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Targeting inflammation to reduce ASCVD in type 2 diabetes

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ABSTRACT

ASCVD is the leading cause of mortality in T2DM. Inflammation appears to be pivotal in the genesis of ASCVD. As T2DM is also a pro-inflammatory state, our aim was to determine the benefit of anti-inflammatory strategies on ASCVD in T2DM.

PubMed searches were conducted using the keywords of T2DM, ASCVD, Inflammation and clinical trials. Our data review suggests that the Mediterranean diet, GLP1 receptor agonists and a monoclonal antibody against IL-1 reduces ASCVD events in T2DM. The former 2 therapies appear to be safe. Anti-IL-1 therapy resulted in an increase mortality from infections.

We conclude that only the Mediterranean diet and GLP1 receptor agonists can be safely incorporated into mainstay therapy for patients with T2DM to reduce ASCVD. Further studies are required with respect to biologics targeting Inflammation to establish benefit to risk ratio.

It is well known that patients with type 2 diabetes are at a 2–4-fold increased risk of atherosclerotic cardiovascular disease (ASCVD) and it is the leading cause of mortality.[1,2] There are several mechanisms that can contribute to the increased propensity to ASCVD in T2DM. These include dyslipidemia, the pro-coagulant state, increased oxidative stress, advanced glycation end products and inflammation.[2,3] Type 2 diabetes is a pro-inflammatory state evidenced by both circulating and cellular biomarkers of inflammation including high sensitivity C-reactive protein (hs CRP), toll-like receptors (TLR) and signal transduction pathways including MAP kinases and NFkB activity.[3] Furthermore, hs CRP predicts ASCVD events in diabetic patients.[4] Prompted by the recent clinical trials showing benefit of certain therapies on ASCVD in diabetic patients we highlight their anti-inflammatory effects as a plausible mechanism of benefit of these therapies in this perspective and suggest future directions.

With respect to therapeutic lifestyle approaches we need to point out that the Mediterranean diet which is clearly anti-inflammatory has been shown to reduce ASCVD in the diabetic sub-cohort of the PREDIMED study; n = 3614 with a hazards ratio of 0.71 (CI 0.51–0.98).[5]

Other existing therapies for diabetes that are both anti-inflammatory and reduce ASCVD in diabetic patients include Metformin, ACE/ARBS, statins and pioglitazone. However given the constraints of space these established therapies will not be discussed further and have been reviewed previously.[1] However it is worth mentioning that demonstration of the anti-inflammatory effects of statins and more importantly many clinical trials with statins showing that the best benefit was accrued in patients achieving concomitant reduction in both LDL-cholesterol and hs CRP has ushered in much of the research on anti-inflammation as a strategy to reduce ASCVD.[6]

GLP-1 receptor agonists lower glucose by increasing glucose dependent insulin secretion, suppressing glucagon, reducing gastric emptying and improving satiety. They also result in weight loss and a reduction in systolic blood pressure.[2,7] In a study investigating the anti-inflammatory effect of exenatide in 24 subjects with T2DM after a single injection and after administration for 12 weeks, there was a suppression of Reactive oxygen species (ROS) generation and inflammatory indices within 2 h of the initial injection, and at 12 weeks.[7] The inhibition of Nuclear Factor kappa B (NFkB) binding was associated with reduction in the expression of two key pro-inflammatory cytokines, Tumor necrosis Factor alpha (TNFα) and Interleukin-1 beta (IL-1β).[7,8] There were reductions in the expression of Jun N terminal Kinase (JNK-1), TLR-2 and TLR-4. In addition, there were reductions in plasma concentrations of Monocyte Chemoattractant protein-1 (MCP-1), Matrix metalloproteinase (MMP-9) and Serum Amyloid A (SAA).[7] Recently, exenatide was shown to induce a marked increase in plasma concentrations of interleukin-1 receptor antagonist (IL-1RA).[9] A longer acting GLP-1 agonist, Liraglutide promotes AMPK phosphorylation, increases eNOS expression and decreases NF-kB activation in HUVECs treated with TNFα.[9,10]

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Liraglutide also decreases TNF alpha, IL-1 beta and IL-6.[9,10] Both exenatide and Liraglutide have been shown to reduce CRP by 61% and 23% respectively.[10] Clearly, GLP-1 agonists exert powerful anti-inflammatory effect and therefore can improve CV events in diabetes.[11,12]

Recent studies on cardiovascular outcomes have shown that liraglutide and semaglutide have a cardio-protective effect as reflected by significantly decreased cardiovascular events in patients with type 2 diabetes. The LEADER study was carried out with liraglutide in 9340 patients with T2DM with either established cardiovascular, renal disease or those at high risk of CVD.[13] 80% of the subjects were in the secondary prevention cohort which was defined as subjects who were more than 50 years old with at least one cardiovascular disorder (coronary artery, cerebrovascular, peripheral vascular disease, chronic kidney disease stage 3 or higher, or chronic heart failure of NYHA class II or III). Major exclusion criteria were Type 1 diabetes, use of GLPI-receptor agonists, DPP-4 inhibitors and rapid acting insulin and acute coronary or cerebrovascular event in the 14 days prior to randomization. In this study, there was a 13% reduction in the primary end point comprising cardiovascular death, non-fatal MI, and non-fatal stroke. In addition there were significant decreases in overall mortality by 15%, and cardiovascular mortality by 22%. These benefits were primarily seen in subjects with established cardiovascular or renal disease.

In the SUSTAIN-6 study which was a trial designed to demonstrate CV safety of Semaglutide, 83% of the patients had ischemic heart disease, chronic kidney disease, or both.[14] Nonfatal myocardial infarction was reduced by 26%, and nonfatal stroke by 39% in the semaglutide group but rates of death from cardiovascular causes were similar in the two groups. There was an increase in the rates of complications of diabetic retinopathy (vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) in the Semaglutide group, which was hypothesized to be secondary to the induction of rapid decline in HbA1c in poorly controlled patients. This phenomenon has previously been shown to occur following rapid declines in glycemia and HbA1c with intensive insulin therapy. Semaglutide is the most powerful of the GLP-1RA inducing mean reduction in HbA1c of 1.8% in patients with type 2 diabetes. In contrast to liraglutide and semaglutide, lixisenatide and exenatide weekly have not shown significant cardiovascular benefit. This may be attributable to different patient populations with different cardiovascular risks included in the study.

Although mechanisms for the cardiovascular benefits were not studied in these trials, it has been postulated that the anti-inflammatory effects of GLP-1 receptor agonists could have stabilized the plaque and reduced the atherosclerotic burden in these subjects. In addition the favorable effects of these agents on glycemic control, systolic blood pressure, weight, lipids and avoidance of severe hypoglycemia would have also contributed collectively. GLP-1 receptor agonists improve endothelial function and myocardial contractility and reduce albuminuria and these benefits also need to be considered.[10,15,16] Thus while the precise mechanism for the benefit on ASCVD reduction needs to be elucidated one potential mechanism is the well-established anti-inflammatory effect.

Intravenous insulin has been shown to have a vasodilatory and anti-inflammatory effect in addition to its glucose lowering effect.[17] The infusion of insulin in patients with acute myocardial infarction demonstrated that it had a suppressive effect on CRP, SAA, PAI-1, oxidative stress and creatine kinase-MB, CKMB.[18] However the cardio-protective effect of insulin has not been seen consistently in multicenter trials. A recent multicenter trial has shown an 80% reduction in infarct size and a 52% reduction in cardiac arrest and in-hospital mortality, in AMI subjects who were administered insulin in a GIK cocktail in the ambulance, however, this was secondary endpoint in this trial.[19] Contrary to intravenous insulin, there is no conclusive evidence of anti-inflammatory effects with subcutaneous insulin. Intensive glycemic control trials in which majority of the subjects in the intensive arm were on subcutaneous insulin did not show any cardiovascular benefits. Insulin glargine U100 was neutral in terms of CV benefits in a large trial of type 2 DM subjects at high risk of CV events.[20] As hypoglycemia, which is pro-inflammatory, is a side effect of insulin administration, it clearly needs to be avoided when using insulin in subjects with established ASCVD.

The most promising study to date that has shown a reduction in ASCVD with a specific anti-inflammatory therapy, a monoclonal antibody targeting IL-1 beta, was the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS).[21] CANTOS was a randomized double blind placebo controlled study testing the effect of canakinumab on the prevention of recent vascular events in 10,061 patients (40% diabetic) with ASCVD and a hs CRP >2.0 mg/L with a median follow-up of 3.7 years. The primary end point was the classical composite of death, non-fatal MI and non-fatal stroke. While there were significant reductions in hs CRP at 48 months (37% reduction in the 150 mg dose group) and IL-6 (12 months) there was no significant effect on LDL-cholesterol levels. A significant reduction in the primary end point was seen in the 150 mg group with a hazards ratio (HR) of 0.85; CI 0.76–0.97, $p = 0.02$. There was no significant effect on all-cause mortality but a significant reduction in cancer mortality. Also there was a significant increase in deaths due to infections. In the 4960 patients with T2DM the HR was 0.85, similar to the entire group and the benefit on reduction in ASCVD was similar to the non-diabetic patients (p for heterogeneity of 0.86).[22] Although both IL-6 and hs CRP predicted new onset diabetes and the reduction in CRP and IL-6 were significant in both the diabetic and pre-diabetic groups there was no reduction in rates of new onset diabetes.[22] While canakinumab was not associated with an increased risk of infections in the diabetic patients, a concern was the significant increase of fatal infections in the diabetics receiving Canakinumab. However one can conclude that Canakinumab reduces ASCVD in diabetic patients with ASCVD and a hs CRP >2.0 mg/L. The experimental data that support the biological plausibility of this benefit include pro-inflammatory effects on vascular cells such as endothelium and macrophages and the reduction in atherosclerosis in mice and porcine models by interfering with IL1/IL1 receptor interaction.[23] Also IL-1 beta is a major product of activated cells such as macrophages via the intracellular multi-protein NLRP3 inflammasome complex.[23]

Conclusion: While the incidence of CV events has improved in subjects with type 2 DM especially with statin and anti-hypertensive therapies, they still have a much higher residual risk than the general population. HbA1c lowering has been shown to improve microvascular complications; however, there is no conclusive evidence that intensive lowering of this biomarker can reduce ASCVD in this population.[2] We now have anti-hyperglycemic agents, which have anti-inflammatory effects and have been shown to improve ASCVD events in subjects with type 2 diabetes with ASCVD. Both ADA and AACE recommend that following lifestyle changes and metformin, we should preferentially use these therapies if subjects with diabetes have established ASCVD.

In this regard it needs to be pointed out that another anti-inflammatory therapy, Salsalate (3.5 g/d) which inhibits NFkB and reduces HbA1c in T2DM, had no significant effect on hs CRP levels and progression of non-calcified plaque volume by CT angiography, but increased albuminuria and atrial arrhythmias in patients with ASCVD of which 23.5% were diabetic.[24,25] Thus it does not appear to be a viable therapy to reduce ASCVD in diabetes. Hence the results of CANTOS need to be interpreted in this light. It clearly is the first anti-inflammatory therapy to reduce hs CRP and ASCVD events in patients with diabetes.

Presently studies are ongoing with 2 other anti-inflammatory therapies, methotrexate and colchicine.[26] Colchicine in a PROBE design study of 532 patients with ASCVD (31.5% diabetic) reduced ASCVD events significantly (Hazards Ratio 0.33; $p < 0.001$) but this should be viewed as a preliminary observation and a larger placebo controlled trial is in progress and will better inform us given the gastro-intestinal side effects with this drug.[27] Other potential strategies that need to be tested include anti-IL6 therapies which have the disadvantage of increasing LDL-cholesterol,[28] anti-TNF therapy that also lowers plasma glucose and increased adiponectin,[29] anti-IL18 (another product of the NLRP3

inflammasome), upregulation of Sirtuin1, modulation of histone deacetylases and regulation of lipid mediators.[23,30] Therefore, it is possible that in subjects with type 2 diabetes and ASCVD, the focus could change from targeting A1C to using anti-inflammatory and anti-hyperglycemic therapy proven to reduce ASCVD. This would be especially important, when further lowering of A1C could increase the risk of hypoglycemia.

Hence in addition to reducing LDL-C to around 50 mg/dL, BP <130/80, HbAlc <7%, targeting a hs CRP <2 mg/L might emerge as a future target based on CANTOS and future ongoing studies targeting biomediators of inflammation in T2DM with and without ASCVD. However CANTOS alone is not sufficient to introduce Canakinumab as mainstream therapy to prevent ASCVD in T2DM. Also we have no data in T2DM without ASCVD (primary prevention) in this regard. Thus while these new trials have put anti-inflammatory therapies in the limelight there is an urgent need for further studies especially with specific anti-inflammatory therapies that lower hs CRP, to change recommendations in T2DM. The increased mortality from infectious causes needs to be mitigated substantially by these other therapies to improve the important benefit to risk ratio and the issue of cost will need to be addressed. We conclude that at present, only the Mediterranean diet and GLP1 receptor agonists can be safely incorporated into mainstay therapy to target inflammation for patients with T2DM to reduce ASCVD.

POST-SCRIPT

After the acceptance of this paper the Cardiovascular Inflammation Reduction Trial (CIRT) study which included 68% diabetics was published and showed that low dose methotrexate did not reduce hsCRP or events.[31]

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