \downarrow CRP	Effects persisted several weeks after treatment cessation; long-term studies ongoing	88–92
Salsalate	IKK- β -NF- κ B inhibition	\downarrow HbA _{1c} ; \downarrow FBG; \uparrow insulin sensitivity; \uparrow insulin secretion; \downarrow CRP; \uparrow adiponectin	Increased LDL cholesterol and urine albumin levels; further studies needed to confirm cardiovascular and renal safety	94–100
Diacerein	Reduces TNF- α and IL-1 β by unknown mechanism of action	\downarrow HbA _{1c} ; \downarrow FBG; \uparrow insulin secretion	Single study in drug-naïve patients; further studies warranted to clarify long- term efficacy and safety	101
Chloroquine/HCQ	Unknown	\downarrow HbA _{1c} ; \downarrow FBG; \uparrow insulin secretion; \downarrow insulin degradation	Observational or small-scale prospective RCT	106–111

FBG, fasting blood glucose; IKK- β , inhibitory κ B kinase- β ; RCT, randomized controlled trials.

Metabolic Effects of Anti-inflammatory Drugs

Targeted anti-inflammatory therapy has been suggested for both prevention and treatment of diabetes; this has previously been extensively reviewed (82). Herein, we briefly summarize the current data on the metabolic effects of different anti-inflammatory treatments (Table 2).

Anti-TNF- α

TNF- α was the first proinflammatory cytokine implicated in the pathogenesis of insulin resistance and type 2 diabetes; this has been confirmed in preclinical studies in various animal models (2). However, to date, TNF- α antagonism has not demonstrated any clear benefit in type 2 diabetes in man (83–87). Careful analysis of these clinical studies suggests that all have serious limitations, as they were underpowered and of short duration (13). A number of observational studies have demonstrated that treatment of subjects without diabetes and with inflammatory diseases, such as rheumatoid arthritis, psoriasis, and Crohn disease, with TNF- α antagonists has improved glycemia and reduced the risk for developing diabetes. While the majority of these studies are not prospective, and the improvement is not a direct effect on glucose metabolism necessarily but, rather, improvement in the underlying disease, these observations warrant a well-designed clinical study of

TNF antagonism in patients with type 2 diabetes.

Anti-IL-1 β

Since the discovery of the central role of IL-1 β in the pathogenesis of type 2 diabetes, numerous studies have investigated the role of IL-1 β blockade on insulin resistance and type 2 diabetes. To date, eight independent clinical studies conducted with an IL-1 receptor antagonist (anakinra) or IL-1 β -specific antibody (gevokizumab, canakizumab, and LY21891020) have demonstrated beneficial effects on metabolic parameters including decreased HbA_{1c} and enhanced insulin sensitivity and β -cell secretory function, with concomitant improvement in inflammatory markers (82,88–91). In a double-blind, placebo-controlled, parallel-group study involving 70 patients with type 2 diabetes, IL-1 blockade with anakinra reduced HbA_{1c}, CRP, IL-6 levels, and the proinsulin-to-insulin ratio, while enhancing C-peptide secretion, indicating improved β -cell function; these beneficial effects persisted up to several weeks after treatment cessation (92). Although the duration of these studies does not provide definitive proof, the findings suggest a role for IL-1 β blockade in modulating diabetes-associated inflammation and metabolic dysregulation. With regard to safety, IL-1 β antagonism was generally well tolerated, with the main concern being that anakinra requires daily injections and

often causes adverse reactions at the injection site. The humanized antibodies against IL-1 β allow for monthly injections, which minimize these localized reactions.

Salsalate

Salsalate, a prodrug of salicylate, with fewer adverse reactions than aspirin and sodium salicylate, has demonstrated beneficial effects on glycemia and insulin sensitivity, probably through inhibition of the NF- κ B pathway (93). To date, there are seven independent clinical trials that consistently demonstrate improvement in glycemia with salsalate (94–100). These data support the role of inflammation and of the NF- κ B pathway in the pathogenesis of type 2 diabetes that might become novel therapeutic targets for type 2 diabetes. Salsalate also reduces insulin clearance and may therefore partly improve glycemia via noninflammatory mechanisms. The safety of salsalate was studied in a well-designed multicenter, placebo-controlled study of 48 weeks' duration (96). While the drug was well tolerated, a small increase in LDL cholesterol level was observed. Further, urinary albumin secretion was also increased and returned to baseline upon discontinuation of treatment. While salsalate may be an effective and inexpensive adjunct to type 2 diabetes treatment, further studies are needed to confirm its long-term cardiovascular and renal safety and to determine whether these effects are sustainable with continued administration.

Diacerein

A drug currently used in the treatment of arthritis, diacerein decreases levels of IL-1 β , although its mechanism of action is unknown. In drug-naïve patients with type 2 diabetes, diacerein treatment improved insulin secretion and HbA_{1c} levels, while reducing IL-1 β and TNF- α levels (101). Further studies are warranted to clarify its long-term efficacy and safety.

Chloroquine/Hydroxychloroquine

Antimalarials such as hydroxychloroquine (HCQ) are commonly used to treat autoimmune rheumatic diseases, including rheumatoid arthritis and lupus. The precise anti-inflammatory mechanism of HCQ is not known and is probably related to alkalinization of endosomal organelles in immune cells. HCQ has been shown to reduce the incidence of diabetes among patients with rheumatoid arthritis and lupus and to improve glycemia in patients with rheumatic disorders and diabetes (102,103). Animal studies have shown that antimalarials improve insulin secretion and peripheral insulin sensitivity in diabetic rats (104). HCQ also has been shown to inhibit insulin degradation in rat hepatocytes (105). A few small randomized controlled trials showed that HCQ lowers HbA_{1c} and LDL cholesterol levels in patients with type 2 diabetes (106–110). The mechanisms of hypoglycemia with HCQ are inferred from studies of the parent drug, chloroquine, which has been shown to increase insulin levels in man by both increasing insulin secretion and inhibiting its degradation (111). Well-designed clinical studies are needed to further evaluate the effect of HCQ in individuals with type 2 diabetes and whether its beneficial metabolic effects are related to its anti-inflammatory properties.

Discussion

The association between hyperglycemia, inflammation, and vascular complications in diabetes is now well established. Different antidiabetes drugs, such as TZDs, DPP-4 inhibitors, GLP-1 RAs, and insulin, have bona fide anti-inflammatory effects. Since metabolic dysregulation itself induces inflammation, effective antidiabetes treatments may alleviate inflammation by virtue of improving the metabolic state. It is therefore difficult to clearly differentiate the effects of the drugs on metabolism from their

direct effects on the immune system. However, the anti-inflammatory effects of different medications are partial and inconsistent, probably due to incomplete normalization of metabolic dysregulation or because diabetes-associated inflammation is multifactorial; the mechanisms involved include, but are not limited to, hyperglycemia. This rationalizes testing the impact of anti-inflammatory treatments on glycemia, diabetes progression, and cardiovascular morbidity. Exciting new data show that different treatments designed to modulate the immune response have beneficial metabolic effects; this opens new venues for the treatment of diabetes. However, it should be emphasized that the impact of such treatments on glycemia over long periods of time and more importantly on cardiovascular complications is still unknown. Moreover, a number of the anti-inflammatory drugs may have metabolic effects that are unrelated to their anti-inflammatory effects. This complicates the interpretation of the findings as to the metabolic effects of anti-inflammatory medications. It also remains a challenge to adequately assess inflammation in man, since crude surrogate markers are being used, and it is currently difficult to appreciate tissue-specific variations in the level and type of inflammation. Preclinical studies in animal models are most helpful in this regard; however, it may be difficult to extrapolate from findings in animal models to the clinical setting. Finally, there are important questions as to the safety and cost of these treatments.

Inflammation may have an important role in the development and progression of diabetes and its complications; however, the impact of experimental anti-inflammatory treatments on diabetes deterioration over time and cardiovascular outcomes is still elusive. To date, there is limited evidence showing that current antidiabetes medications have sustainable effects on glycemia and are able to prevent cardiovascular events. EMPA-REG showed that treatment with the SGLT2 inhibitor empagliflozin dramatically decreased cardiovascular mortality (81). It is of great interest to see whether empagliflozin has anti-inflammatory effects and if this plays a role in mediating its effects on mortality. It remains to be shown whether anti-inflammatory treatments administered alone or together with

current antidiabetes drugs can prevent the vascular complications of diabetes. Further studies are required to clarify the role of anti-inflammatory therapy in the management of type 2 diabetes. Better understanding of the inflammatory basis for diabetes may provide for improved modalities for diabetes prevention and treatment, using novel targeted approaches in conjunction with current pharmacologic and lifestyle interventions.

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References

1. International Diabetes Federation. *IDF Diabetes Atlas*, 7 ed. Brussels, Belgium, International Diabetes Federation, 2015
2. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor- α : direct role in obesity-linked insulin resistance. *Science* 1993;259:87–91
3. Maedler K, Sergeev P, Ris F, et al. Glucose-induced beta cell production of IL-1 β contributes to glucotoxicity in human pancreatic islets. *J Clin Invest* 2002;110:851–860
4. Zhou R, Tardivel A, Thorens B, Choi I, Tschopp J. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. *Nat Immunol* 2010;11:136–140
5. Isoda K, Young JL, Zirlik A, et al. Metformin inhibits proinflammatory responses and nuclear factor- κ B in human vascular wall cells. *Arterioscler Thromb Vasc Biol* 2006;26:611–617
6. Lee HM, Kim JJ, Kim HJ, Shong M, Ku BJ, Jo EK. Upregulated NLRP3 inflammasome activation in patients with type 2 diabetes. *Diabetes* 2013;62:194–204
7. Ricote M, Li AC, Willson TM, Kelly CJ, Glass CK. The peroxisome proliferator-activated receptor- γ is a negative regulator of macrophage activation. *Nature* 1998;391:79–82
8. Jiang C, Ting AT, Seed B. PPAR- γ agonists inhibit production of monocyte inflammatory cytokines. *Nature* 1998;391:82–86
9. Omar BA, Vikman J, Winzell MS, et al. Enhanced beta cell function and anti-inflammatory effect after chronic treatment with the dipeptidyl peptidase-4 inhibitor vildagliptin in an advanced diet-induced obesity mouse model. *Diabetologia* 2013;56:1752–1760
10. Makdissi A, Ghanim H, Vora M, et al. Sitagliptin exerts an antiinflammatory action. *J Clin Endocrinol Metab* 2012;97:3333–3341
11. Chaudhuri A, Ghanim H, Vora M, et al. Exenatide exerts a potent antiinflammatory effect. *J Clin Endocrinol Metab* 2012;97:198–207
12. Ferdaoussi M, Abdelli S, Yang JY, et al. Exendin-4 protects beta-cells from interleukin-1 beta-induced apoptosis by interfering with the c-Jun NH2-terminal kinase pathway. *Diabetes* 2008;57:1205–1215
13. Donath MY, Dalmas É, Sauter NS, Böni-Schnetzler M. Inflammation in obesity and

- diabetes: islet dysfunction and therapeutic opportunity. *Cell Metab* 2013;17:860–872
14. Böni-Schnetzler M, Boller S, Debray S, et al. Free fatty acids induce a proinflammatory response in islets via the abundantly expressed interleukin-1 receptor I. *Endocrinology* 2009;150:5218–5229
15. Ehses JA, Perren A, Eppler E, et al. Increased number of islet-associated macrophages in type 2 diabetes. *Diabetes* 2007;56:2356–2370
16. Richardson SJ, Willcox A, Bone AJ, Foulis AK, Morgan NG. Islet-associated macrophages in type 2 diabetes. *Diabetologia* 2009;52:1686–1688
17. Nguyen MT, Favelukis S, Nguyen AK, et al. A subpopulation of macrophages infiltrates hypertrophic adipose tissue and is activated by free fatty acids via Toll-like receptors 2 and 4 and JNK-dependent pathways. *J Biol Chem* 2007;282:35279–35292
18. Vandanmagsar B, Youm YH, Ravussin A, et al. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. *Nat Med* 2011;17:179–188
19. Cai D, Yuan M, Frantz DF, et al. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. *Nat Med* 2005;11:183–190
20. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol* 2009;27:519–550
21. Böni-Schnetzler M, Thorne J, Parnaud G, et al. Increased interleukin (IL)-1beta messenger ribonucleic acid expression in beta-cells of individuals with type 2 diabetes and regulation of IL-1beta in human islets by glucose and autostimulation. *J Clin Endocrinol Metab* 2008;93:4065–4074
22. Williams MD, Nadler JL. Inflammatory mechanisms of diabetic complications. *Curr Diab Rep* 2007;7:242–248
23. Kim JA, Montagnani M, Koh KK, Quon MJ. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. *Circulation* 2006;113:1888–1904
24. Masters SL, Dunne A, Subramanian SL, et al. Activation of the NLRP3 inflammasome by islet amyloid polypeptide provides a mechanism for enhanced IL-1 β in type 2 diabetes. *Nat Immunol* 2010;11:897–904
25. Cani PD, Bibiloni R, Knauf C, et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 2008;57:1470–1481
26. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A* 2005;102:11070–11075
27. Sell H, Habich C, Eckel J. Adaptive immunity in obesity and insulin resistance. *Nat Rev Endocrinol* 2012;8:709–716
28. Ye J. Emerging role of adipose tissue hypoxia in obesity and insulin resistance. *Int J Obes* 2009;33:54–66
29. van der Zijl NJ, Moors CC, Goossens GH, Blaak EE, Diamant M. Does interference with the renin-angiotensin system protect against diabetes? Evidence and mechanisms. *Diabetes Obes Metab* 2012;14:586–595
30. Jandeleit-Dahm KA, Tikellis C, Reid CM, Johnston CI, Cooper ME. Why blockade of the renin-angiotensin system reduces the incidence of new-onset diabetes. *J Hypertens* 2005;23:463–473
31. Fliser D, Buchholz K, Haller H; European Trial on Olmesartan and Pravastatin in Inflammation and Atherosclerosis (EUTOPIA) Investigators. Antiinflammatory effects of angiotensin II subtype 1 receptor blockade in hypertensive patients with microinflammation. *Circulation* 2004;110:1103–1107
32. Manabe S, Okura T, Watanabe S, Fukuoka T, Higaki J. Effects of angiotensin II receptor blockade with valsartan on pro-inflammatory cytokines in patients with essential hypertension. *J Cardiovasc Pharmacol* 2005;46:735–739
33. Sauter NS, Thienel C, Plutino Y, et al. Angiotensin II induces interleukin-1 β -mediated islet inflammation and β -cell dysfunction independently of vasoconstrictive effects. *Diabetes* 2015;64:1273–1283
34. Foretz M, Guigas B, Bertrand L, Pollak M, Viollet B. Metformin: from mechanisms of action to therapies. *Cell Metab* 2014;20:953–966
35. Kelly B, Tannahill GM, Murphy MP, O'Neill LA. Metformin inhibits the production of reactive oxygen species from NADH:ubiquinone oxidoreductase to limit induction of interleukin-1 β (IL-1 β) and boosts interleukin-10 (IL-10) in lipopolysaccharide (LPS)-activated macrophages. *J Biol Chem* 2015;290:20348–20359
36. Kim SA, Choi HC. Metformin inhibits inflammatory response via AMPK-PTEN pathway in vascular smooth muscle cells. *Biochem Biophys Res Commun* 2012;425:866–872
37. Vasamsetti SB, Karnewar S, Kanugula AK, Thaipallli AR, Kumar JM, Kotamraju S. Metformin inhibits monocyte-to-macrophage differentiation via AMPK-mediated inhibition of STAT3 activation: potential role in atherosclerosis. *Diabetes* 2015;64:2028–2041
38. Shaked M, Ketzinel-Gilad M, Cerasi E, Kaiser N, Leibowitz G. AMP-activated protein kinase (AMPK) mediates nutrient regulation of thioredoxin-interacting protein (TXNIP) in pancreatic beta-cells. *PLoS One* 2011;6:e28804
39. Haffner S, Tempresa M, Crandall J, et al.; Diabetes Prevention Program Research Group. Intensive lifestyle intervention or metformin on inflammation and coagulation in participants with impaired glucose tolerance. *Diabetes* 2005;54:1566–1572
40. Caballero AE, Delgado A, Aguilar-Salinas CA, et al. The differential effects of metformin on markers of endothelial activation and inflammation in subjects with impaired glucose tolerance: a placebo-controlled, randomized clinical trial. *J Clin Endocrinol Metab* 2004;89:3943–3948
41. Pradhan AD, Everett BM, Cook NR, Rifai N, Ridker PM. Effects of initiating insulin and metformin on glycemic control and inflammatory biomarkers among patients with type 2 diabetes: the LANCET randomized trial. *JAMA* 2009;302:1186–1194
42. Gallagher EJ, LeRoith D. Diabetes, cancer, and metformin: connections of metabolism and cell proliferation. *Ann N Y Acad Sci* 2011;1243:54–68
43. Koh SJ, Kim JM, Kim IK, Ko SH, Kim JS. Anti-inflammatory mechanism of metformin and its effects in intestinal inflammation and colitis-associated colon cancer. *J Gastroenterol Hepatol* 2014;29:502–510
44. Lamkanfi M, Mueller JL, Vitari AC, et al. Gliburide inhibits the Cryopyrin/Nalp3 inflammasome. *J Cell Biol* 2009;187:61–70
45. Räkel A, Renier G, Roussin A, Buithieu J, Mamputu JC, Serri O. Beneficial effects of gliclazide modified release compared with glibenclamide on endothelial activation and low-grade inflammation in patients with type 2 diabetes. *Diabetes Obes Metab* 2007;9:127–129
46. Derosa G, Cicero AF, Fogari E, D'Angelo A, Bianchi L, Maffioli P. Pioglitazone compared to glibenclamide on lipid profile and inflammation markers in type 2 diabetic patients during an oral fat load. *Horm Metab Res* 2011;43:505–512
47. Derosa G, Maffioli P, Salvadeo SA, et al. Exenatide versus glibenclamide in patients with diabetes. *Diabetes Technol Ther* 2010;12:233–240
48. Schöndorf T, Musholt PB, Hohberg C, et al. The fixed combination of pioglitazone and metformin improves biomarkers of platelet function and chronic inflammation in type 2 diabetes patients: results from the PLOfix study. *J Diabetes Sci Technol* 2011;5:426–432
49. Erem C, Ozbas HM, Nuhoglu I, Deger O, Civan N, Ersoz HO. Comparison of effects of gliclazide, metformin and pioglitazone monotherapies on glycemic control and cardiovascular risk factors in patients with newly diagnosed uncontrolled type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2014;122:295–302
50. Wajchenberg BL. beta-Cell failure in diabetes and preservation by clinical treatment. *Endocr Rev* 2007;28:187–218
51. LeBrasseur NK, Kelly M, Tsao TS, et al. Thiazolidinediones can rapidly activate AMP-activated protein kinase in mammalian tissues. *Am J Physiol Endocrinol Metab* 2006;291:E175–E181
52. Ceriello A. Thiazolidinediones as anti-inflammatory and anti-atherogenic agents. *Diabetes Metab Res Rev* 2008;24:14–26
53. Esterson YB, Zhang K, Koppaka S, et al. Insulin sensitizing and anti-inflammatory effects of thiazolidinediones are heightened in obese patients. *J Invest Med* 2013;61:1152–1160
54. Boettcher E, Csako G, Pucino F, Wesley R, Loomba R. Meta-analysis: pioglitazone improves liver histology and fibrosis in patients with non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2012;35:66–75
55. Reiss AB, Vagell ME. PPARgamma activity in the vessel wall: anti-atherogenic properties. *Curr Med Chem* 2006;13:3227–3238
56. Zhao Y, He X, Huang C, et al. The impacts of thiazolidinediones on circulating C-reactive protein levels in different diseases: a meta-analysis. *Diabetes Res Clin Pract* 2010;90:279–287
57. Esposito K, Ciotola M, Carleo D, et al. Effect of rosiglitazone on endothelial function and inflammatory markers in patients with the metabolic syndrome. *Diabetes Care* 2006;29:1071–1076
58. Stocker DJ, Taylor AJ, Langley RW, Jezior MR, Vigersky RA. A randomized trial of the effects of rosiglitazone and metformin on inflammation and subclinical atherosclerosis in

- patients with type 2 diabetes. *Am Heart J* 2007;153:445.e1–6
59. Hanefeld M, Pfützner A, Forst T, Kleine I, Fuchs W. Double-blind, randomized, multicentre, and active comparator controlled investigation of the effect of pioglitazone, metformin, and the combination of both on cardiovascular risk in patients with type 2 diabetes receiving stable basal insulin therapy: the PIONEER study. *Cardiovasc Diabetol* 2011;10:65
60. Nitta Y, Tahara N, Tahara A, et al. Pioglitazone decreases coronary artery inflammation in impaired glucose tolerance and diabetes mellitus: evaluation by FDG-PET/CT imaging. *JACC Cardiovasc Imaging* 2013;6:1172–1182
61. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007;298:1180–1188
62. Scheen AJ. Cardiovascular effects of glipitins. *Nat Rev Cardiol* 2013;10:73–84
63. Ussher JR, Drucker DJ. Cardiovascular biology of the incretin system. *Endocr Rev* 2012;33:187–215
64. Zhao Y, Yang L, Zhou Z. Dipeptidyl peptidase-4 inhibitors: multitarget drugs, not only antidiabetes drugs. *J Diabetes* 2014;6:21–29
65. Dai Y, Wang X, Ding Z, Dai D, Mehta JL. DPP-4 inhibitors repress foam cell formation by inhibiting scavenger receptors through protein kinase C pathway. *Acta Diabetol* 2014;51:471–478
66. Matsubara J, Sugiyama S, Akiyama E, et al. Dipeptidyl peptidase-4 inhibitor, sitagliptin, improves endothelial dysfunction in association with its anti-inflammatory effects in patients with coronary artery disease and uncontrolled diabetes. *Circ J* 2013;77:1337–1344
67. Derosa G, Maffioli P, Salvadeo SA, et al. Effects of sitagliptin or metformin added to pioglitazone monotherapy in poorly controlled type 2 diabetes mellitus patients. *Metabolism* 2010;59:887–895
68. Derosa G, Carbone A, D'Angelo A, et al. Variations in inflammatory biomarkers following the addition of sitagliptin in patients with type 2 diabetes not controlled with metformin. *Intern Med* 2013;52:2179–2187
69. Khan S, Khan S, Imran M, Pillai KK, Akhtar M, Najmi AK. Effects of pioglitazone and vildagliptin on coagulation cascade in diabetes mellitus—targeting thrombogenesis. *Expert Opin Ther Targets* 2013;17:627–639
70. Yamagishi S, Ishibashi Y, Ojima A, Sugiura T, Matsui T. Linagliptin, a xanthine-based dipeptidyl peptidase-4 inhibitor, decreases serum uric acid levels in type 2 diabetic patients partly by suppressing xanthine oxidase activity. *Int J Cardiol* 2014;176:550–552
71. Scirica BM, Bhatt DL, Braunwald E, et al.; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 2013;369:1317–1326
72. White WB, Bakris GL, Bergenstal RM, et al. EXamination of cArdiovascular outcOMes with alogliptin versus standard of care in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE): a cardiovascular safety study of the dipeptidyl peptidase 4 inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome. *Am Heart J* 2011;162:620–626.e1
73. Green JB, Bethel MA, Armstrong PW, et al.; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;373:232–242
74. Hogan AE, Gaoatswe G, Lynch L, et al. Glucagon-like peptide 1 analogue therapy directly modulates innate immune-mediated inflammation in individuals with type 2 diabetes mellitus. *Diabetologia* 2014;57:781–784
75. Wu JD, Xu XH, Zhu J, et al. Effect of exenatide on inflammatory and oxidative stress markers in patients with type 2 diabetes mellitus. *Diabetes Technol Ther* 2011;13:143–148
76. Sun Q, Li J, Gao F. New insights into insulin: the anti-inflammatory effect and its clinical relevance. *World J Diabetes* 2014;5:89–96
77. Dandona P, Aljada A, Mohanty P. The anti-inflammatory and potential anti-atherogenic effect of insulin: a new paradigm. *Diabetologia* 2002;45:924–930
78. Mao XM, Liu H, Tao XJ, Yin GP, Li Q, Wang SK. Independent anti-inflammatory effect of insulin in newly diagnosed type 2 diabetes. *Diabetes Metab Res Rev* 2009;25:435–441
79. Gerstein HC, Bosch J, Dagenais GR, et al.; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 2012;367:319–328
80. Tahara A, Kurosaki E, Yokono M, et al. Effects of SGLT2 selective inhibitor ipragliflozin on hyperglycemia, hyperlipidemia, hepatic steatosis, oxidative stress, inflammation, and obesity in type 2 diabetic mice. *Eur J Pharmacol* 2013;715:246–255
81. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117–2128
82. Donath MY. Targeting inflammation in the treatment of type 2 diabetes: time to start. *Nat Rev Drug Discov* 2014;13:465–476
83. Ofei F, Hurel S, Newkirk J, Sopwith M, Taylor R. Effects of an engineered human anti-TNF- α antibody (CDP571) on insulin sensitivity and glycemic control in patients with NIDDM. *Diabetes* 1996;45:881–885
84. Paquot N, Castillo MJ, Lefebvre PJ, Scheen AJ. No increased insulin sensitivity after a single intravenous administration of a recombinant human tumor necrosis factor receptor: Fc fusion protein in obese insulin-resistant patients. *J Clin Endocrinol Metab* 2000;85:1316–1319
85. Stanley TL, Zanni MV, Johnsen S, et al. TNF- α antagonism with etanercept decreases glucose and increases the proportion of high molecular weight adiponectin in obese subjects with features of the metabolic syndrome. *J Clin Endocrinol Metab* 2011;96:E146–E150
86. Bernstein LE, Berry J, Kim S, Canavan B, Grinspoon SK. Effects of etanercept in patients with the metabolic syndrome. *Arch Intern Med* 2006;166:902–908
87. Dominguez H, Storgaard H, Rask-Madsen C, et al. Metabolic and vascular effects of tumor necrosis factor- α blockade with etanercept in obese patients with type 2 diabetes. *J Vasc Res* 2005;42:517–525
88. van Asseldonk EJ, Stienstra R, Koenen TB, Joosten LA, Netea MG, Tack CJ. Treatment with Anakinra improves disposition index but not insulin sensitivity in nondiabetic subjects with the metabolic syndrome: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2011;96:2119–2126
89. Cavelti-Weder C, Babians-Brunner A, Keller C, et al. Effects of gevokizumab on glycemia and inflammatory markers in type 2 diabetes. *Diabetes Care* 2012;35:1654–1662
90. Sloan-Lancaster J, Abu-Raddad E, Polzer J, et al. Double-blind, randomized study evaluating the glycemic and anti-inflammatory effects of subcutaneous LY2189102, a neutralizing IL-1 β antibody, in patients with type 2 diabetes. *Diabetes Care* 2013;36:2239–2246
91. Hensen J, Howard CP, Walter V, Thuren T. Impact of interleukin-1 β antibody (canakinumab) on glycaemic indicators in patients with type 2 diabetes mellitus: results of secondary endpoints from a randomized, placebo-controlled trial. *Diabetes Metab* 2013;39:524–531
92. Larsen CM, Faulenbach M, Vaag A, Ehses JA, Donath MY, Mandrup-Poulsen T. Sustained effects of interleukin-1 receptor antagonist treatment in type 2 diabetes. *Diabetes Care* 2009;32:1663–1668
93. Yuan M, Konstantopoulos N, Lee J, et al. Reversal of obesity- and diet-induced insulin resistance with salicylates or targeted disruption of Ikk β . *Science* 2001;293:1673–1677
94. Fleischman A, Shoelson SE, Bernier R, Goldfine AB. Salsalate improves glycemia and inflammatory parameters in obese young adults. *Diabetes Care* 2008;31:289–294
95. Goldfine AB, Conlin PR, Halperin F, et al. A randomized trial of salsalate for insulin resistance and cardiovascular risk factors in persons with abnormal glucose tolerance. *Diabetologia* 2013;56:714–723
96. Goldfine AB, Fonseca V, Jablonski KA, et al.; Targeting Inflammation Using Salsalate in Type 2 Diabetes Study Team. Salicylate (salsalate) in patients with type 2 diabetes: a randomized trial. *Ann Intern Med* 2013;159:1–12
97. Goldfine AB, Fonseca V, Jablonski KA, Pyle L, Staten MA, Shoelson SE; TINSAL-T2D (Targeting Inflammation Using Salsalate in Type 2 Diabetes) Study Team. The effects of salsalate on glycemic control in patients with type 2 diabetes: a randomized trial. *Ann Intern Med* 2010;152:346–357
98. Goldfine AB, Silver R, Aldhahi W, et al. Use of salsalate to target inflammation in the treatment of insulin resistance and type 2 diabetes. *Clin Transl Sci* 2008;1:36–43
99. Koska J, Ortega E, Bunt JC, et al. The effect of salsalate on insulin action and glucose tolerance in obese non-diabetic patients: results of a randomized double-blind placebo-controlled study. *Diabetologia* 2009;52:385–393
100. Faghihiyani E, Aminorroaya A, Rezvanian H, Adibi P, Ismail-Beigi F, Amini M. Salsalate improves glycemic control in patients with newly diagnosed type 2 diabetes. *Acta Diabetol* 2013;50:537–543
101. Ramos-Zavala MG, González-Ortiz M, Martínez-Abundis E, Robles-Cervantes JA, González-López R, Santiago-Hernández NJ. Effect of diacerein on insulin secretion and metabolic control in drug-naïve patients with type 2 diabetes: a randomized clinical trial. *Diabetes Care* 2011;34:1591–1594
102. Wasko MC, Hubert HB, Lingala VB, et al. Hydroxychloroquine and risk of diabetes in

- patients with rheumatoid arthritis. *JAMA* 2007; 298:187–193
103. Chen YM, Lin CH, Lan TH, et al. Hydroxychloroquine reduces risk of incident diabetes mellitus in lupus patients in a dose-dependent manner: a population-based cohort study. *Rheumatology (Oxford)* 2015;54:1244–1249
104. Emami J, Gerstein HC, Pasutto FM, Jamali F. Insulin-sparing effect of hydroxychloroquine in diabetic rats is concentration dependent. *Can J Physiol Pharmacol* 1999;77: 118–123
105. Emami J, Pasutto FM, Mercer JR, Jamali F. Inhibition of insulin metabolism by hydroxychloroquine and its enantiomers in cytosolic fraction of liver homogenates from healthy and diabetic rats. *Life Sci* 1999;64:325–335
106. Gerstein HC, Thorpe KE, Taylor DW, Haynes RB. The effectiveness of hydroxychloroquine in patients with type 2 diabetes mellitus who are refractory to sulfonylureas—a randomized trial. *Diabetes Res Clin Pract* 2002;55:209–219
107. Rekedal LR, Massarotti E, Garg R, et al. Changes in glycosylated hemoglobin after initiation of hydroxychloroquine or methotrexate treatment in diabetes patients with rheumatic diseases. *Arthritis Rheum* 2010;62:3569–3573
108. Quatraro A, Consoli G, Magno M, et al. Hydroxychloroquine in decompensated, treatment-refractory noninsulin-dependent diabetes mellitus. A new job for an old drug? *Ann Intern Med* 1990; 112:678–681
109. Kang L, Mikuls TR, O'Dell JR. Hydroxychloroquine: a diabetic drug in disguise? *BMJ Case Rep* 2009;pii: bcr08.2008.0654. DOI: 10.1136/bcr.08.2008.0654
110. Shojania K, Koehler BE, Elliott T. Hypoglycemia induced by hydroxychloroquine in a type II diabetic treated for polyarthritis. *J Rheumatol* 1999;26:195–196
111. Powrie JK, Smith GD, Shojaaee-Moradie F, Sönksen PH, Jones RH. Mode of action of chloroquine in patients with non-insulin-dependent diabetes mellitus. *Am J Physiol* 1991;260: E897–E904