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REVIEW

Utilization of lipoxins and other specialised pro-resolving mediators in the prevention and treatment of diabetic nephropathy and diabetic cardiovascular disease

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Diabetes mellitus type 2 is a chronic disease caused by insulin resistance. Whilst first originating in the adipose tissue, this pathophysiological process later affects the muscles and the liver as well. This induces high plasma levels of glucose and fatty acids, leading to the inflammatory-related chronic complications of diabetes, such as diabetic nephropathy and diabetic cardiovascular disease. Specialized pro-resolving mediators are lipid mediators responsible for resolving inflammation and could therefore be beneficial in the management of chronic diabetes complications. The aim of this review is to assess if specialised pro-resolving mediators have the potential to attenuate the chronic complications of diabetes. Specialised pro-resolving mediators, especially lipoxins, can modulate both diabetic nephropathy and diabetic cardiovascular disease. In mice it was demonstrated that, at the glomerular level, lipoxins reduced collagen deposition and expression of pro-inflammatory markers. In human saphenous vein smooth muscle cells instead, lipoxins were able to reduce collagen deposition and vascular smooth muscle cells proliferation and chemotaxis. Aspirin is a medication that could be used to modulate specialised pro-resolving mediator levels, as aspirin triggered-specialised pro-resolving mediators exist. Aspirin triggered-specialised pro-resolving mediators are pro-resolving substances with similar effects, but synthetised in a different way, requiring the partial blockage of the cyclooxygenase 2 enzyme. These results demonstrate how such substances could be useful in the treatment of diabetic patients and why further research is needed to create efficient and economical medications.

Keywords: diabetes mellitus type 2, chronic complications of diabetes mellitus, specialised pro-resolving mediators, inflammation resolution, obesity-associated inflammation

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Introduction

Pathophysiology of DM

Diabetes mellitus (DM) type 2 is a multifactorial disease of insidious onset associated with insulin resistance (IR). IR is caused by both modifiable and non-modifiable risk factors. Non-modifiable risk factors are mainly associated with genetic mutations. These elements alone, however, are not enough to cause the development of type 2 diabetes and need to be associated with modifiable risk factors. The main modifiable risk factors are obesity and inflammation. Accumulation of fatty acids (FA) in obesity leads to the development of local and low-grade systemic inflammation (LGSI) by two mechanisms: hypoxia, and activation of toll like receptor-4 (TLR-4) [1,2] . In addition, both leptin and adiponectin levels are affected by obesity-associated inflammation. LGSI and the subsequent raise in leptin and decrease of adiponectin in obesity are mainly responsible for increasing IR. IR, consecutively, affects the adipose tissue, followed by skeletal muscles, and liver [3]. From a histological point of view, this process is due to free fatty acids (FFA)-induced accumulation of M1-polarised macrophages [1,4]. M1-polarised macrophages are macrophages which exhibit a pro-inflammatory phenotype and secrete pro-inflammatory cytokines[1,3]. At the level of the adipose tissue, crown-like structures are created; they are secondary to ischemia-induced adipocyte necrosis and feature infiltration and accumulation of M1-polarised pro-inflammatory macrophages around necrotic adipocytes [2,5]. IR causes a need for increased insulin biosynthesis and release which, at first, is produced by the pancreas in higher levels. Especially inflammation, but also amyloid accumulation, eventually induces cell apoptosis and loss of ß-cell mass [1,6]. The main cytokines responsible for ß cell apoptosis are interleukin-1 (IL-1) and tumour-necrosis-factor α (TNF-α) [6]. However, abnormal T cell activation may also play a role [1,6]. Hyperglycaemia and FFA further accentuate this inflammatory process [1]. Oxidative stress is another important pathological mechanism that explains ß-cell dysfunction. ß-cells are very susceptible to reactive oxygen species (ROS) since they present few antioxidant molecules and, as a result, the damage caused by ROS is more severe than it would be in other tissues (Figure 1) [6].

The subsequently occurring hyperglycaemia leads to chronic complications of DM via glucose and FFA-induced activation of inflammatory processes at different sites, with the most important being the renal and the cardiovascular (CV) systems. At the level of the kidneys, diabetic nephropathy (DN) develops; this disorder is char-

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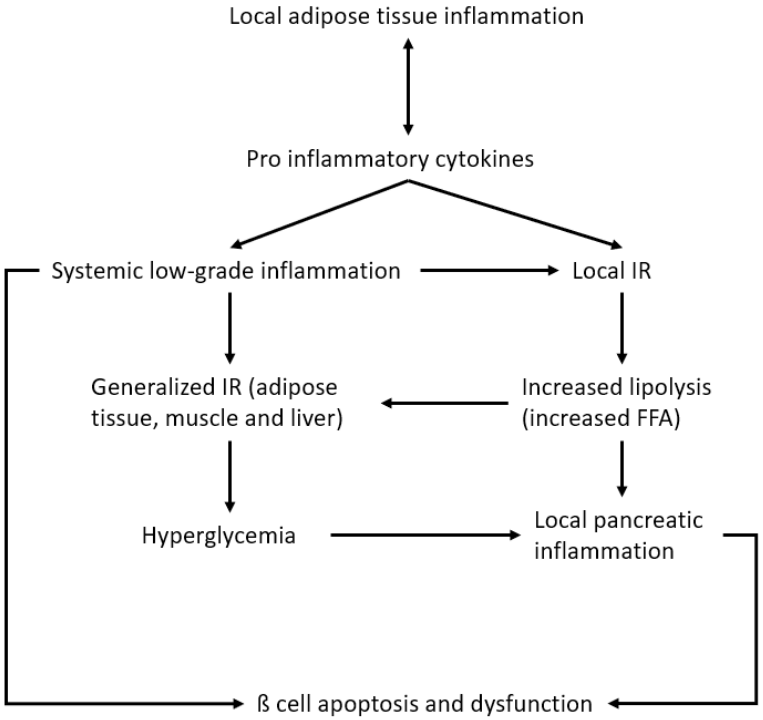

Fig. 1. Pathophysiology of IR development and ß cell dysfunction: Adipose tissue inflammation leads to generalised IR, metabolic disturbances and systemic low-grade inflammation. All these factors together induce ß islets inflammation, ß cell apoptosis, and dysfunction.

acterised by both increased permeability and extracellular matrix deposition [7]. Hyperglycaemia induces inflammation promoting mesangial cell proliferation, podocyte foot effacement, leukocyte chemotaxis, and increased levels of pro-inflammatory cytokines. Pro-inflammatory cytokines are particularly responsible for increased extracellular matrix deposition [8]. At the level of the CV system, hyperglycaemia accelerates atherosclerosis development. This is achieved by hyperglycaemia-induced inflammation which increases vascular smooth muscle cell (VSMC) proliferation, collagen deposition and chemotaxis [7]. Worthy of notice is that all these complications present an inflammatory background, therefore new medications that could inhibit aberrant inflammation are under exploration, as they could represent preventive tools against this mechanism.

Physiology of specialised pro resolving lipid mediators

Specialised pro-resolving mediators (SPMs) are a group of lipid-derived molecules able to induce the resolution of inflammation. These molecules can be further divided into lipoxins (Lx), protectins, maresins (MaR) and resolvins (Rv). SPMs are either derived from arachidonic acid (AA), docosahexaenoic acid (DHA) or eicosapentaenoic acid (EPA), all known polyunsaturated fatty acids (PUFA). The prototype of the SPM family, and the most studied, are Lxs, hence in this article the focus will be mainly on them. When an inflammatory reaction is started different pro-inflammatory cytokines such as interleukins (IL) and prostaglandins (PG) are released. The role of these mediators is to strengthen the inflammatory response in such a way that the initial stimulus is removed. As a result, they will induce typical physiologic processes of acute inflammation such as vasodilation, increased permeability, and chemotaxis of neutrophils and other polymorphonuclear cells (PMN). These cells can be considered as the first line of defence against invading organisms. What is less known, however, is that some PG, namely PGE2 and PGD2, act on these same inflammatory cells and induce the so called “lipid class switch” [9–11]. Lipid class switch occurs when PGE2 and PGD2 act on inflammatory cells to change their enzymatic milieu from enzymes producing pro-inflammatory mediators to pro-resolving mediators [12]. It should be noted that SPMs are produced via a process of transcellular synthesis [3]. As a result, different cell types ranging from inflammatory to endothelial cells start to produce SPMs which have multiple beneficial effects in resolving inflammation. Indeed, SPMs reduce the influx of PMN cells, favour the influx of monocytes, favour neutrophil apoptosis, induce-together with the process of efferocytosis of neutrophils-the polarisation of macrophages from a pro-inflammatory M1 phenotype to a pro-resolving/anti-inflammatory M2 phenotype, induce the formation of T regulatory (Treg) cells, and lead to the efflux of macrophages to terminate resolution [13]. It should be noted that, whilst SPMs resolve inflammation, they do not weaken host immunity [11]. Efferocytosis is especially important for removing already present apoptotic neutrophils, as it is a process involving the uptake of apoptotic cells in order to prevent cell lysis and release of the pro-inflammatory intracellular milieu into the surrounding tissue [14]. Efferocytosis is furthermore relevant, as it induces the polarisation of

macrophages from a pro-inflammatory to a pro-resolving phenotype [15]. Another important process to resolve inflammation is the egress of pro-resolving macrophages towards lymph nodes, where they also exert pro-resolving effect on the adaptative immune system. Egress occurs after completion of efferocytosis, as the resulting pro-resolving macrophages are characterised by reduced levels of Mac-1 (αMβ2) integrins and can therefore leave the inflamed tissue to reach the lymph nodes [15]. A fundamental receptor through which some SPMs can act is the formyl peptide receptor 2/ lipoxin A4 receptor (FPR2/ALX) [14]. When the inducing stimulus cannot be removed or when there is a reduced production of SPMs, however, resolution cannot be completed, and chronic inflammation will ensue (Figure 2) [11].

The SPM family

As already stated, Lxs can be considered as the prototype of the group. Lxs are the only SPMs that use AA as a precursor. Lxs can be mainly biosynthesised via 2 pathways, the 5-/15-lipoxygenase(LO) pathway and the 5-/12-LO pathway [16]. There are simple Lxs released during the resolution phase of an inflammatory reaction and there are also the so-called aspirin triggered-Lxs (ATL). ATL have been first identified in a culture containing both human endothelial and PMN cells [16]. The biosynthesis of ATL is different from the normal biosynthesis of lipoxins, i.e. they do not utilise the above-mentioned pathways. ATLs are induced by aspirin due to the partial blockage of cyclooxygenase 2 (COX 2). COX 2 partial blockage does not however block the formation of the Lx intermediate 15R-hydroxy eicosatetraenoic acid (HETE) [16]. Logically, we could deduce that since the other COX2 pathways have been temporarily abolished, all the AA released from the cell membrane will be directed to the Lx pathway and therefore increase ATL. The main effect of lipoxins is blockage of PMN cells activation and reduced nuclear factor kappa B (NF-κB) activation [17]. In addition lipoxin A4 appears to be able to attract monocyte to the inflamed area [18]. Lx effects are mediated by the FPR2/ALX receptor [17,18]. MaRs use DHA as precursor acids and are SPMs released mainly by M2 macrophages [11]. Their main effect is transformation of M1 macrophages to M2 macrophages, but they also appear to favour efferocytosis, phagocytosis, reduced neutrophil infiltration, reduced pro-inflammatory cytokine release and formation of peripheral Treg cells [11,13,19]. Rvs can derive either from DHA or EPA. Depending on which substance they derive from, they can be classified either in E-Rvs or in D-Rvs [20]. As the other SPMs, they reduce pro-inflammatory cytokines, decrease PMN cell infiltration, and help with the efferocytosis of apoptotic cells by macrophages [11,13]. Via efferocytosis they can raise Treg by increasing the release of certain cytokines such as transforming growth factor-beta (TGF-ß) [13]. Protectins are derived from DHA and can reduce the release of pro-inflammatory cytokines whilst also favouring polarisation of M1-macrophages to M2-macrophages [13]. It is worth mentioning that aspirin is not only able to produce ATLs, but also aspirin-triggered Rvs, both D and E series, as well as protectins [20].

As the chronic complications of DM present with features of both unregulated inflammation and reduced SPMs, this literature review aimed to explore how the administration of SPMs, with a special focus on Lxs, could attenuate or even resolve this process.

Methodology

A comprehensive English literature review was conducted on PubMed and Google Scholar from the 1st of March to the 13th of August, with a total of 34 articles being selected.

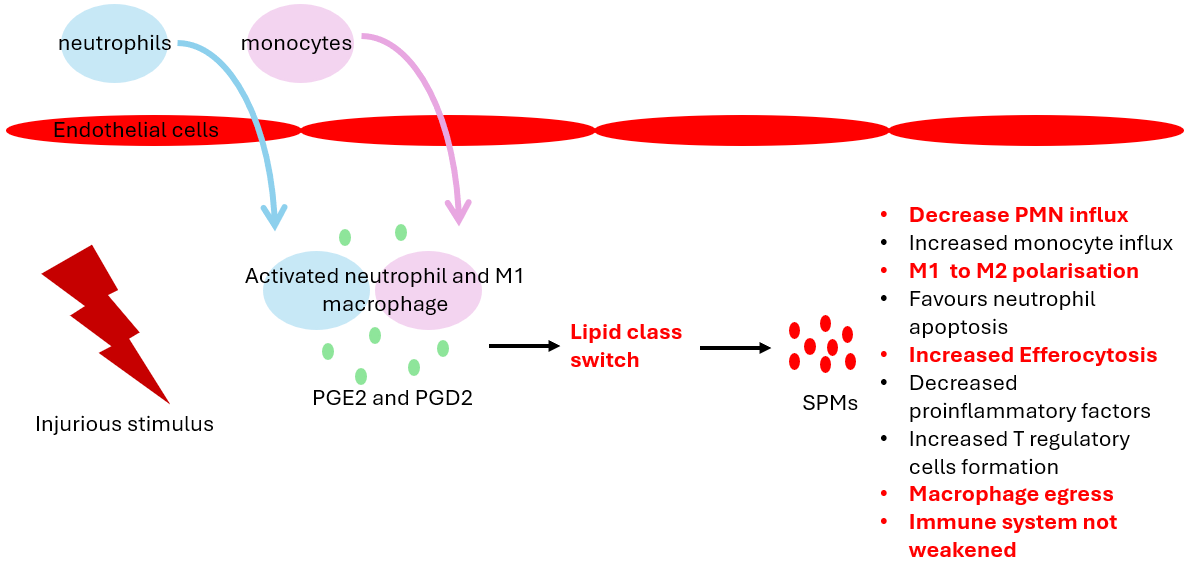

Fig. 2. Physiology of SPM-short summary: The injurious stimulus induces an inflammatory response and leads to the release of pro-inflammatory factors, among wich there are PGD2 and PGE2. These two molecules induce the lipid class switch and production of SPMs. SPMs then favour inflmmation resolution via several processes, the most important ones being reduced influx of PMN cells, M1 to M2 polarisation, increased efferocytosis, and macrophage egress. SPMs do not weaken the immune system.

Articles written in the last 15 years and containing the key words “diabetes mellitus type 2”, “chronic complications of diabetes mellitus”, “specialised pro-resolving mediators”, “inflammation resolution”, “obesity-associated inflammation” or synonyms were included.

Results

SPM disbalances play a role in all the different stages of DM, not only in its chronic complications. In fact, it was noted that SPM disbalances are relevant in obesity-associated inflammation, an important factor in initiating IR.

SPMs and obesity

SPMs in adipose tissue are pathologically changed. This SPM disbalance is in part responsible for the developing LGSI and abnormal adipokine levels. The levels of protectin D1 (PD1) and its precursor 17-hydroxydocosahexaenoic acid (17-HDHA) were both reduced in adipose tissue of obese mice. This deficiency mildly responded to increased administration of DHA; however, it was strongly responsive to increased administration of 17-HDHA [4]. In another study, it appeared that the specific step required to transform DHA to 17-HDHA was in part responsible for this deficiency, as other metabolites originating from DHA were not reduced. If the problem was related to the uptake, these substances would have had to be decreased as well [21]. Kwon et al. found it to be a complication at the level of the 12/15 LO [20]. This implication that obesity and the subsequent inflammation may blunt the resolution process by affecting the enzymes responsible in transforming DHA to 17-HDHA, explains why supplementation of DHA is not as efficient in resolving this deficiency as 17-HDHA supplementation. Whilst PD1 disbalance is very significant, it appears that this SPM is not the only deficient one. RvD1 also seems to be reduced. This reduction, however, is not due to a deficient synthesis, but to an increased conversion to a less active/inactive form. This deficiency is present in mice and also humans, where it is more accentuated [20]. RvD1 exerts its anti-inflammatory actions by modulating the effects of IL10 [22]. Even though the above-mentioned SPMs are mostly affected, other SPMs are also able to modulate adipose tissue inflammation. 17-HDHA and several SPMs, such as RvD1, RvD2, RvE1, MaR1, PD1 and LxA4 all modulate obesity-associated IR and inflammation in different ways. They exert a wide array of effects ranging from increasing adiponectin, decreasing leptin, decreasing macrophage infiltration and polarisation towards a M1 phenotype, favouring macrophage polarisation towards a M2 phenotype, and reducing inflammation and inflammatory cytokines [5]. Therefore, the administration of PUFA and SPMs represents also an interesting approach as a potential treatment option. PUFA and SPM precursors appear to be beneficial, but more data and research is required to fully validate this statement [20].

SPMs and diabetic complications

Lxs and the other SPMs display very beneficial effects in preventing the progression of diabetic atherosclerosis and DN, via the reduction of both inflammatory and pro-fibrotic mediators.

DN is a disease associated with a hyperglycaemia-activated inflammatory process. Hyperglycaemia activates NF-κB and thus increases cytokine release [7]. This inflammatory process favours the release of more pro-inflammatory and pro-fibrotic markers leading to leukocyte infiltration, further accentuating inflammation and extracellular matrix deposition. The main cells affected by DN are glomerular endothelial cells, mesangial cells, podocytes and renal tubule epithelial cells. The damage observed in DN affects in fact not only the glomerulus, but also the proximal tubule [17]. When considering DN from a molecular point of view, an increased expression of TGF-ß, intercellular adhesion molecule 1 (ICAM1), vascular cell adhesion molecule 1 (VCAM1), tumor necrosis factor-alpha (TNF-α) and monocyte chemoattracting process (MCP-1) is noticed [8]. Lxs display a protective effect in chronic kidney disease (CKD) [23,24]. In addition, LxA4 and Benzo-LxA4 block collagen expression and deposition, while Lxs also reduce matrix metalloproteinase (MMP) 2 release. By reducing MMP2, there is a reduced activation of TGF-ß1 [23]. Furthermore, LxA4 and the more stable analogue Benzo-LxA4 have been shown to reduce the levels of these pro-inflammatory and pro-fibrotic markers, however, only LxA4 could decrease the overall extracellular matrix deposition [8]. Whilst not directly administered as molecules, mesenchymal stem cells (MSC) delivery is also able to attenuate the progression of DN via the release of LxA4. This is evidenced by the 12 week survival difference of 75% in DN mice that received MSCs, versus 33% in DN mice without MSC administration [25]. In the same study the pro-inflammatory markers were reduced by LxA4 [25]. Therefore, whilst Lxs didn’t completely block the progression of disease, they could significantly slow it down. Even though there is plenty of evidence that Lxs exert protective effects on the kidney, the other SPMs also appear to be renoprotective. Some protectins, Rvs and MaRs, i.e. MaR1, the resolving D group and PD1 all display pro-resolving effects through either reduced leukocyte infiltration or inflammation modulation in mesangial cells [17]. In a model of kidney ischemia-reperfusion injury, the D group of Rvs and PD1 induced decreased infiltration of leukocytes, whilst MaR1 reduced inflammatory pathways [3]. MaR1 acts by blocking TLR4-MAPK-NF-κB, activating the Nrf2 pathway and inhibiting glucose-induced fibrosis [3]. An important question to take into consideration would be how to stimulate the nephrotic tissue to increase Lx levels. Aspirin has shown potential in partially resolving this issue, since it is able to replenish 15-epi-LxA levels found to be diminished in diabetic patients compared to their non-diabetic counterpart [26].

Atherosclerosis is a disease associated with metabolic dysfunctions such as high low-density lipoprotein (LDL) levels and inflammation. The three cells of the vascular system most affected by inflammation are endothelial cells, macrophages and, most importantly, VSMC [27]. The abnormally high levels of LDL deposit underneath the intima where they initiate monocyte activation and polarisation towards the M1 phenotype. These cells further attract other leukocytes, including monocytes, and release pro-inflammatory and pro-fibrotic mediators. It has been noted that advanced atherosclerotic plaques present a deficiency of SPMs such as RvD1, RvD2, MaR1 and ATL compared to stable plaques [28]. The reduction affecting some of the SPMs can in part be explained. Regarding RvD1 for example, it has been shown that continuous oxidative stress is responsible for nuclear-localisation of the enzyme 5-Lox. This nuclear localisation blocks the production of RvD1 and favours Leukotriene B4 (LTB4) biosynthesis [14]. The association between the progression of atherosclerosis and the deficiency of SPMs has then been further studied via the administration of the missing SPMs. Administering these lacking substances blocked disease progression [28]. From an inflammatory point of view, the pro-inflammatory mediators mainly act by increasing the adhesion molecules VCAM-1 and ICAM-1 and via chemotaxis of monocytes by MCP-1 [7,27]. These pro-fibrotic mediators then attract VSMC via chemotaxis and cause collagen deposition, leading to the formation of the fibrotic cap. The most important chemokine involved in this process seems to be platelet derived growth factor-beta (PDGF-ß) [7,27]. Several SPMs are very beneficial in reducing the inflammatory profile of both endothelial cells and VSMC. RvD1, RvD2, MaR1, PD1 and LxA4 all appear to reduce inflammation and expression of the adhesion molecules on endothelial cells , whilst LxA4, RvD1, RvD2 and RvE1 mitigate VSMC movement [12,14]. Chronic hyperglycaemia exacerbates and accelerates this process by increasing inflammation. LxA4 displays effects on both endothelial cells and VSMC; it reduces the expression of VCAM-1, ICAM-1 and MCP1 from endothelial cells activated by TNF-α [27]. On VSMCs, Lxs limit the effects of PDGF-ß on chemotaxis, proliferation, and collagen deposition [27]. Aspirin triggers the production of a subgroup of Lxs, the ATLs. ATLs are reduced in diabetic patients and patients with peripheral artery disease (PAD), implying their protective role. In fact, it was demonstrated that both ATL and RvE1 could decrease the PDGF-ß-mediated chemotaxis of VSMCs. When administered before exposure to PDGF-ß, these mediators inhibited PDGF-ß-modulated VSMC activation [29]. ATL exhibits also pro-resolving effects via an Fpr2-mediated reduction in pro-inflammatory cytokines, as evidenced in apolipoprotein $E^{-/-}$ mice [30]. Other molecules in addition to PDGF-ß stimulating VSMC chemotaxis that SPMs might be able to counteract are thrombin and angiotensin-II [12]. This phenomenon is secondary to suppression of NF-κB and activation of cyclic adenosine monophosphate /protein kinase A [12].

Clinical trials and administration

Whilst now evidence was provided regarding the efficacy of SPMs, their administration has not been explored yet. The least complex and most researched administration strategy involves enriched marine oil (EMO) or n-3 FA supplementation. These oils are rich in EPA, DHA and metabolites such as 17-HDHA. In a randomised double-blind placebo-controlled study conducted on a total of 22 healthy volunteers, administration of EMO supplements elevated SPM levels. The affected SPM included MaR2, MaR2n-3 DPA, RvT3, RvT4 and PD1n-3 DPA. Patient treated with EMO supplementation furthermore showed modulation of the leukocyte phenotype with reduction of adhesion molecules, reduced response towards the pro-inflammatory platelet aggregating factor and phagocytosis regulation [31]. In obesity and other different pathologies involving the CV system and the renal system, EMO and n-3 FA have also demonstrated their potential in increasing SPMs [32–34]. In PAD, administration of EMO lead to augmented n-3 docosapentaenoic acid (DPA) derived maresins, increased SPM precursors 17-HDHA, 14-hydroxy DHA and 18-hydroxy-EPA, and raised SPM:prostaglandin ration [32]. In CKD administration of n-3 FA increased 17-HDHA, 18-HEPE and RvD1 [33]. MO supplementation in obesity increased DPA derived MaR1 and the DHA metabolites 17-HDHA, 13-HDHA and 7-HDHA [34]. Even though DHA metabolites levels were raised, there was no increase of the D series resolvins [34]. Another interesting modality to augment SPMs includes the utilisation of aspirin. This strategy however, despite presenting a well-known theoretical background, has not be thoroughly analysed, with a only a few published studies involving the CV system [29]. Overall, research focusing on the clinical effect of SPM and the best route of SPM administration remains scarce.

Discussion

DM type 2 is a disease affecting many individuals in the world, with approximately 1 in 10 adults suffering from it. Type 2 is the most frequent subtype of diabetes and makes up around 90% of the total cases of DM [6]. Such high prevalence of DM type 2 could be explained by the elevated rates of obesity, which is strictly associated with IR. [5]. Due to the increasing prevalence and morbidity associated with the chronic complications of DM, different strategies are utilised to counteract this pathology. These strategies are based on lifestyle changes, increasing insulin secretion and decreasing IR. Whilst prevention of DM development would represent the best course of action, lifestyle modifications result to be challenging [5]. Blood glucose control and resolution of inflammation represent the management approaches of choice. As already mentioned, antihyperglycemic approaches have been already implemented; how-

ever, valid anti-inflammatory and pro-resolving strategies which do not weaken the immune system are still subject of research [5]. SPMs could be beneficial, since not only does a disbalance in SPMs lead to chronic inflammation, but also because SPMs do not compromise the immune system [11].

Another important aspect in favour of SPM utilisation is that sites of chronic diseases, such as atherosclerosis, present reduced levels of pro-resolving mediators [28]. Therefore, SPMs could be valuable in reducing inflammation by replenishing their levels to normal, and so regulate pathways that in pro-inflammatory conditions would lead to disease progression [8,25,27]. The major problem encountered however is how to administer these substances to the site of disease. The simple form of SPMs is not an option due to its rapid metabolization and degradation, as can be seen with Lx metabolization[7]. Therefore, utilization of stable analogues such as Benzo-Lxs or substances that increase SPM production, such as aspirin, could be implemented. Whilst the production of SPM analogues consists of expensive processes, aspirin presents the advantage of increasing the biosynthesis of SPMs and ATL at very reduced production costs [11,20]. Administration of SPM precursors in forms of EMO and n-3 FA is another cost-effective strategy that has received lots of attention recently due to its simplicity. Hence, aspirin utilization and EMO supplementation could both represent the most promising approaches. Nevertheless, this interpretation on the best administration strategies of SPM is limited by the lack of clinical trials. Hence, aspirin utilization could be the most promising approach. Regarding administration of such SPM analogues to the desired site, innovative methods have been investigated; remarkably, nanoparticles could serve to this use via enrichment of these vehicles with AT-RvD1 and LxA4 [14]. This approach could result even more attractive if receptors specific to the site of disease could be identified and its ligand inserted in the particles.

Conclusions

Overall, SPMs could be very promising substances in preventing and treating chronic diabetic complications, however more studies are needed. The research efforts should further address new ways and routes of administration for these medications. In addition, synthesis and delivery of analogues with selective binding to chronic complication sites could be an intriguing treatment strategy, especially for patients suffering from advanced stages of disease.

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Contributions

IB (Conceptualisation; Data curation; Funding acquisition; Investigation; Resources; Methodology; Project administration; Writing- original draft; Validation)
YP (Conceptualisation; Investigation; Methodology; Supervision; Visualisation; Validation; Writing- review & editing)

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