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Inflammatory markers and cardiometabolic diseases

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ABSTRACT

Objectives : A growing body of evidence emerges that obesity, metabolic syndrome, type 2 diabetes and cardiovascular disease are intimately related to silent chronic inflammation.

Methods : A narrative review summarizing the most recent data of the literature describing the pathological implications of various inflammatory markers in the blood and several key-tissues of obese patients with cardiometabolic disorders.

Results : Besides high-sensitive C-reactive protein, various circulating or in situ inflammatory markers have been identified, presumably reflecting the presence of inflammation in various key-organs (visceral adipose tissue, skeletal muscle, pancreatic islets, liver, intestine, arterial wall). Inflammatory markers predict the risk of developing type 2 diabetes and cardiovascular disease in obese patients. Available data support the concept that targeting inflammation, not only reduces systemic inflammatory markers, but also improves insulin sensitivity and ameliorates glucose control in insulin-resistant patients. Potentially, this approach could also reduce the risk of cardiovascular complications associated with abdominal obesity and type 2 diabetes.

Conclusion : These observations confirm the role of inflammation in cardiometabolic diseases and pave the route for the development of new pharmacological strategies that aim at reducing inflammation, especially in patients with type 2 diabetes.

Key-words : Cardiovascular disease; C-reactive protein; Inflammation; Insulin resistance; Type 2 diabetes mellitus

1. Introduction

The modern world is currently facing an epidemic of obesity and associated metabolic pathologies, including metabolic syndrome (MetS) and type 2 diabetes (T2DM). There is a strong relationship between abdominal obesity and T2DM.[1] The pathophysiology of T2DM is rather complex with multiple actors playing a role to reduce tissue insulin sensitivity and diminish insulin secretion capacity by the β-cell.[2,3] T2DM develops when islet β-cells are deficient in producing sufficient insulin to overcome peripheral insulin resistance (IR), and there is a growing body of evidence for the key-role of inflammation in both IR and β-cell failure.[4,5] Cellular and humoral inflammation is located not only in adipose tissue (more particularly visceral adipose tissue or VAT), but also in skeletal muscle, liver and pancreatic islets, which may explain both tissue IR and β-cell progressive failure (Figure 1). MetS is closely related to IR,[6] and both MetS and T2DM are important cardiovascular risk factors.[7] Almost two third of patients with T2DM will die from a cardiovascular disease (CVD).[7] The initiation and progression of atherosclerotic lesions is currently understood to also have major inflammatory influences that encompass components of both the innate and acquired immune systems.[8] Recent data support the hypothesis that inflammatory mediators of atherosclerosis may converge on the central role of tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) signalling pathway.[9] Thus, there are closed interactions between cytokines and inflammatory cells in islet dysfunction, IR and vascular disease.[10] Thereby, nutritional and pharmacological strategies that inhibit the various inflammatory pathways responsible for obesity-associated metabolic complications and atherosclerosis are the subject of current intensive research (Figure 2).[9, 11, 12]

2. Role of inflammation in cardiometabolic disorders

2.1. Inflammation and visceral adipose tissue : role in metabolically unhealthy obese phenotype

Abdominal obesity corresponds to a sub-clinical inflammatory condition that promotes the production of pro-inflammatory factors involved in the pathogenesis of IR.[13, 14] Inflammatory cytokines, including TNF-α, have been shown to promote IR, and altered expression of cytokines (adipokines) in obese adipose tissue is thought to be an important link between obesity and IR.[15] For instance, the metabolically unhealthy obese phenotype seems to be associated with an increased activation of the NLPR3 (Nucleotide-binding oligomerization

domain, Leucine-rich Repeat and Pyrin domain containing 3) inflammasome in macrophages infiltrating VAT, and a less favourable inflammatory profile compared with the metabolically healthy obese phenotype.[13] Indeed, we found an increased secretion of IL-1β, increased expression of IL1B and NLRP3, increased number of adipose tissue macrophages and decreased number of regulatory T cells in the VAT of metabolically unhealthy obese patients compared with metabolically healthy obese patients and lean subjects. In macrophages derived from VAT, both caspase-1 activity and IL-1β levels were higher in metabolically unhealthy obese patients than in metabolically healthy patients.[13]

2.2. Inflammation and skeletal muscle : role in insulin resistance

Skeletal muscle plays a key role in insulin sensitivity. IR in presence of obesity was mainly explained for decades by the Randle's substrate competition theory, the muscle utilizing free fatty acids instead of glucose as energy source.[1] Later on, the presence of ectopic fat within the muscle has been described and intramuscular triglyceride depots were considered as major players in the muscular metabolic disorders.[16] Now, muscle inflammation is emerging as a potential contributor to IR. Recent reports show that inflammatory macrophage numbers within muscle are elevated during obesity and that muscle cells in vitro can mount autonomous inflammatory responses under metabolic challenge.[17] Finally, the role of various myokines (like irisin) released by skeletal muscle has been pointed out in the regulation of inflammation and IR.[18]

2.3. Inflammation and pancreatic islets : role in β-cell failure

It is becoming clear that inflammation plays a key role in the development of β-cell dysfunction. Inflammatory changes, including accumulation of macrophages, have been documented in islets of T2DM patients.[19] However, little is known about the nature of the pro-inflammatory response within the islet, and there is considerable debate about the triggers for islet inflammation, which may be systemically derived and/or tissue-specific.[20] There are strong arguments to consider that the IL-1β pathway plays a key-role in the pathology of the immune system that leads to islet inflammation and subsequent β-cell failure.[21] Toll-like receptors 2 and 4 and the NLRP3 inflammasome have been recently proposed as triggers for islet inflammation that mediates β-cell dysfunction in T2DM.[20] Therapeutically targeting IL-1β pathway or these receptors may improve hyperglycaemia and protect the β-cell in T2DM.[21]

2.4. Inflammation and liver : role in non-alcoholic fatty liver disease

Abdominal obesity and T2DM are strongly associated with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH).[22] NAFLD is considered as an ectopic fat syndrome, which is closely related to IR.[16] The pathophysiology of NASH involves two steps : 1) IR, which causes steatosis; 2) and oxidative stress, which produces lipid peroxidation and activates inflammatory cytokines.[22] Accumulating evidence reveals that NAFLD and hepatic IR are strongly related to inflammation. [23] Cytokines and adipokines play a pivotal role in inflammatory processes. In addition, these inflammatory mediators regulate various functions including metabolic energy balance, inflammation, and immune response. [23] During development of NASH, CCL2 [chemokine (C-C motif) ligand 2] and its receptor are up-regulated in the liver, where they promote macrophage accumulation, inflammation, fibrosis, and steatosis. CCL2 signaling thereby links hepatic and systemic inflammation related to metabolic disorders and IR.[24] Finally, recent data suggest that altered intestinal microbiota (dysbiosis) may stimulate hepatic fat deposition through several mechanisms including regulation of gut permeability and increased low-grade inflammation.[25] The identification of subjects who may progress from fatty liver to NASH, and from NASH to fibrosis/cirrhosis is an important clinical challenge as well as the finding of appropriate strategies that could prevent such deleterious process.

2.5. Inflammation and intestine : role of microbiota

Gut microbiota has emerged as one of the key factors regulating early events triggering inflammation associated with obesity and metabolic dysfunction.[26] This effect seems to be related to diet- and obesity-associated changes in gut microbiota composition and to increased translocation of immunogenic bacterial products, which activate innate and adaptive immunity in the gut and beyond, contributing to an increase in inflammatory tone.[27] Innate immune receptors, like Toll-like receptors (TLRs), are known to be up-regulated in the tissue affected by most inflammatory disorders and activated by both specific microbial components and dietary lipids. This triggers several signaling transduction pathways, leading to inflammatory cytokine and chemokine (TNF-α, IL-1) production and to inflammatory cell recruitment, causing IR and NAFLD. [25,26] Because perturbation of the intestinal microbiota and subsequent changes in intestinal permeability are potential triggers of inflammation in obesity, prebiotic and probiotic approaches are presented as interesting tools to counteract the drop in target bacteria and thereby improve host metabolism.[27] Thus, further characterisation

of the mechanisms underpinning the triggers of such inflammatory responses in obese individuals could offer unique opportunities for intervention strategies to help ameliorate the risk of obesity-associated disease such as T2DM.[28]

2.6. Inflammation and arterial wall : role in atherosclerosis

Atherosclerosis, the major cause of CVD, is a chronic inflammatory condition involving immune competent cells in lesions producing mainly pro-inflammatory cytokines.[8,29] Even though inflammation and immune activation may be more pronounced in atherosclerosis in T2DM, no major differences could be detected between diabetic and non-diabetic individuals.[29] The cause of immune activation is not known and different mutually non-exclusive possibilities exist. Oxidized forms of low density lipoproteins (oxLDL), which are abundant in atherosclerotic plaques, have proinflammatory and immune-stimulatory properties, cause cell death at higher concentrations and contain inflammatory phospholipids with phosphorylcholine as an interesting epitope. Chronic inflammation may lead to plaque rupture, the major direct cause of CVD death.[8] To prove that inflammation plays a causal role in atherosclerosis and CVD, clinical studies with anti-inflammatory and/or immune-modulatory treatment are needed and some of them are under way.[9]

2.7. Inflammation and small vessels : role in diabetic complications

The underlying mechanisms of diabetic complications imply many biochemical pathways, including also inflammation.[30,31] Many lines of evidence, ranging from in vitro experiments and pathological examinations to epidemiological studies, show that inflammation is a cardinal pathogenetic mechanism in diabetic nephropathy.[32,33] In vitro studies have cast light on the cellular mechanisms whereby diabetes triggers inflammation and in turn inflammation magnifies the kidney injury. Translation of this basic science knowledge into potential practical clinical applications is matter of great interest for future research.[34, 35] Local inflammation plays also a key role in the development of diabetic retinopathy.[36] Inflammation in the diabetic retina is mediated by leukocyte adhesion to the retinal vasculature and chemokine-mediated alteration of the blood-retinal barrier.[37] Thus, modulation of inflammatory processes to attenuate these diabetic complications is a matter of major interest for researchers today.

3. Markers of inflammation and risk of T2DM, CVD and diabetic complications

Various markers of inflammation have been shown to be associated with a higher risk to develop T2DM and CVD.[14] Among those markers, C-reactive protein (CRP), especially high-sensitive (hs) CRP, was the most extensively studied.

3.1.Inflammatory markers and risk of incident T2DM

In a recent meta-analysis, elevated CRP levels were significantly associated with increased risk of T2DM (relative risk [RR] 1.26 [95% confidence interval or 95% CI 1.16-1.37]) based on results of 22 studies, and a significant dose-response association was also observed between the levels of its inducer IL-6 and later occurrence of T2DM (RR 1.31 [95% CI 1.17-1.46]).[38] Alternatively, low levels of anti-inflammatory proteins such as adiponectin, omentin and IL-10 may also be associated with later onset of T2DM, although sometimes conflicting results regarding their association with T2DM have been reported.[39]

3.2.Inflammatory markers and risk of CVD

The Emerging Risk Factors Collaboration group, in a meta-analysis of 52 prospective studies on people without a CVD history, reported that measurements of two inflammatory markers such as CRP and fibrinogen help in the prediction of cardiovascular events.[40] In meta-analysis of up to 29 population-based prospective studies, adjusted relative risks for non-fatal myocardial infarction or coronary heart disease death per 1-standard deviation higher levels were: 1.25 (95% CI 1.19-1.32) for IL-6; 1.13 (1.05-1.20) for IL-18; 1.07 (0.97-1.19) for matrix metalloproteinase-9 (MMP-9); 1.07 (0.95-1.21) for soluble CD40 ligand (sCD40L); and 1.17 (1.09-1.25) for TNF-α. Several different pro-inflammatory cytokines are each associated with coronary heart disease risk independent of conventional risk factors and in an approximately log-linear manner. The findings lend support to the inflammation hypothesis in vascular disease, but further studies are needed to assess causality. [41] Whether inhibiting inflammation with specific agents, beyond statin therapy, would result in reducing the incidence of CVD in high-risk patients, including those with MetS or T2DM, deserves further specific trials.[42, 43]

3.3.Inflammatory markers and risk of diabetic complications

Inflammation appears to play a key-role in the development of diabetic complications. Increased CRP, IL-6, and TNF-α, and especially interstitial cellular adhesion molecule-1, vascular cellular adhesion molecule-1 (VACM-1), and E-selectin are associated with nephropathy, retinopathy, besides CVD, in both type 1 diabetes and T2DM.[44] In diabetic patients, higher CRP levels, but not markers of endothelial function, may be related to more severe diabetic retinopathy. This finding suggests that inflammatory processes are involved in the development and progression of severe diabetic retinopathy.[45]

4. Diet and inflammatory markers

Dietary patterns high in refined starches, sugar, and saturated and trans-fatty acids, poor in natural antioxidants and fiber from fruits, vegetables, and whole grains, and poor in omega-3 fatty acids may cause an activation of the innate immune system, most likely leading to most an excessive production of proinflammatory cytokines associated with a reduced production of anti-inflammatory cytokines.[46] The Mediterranean diet may not only act on classical risk factors (lipid parameters) but also on inflammatory biomarkers such as adhesion molecules and cytokines.[47] In a systematic review of saturated fatty acids (SFAs) on inflammation and circulating levels of adipokines, significant positive associations were observed between saturated fatty acids and hs-CRP, soluble intercellular adhesion molecule-1 (ICAM-1) and IL-6, whereas no significant associations were observed with E-selectin, TNF-α, granulocyte-macrophage colony-stimulating factor, fibrinogen, and adiponectin.[48] SFAs, unlike unsaturated fatty acids, have recently been proposed as triggers of the NLRP3 inflammasome.[49] We recently reviewed how SFA-mediated NLRP3 inflammasome activation could contribute to the development of both insulin resistance and deficiency associated with obesity/T2DM.[50]

Previous research has shown that nutrients and certain food items influence inflammation but little is known about the associations between diet, as a whole, and inflammatory markers. In a Belgian cross-sectional study (ASKLEPIOS), multivariable analyses showed significant positive associations between the food frequency questionnaire (FFQ)-derived dietary inflammatory index and the inflammatory markers IL-6 and homocysteine, but no significant associations with the inflammatory markers CRP and fibrinogen.[51]

5. Targeting inflammation , a new paradigm in cardiometabolic diseases

5.1. Anti-inflammatory effects of Mediterranean diet

The whole diet approach seems particularly promising to reduce the inflammation associated with the metabolic syndrome[46]. A recent systematic review and meta-analysis of interventional trials provides evidence that a Mediterranean diet decreases various inflammatory markers : hs-CRP, IL-6, and ICAM-1.[52]

Because unsaturated fatty acids, especially ω-3 fatty acids, inhibit NLRP3 inflammasome activation in various settings, the potential clinical use of ω-3 fatty acids as anti-inflammatory compounds may be considered.[49,50]

5.2. Anti-inflammatory effects of lipid-lowering agents

Lipid-lowering agents (statins, ezetimibe and fibrates) may reduce markers of inflammation, especially CRP.[53, 54]Most of the anti-inflammatory effect of LDL-lowering therapies is related to the magnitude of change in LDL while the potential non-LDL effects of statins on inflammation appear much smaller in magnitude.[55] However, in the JUPITER trial of apparently healthy persons without hyperlipidaemia but with elevated hsCRP levels, rosuvastatin significantly reduced hs-CRP levels and the incidence of major cardiovascular events.[56] In a prospective study of this trial, achieved hsCRP concentrations with rosuvastatin were predictive of event rates irrespective of the lipid endpoint used.[57] However, a recent meta-analysis of 22 randomized trials showed that statin-induced changes in CRP do not correlate with major cardiovascular events apart from the risk of myocardial infarction nor with overall survival in high-risk patients.[58]

5.3. Anti-inflammatory effects of blocking the renin-angiotensin-aldoserone system

Evidence shows that inhibition of renin-angiotensin-aldosterone system (RAAS) positively influences vascular remodeling thus improving CVD outcomes. The beneficial vascular effects of RAAS inhibition are likely due to decreasing vascular inflammation, oxidative stress, endothelial dysfunction, and positive effects on regeneration of endothelial progenitor cells. Inflammatory factors such as ICAM-1, VCAM-1, TNF-α, IL-6, and CRP

have key roles in mediating vascular inflammation and blocking RAAS negatively modulates the levels of these inflammatory molecules.[59]

5.4. Anti-inflammatory effects of antidiabetic agents

The management of T2DM is evolving[60] and many therapies are now available.[61] Among currently used glucose-lowering agents, several of them also exert some anti-inflammatory effects, which may contribute to impact positively patient's outcome.[62] Overall, insulin-sparing agents or insulin-sensitizers such as metformin and thiazolidinediones (glitazones) appear to exert a greater anti-inflammatory activity than insulin-secreting agents as sulphonylureas or glinides.[62] Incretin-based therapies (dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists) showed promising results with reduction in various inflammatory markers in patients with T2DM, but these preliminary results should be confirmed and if possible translated into improvement of hard clinical outcomes.[62] An emerging body of evidence also suggests that insulin suppresses the inflammatory process, not only through preventing hyperglycaemia but also by modulating key inflammatory molecules.[63]

5.5.Innovative anti-inflammatory strategies

The prominent role of inflammation paves the route for future specific anti-inflammatory therapies to prevent or treat T2DM and CVD. [64-67] Numerous novel strategies, using either small molecules or monoclonal antibodies, have been recently investigated and are still in development : approaches targeting IKK-b-NF-kB (salicylates, salsalate), TNF-α (etanercept, infliximab, adalimumab), IL-1β (anakinra, canakinumab) and IL-6 (tocilizumab), AMP-activated protein kinase activators, sirtuin-1 activators, mTOR inhibitors and CCR-2 inhibitors[12]. Because the increasingly recognized role of infammasome in obesity-associated metabolic disorders such as T2DM,[13,68] IL-1 blocking strategies are specific pathway targeting therapies in autoinflammatory disorders[69] and may open new perspectives for the management of chronic diseases like T2DM.[70] However, even promising, the observed metabolic effects remain rather modest in most clinical trials published so far. The potential use of combined anti-inflammatory agents targeting both insulin resistance and insulin secretion appears appealing but remains unexplored. As recently reviewed,[9] emerging anti-inflammatory approaches to vascular protection can be categorized into two broad groups, those that target the central IL-6 inflammatory signalling pathway and those that do not. Large scale prospective clinical trials are underway to investigate the safety and efficacy of different

anti-inflammatory drugs.[12] Further evidence is needed to support the concept that targeting inflammation pathways may represent a valuable option to tackle the cardiometabolic complications of obesity.

Conclusion

There is a growing body of evidence that metabolic diseases that accompanied abdominal obesity, like MetS and T2DM, and lead to CVD, are associated with activation of the innate immune system in various tissues involved in metabolism. All these pathologies are characterized by elevated proinflammatory factors (TNF-α, IL-1, IL-6), decreased anti-inflammatory factors (adiponectin) and the presence of activated immune cells (macrophages, T lymphocytes). Inflammation is present both in tissues implicated in insulin sensitivity (adipose tissue, skeletal muscle, liver), contributing to worsen IR, and pancreatic islets, where it can induce β-cell dysfunction and death via intra-islet IL-1β activity. Thereby, inflammation may play a crucial role in the pathophysiology of T2DM. Furthermore, atherosclerosis, which is accelerated and more pronounced in patients with MetS and T2DM and responsible for a high morbi-mortality rate in this population, is also characterized by increased silent inflammation, especially in the arterial wall. Patients with elevated hs-CRP levels are at higher risk to develop T2DM and CVD. Therefore, tartgeting inflammation with anti-inflammatory agents make sense for the management of patients with T2DM and patients at high risk of CVD. Anti-inflammatory agents have shown favourable effects on surrogate endpoints (especially a significant reduction in various inflammatory markers among which hs-CRP), but the demonstration of a positive effect on hard metabolic and cardiovascular outcomes is still lacking. The results of several ongoing prospective trials are awaited with great interest.

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Figure 1 : Role of local and systemic inflammation in metabolic and vascular abnormalities. hs-CRP : high-sensitive C-reactive protein. NASH : non-alcoholic liver disease. VAT : visceral adipose tissue.

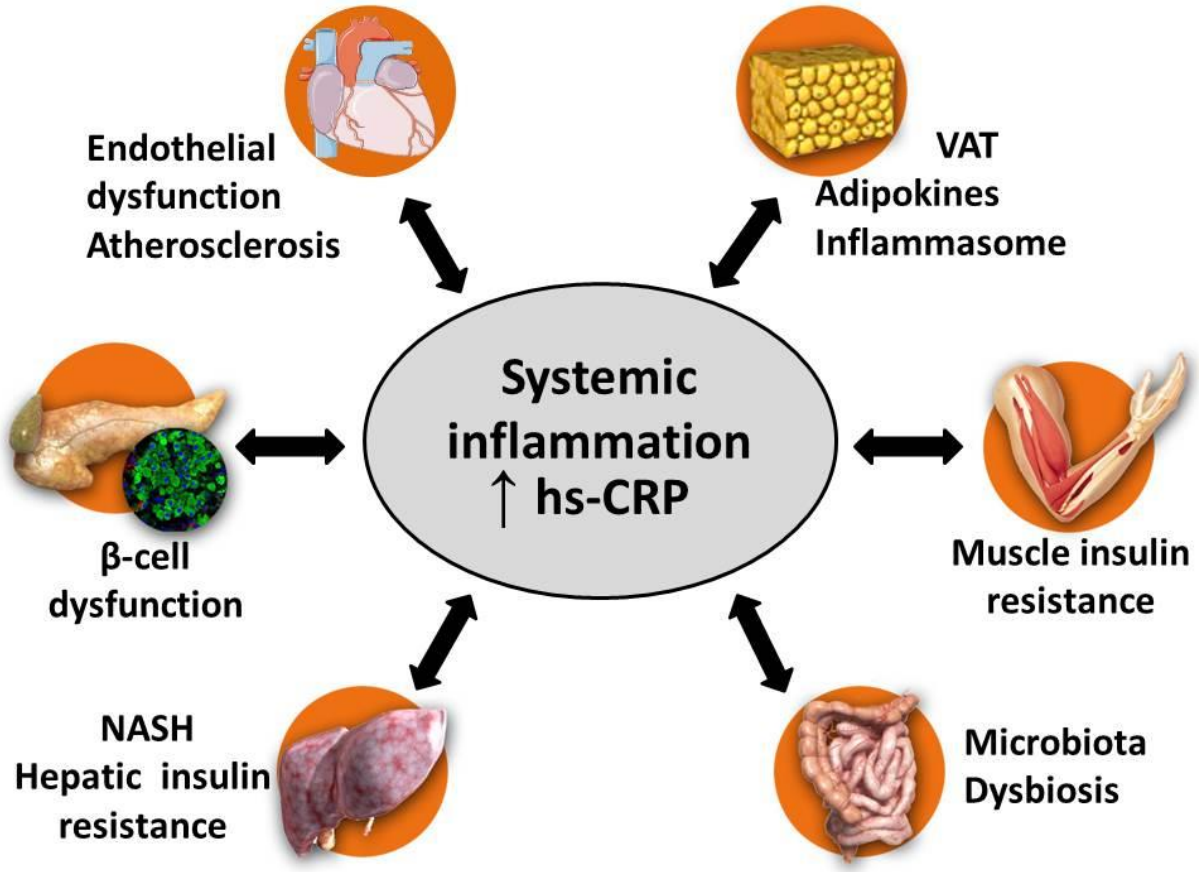
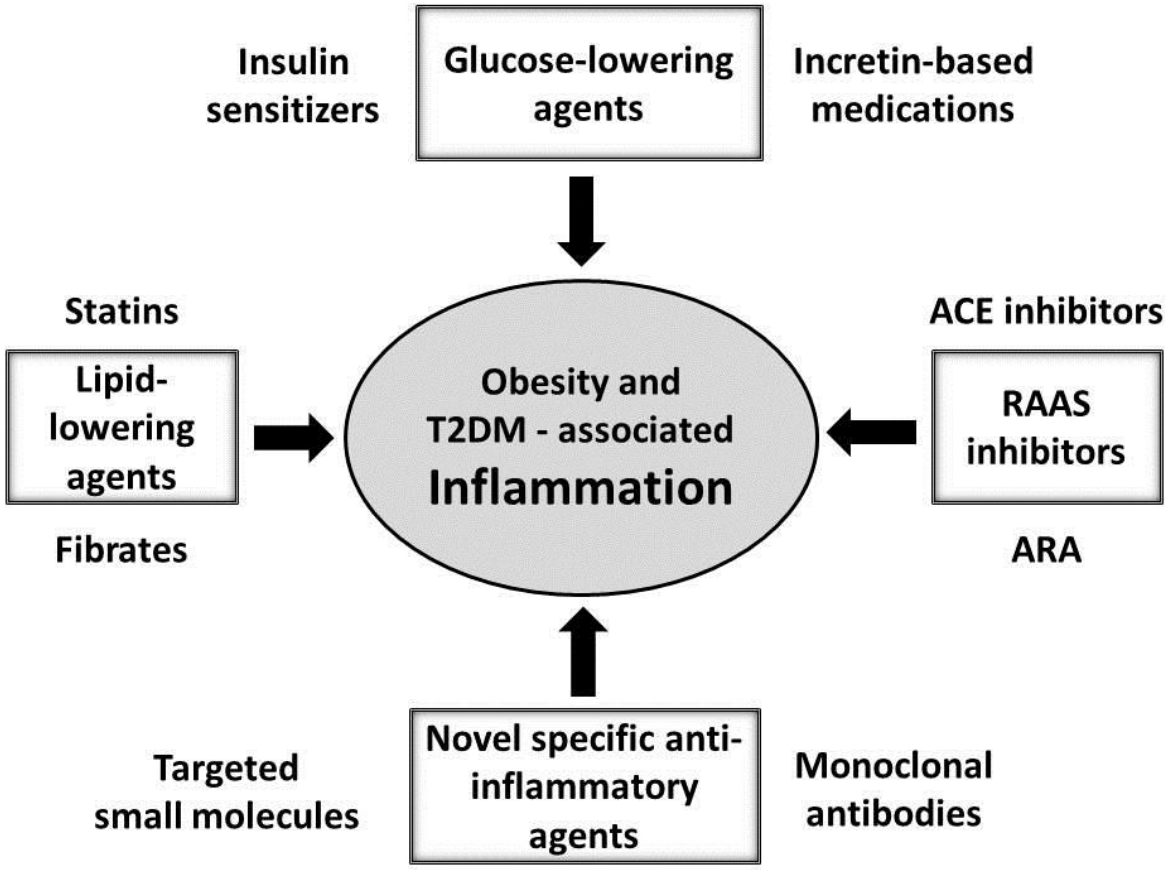


Figure 2 : Various strategies targeting obesity-associated silent inflammation in cardiometabolic diseases. ACE : angiotensin-converting enzyme. ARA : Angiotensin receptor antagonists. RAAS : renin-angiotensin-aldosterone system. T2DM : type 2 diabetes mellitus.



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