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The Immune System: The Link Factor in Obesity, Hypertension and Diabetes 2

Hernan A Prat Martorell

Cardiovascular Department, University of Chile, Santiago, Chile

Correspondence should be addressed to Hernan A Prat Martorell, hprat@hcuch.cl

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ABSTRACT

Hypertension (HT), Diabetes type 2 (T2D) and Obesity are highly prevalent pathologies in the world. In the past, they were treated and studied independently by specialists in each subject. Even though the pathophysiologycal mechanisms may seem independent, there is enough evidence of an immunological -inflammatory mechanism, which could be the common pathway for them.

The immune system includes adaptive and innate immunities, including T lymphocytes (LT) and antigen presenting cells (APCs) as immune system components capable of generating proinflammatory cytokines. These can cause endothelial damage, vasoconstriction, and decreased urinary sodium excretion. $CD4^+$ and $CD8^+$ LTs are effector cells, causally involved in the development of these pathologies. Additionally, a decreased immunomodulation by regulatory LT, worsens endothelial dysfunction and reduce vasodilation in experimental HT. Results of recent studies indicate that lymphocyte activation would be mediated by antigens captured by APCs for subsequent presentation to "naive" LT. On the other hand, it has been observed that proinflammatory states in obesity, the change of the intestinal microbiota and the increase in salt intake, favors the LT and APCs activation. A metabolic inflammation is characterized by moderate cytokine generation that adversely influence cell insulin flags and prompt insulin resistance, which leads to T2D.

Finally, we briefly discuss whether immunotherapy may be a new therapeutic target, or if the used drugs may modify the clinical evolution in the immune system.

KEYWORDS

Hypertension; Diabetes type 2; T lymphocytes; immune system

THE IMMUNE SYSTEM

The immune system has a central role in many processes involving chronic diseases. New evidence suggests that the immune system may be mounting adaptive responses to chronic stressors. Pathological conditions can be associated with disturbance in the signaling mediated by nucleotides and nucleosides of adenine, as seen in atherosclerosis, hypertension, cancer, epilepsy and others [1].

Adaptive Immunity

For most antibodies, their generation depended on co-operation between at least two types of cell: A antigen-presenting cell (APC) that process and present targets (antigens) from the environment; and a lymphocyte that recognized the target antigen on the APC. This

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lymphocyte (T-lymphocyte) direct either the production of antibodies or phagocytes and destroys the antigen.

Cells

T lymphocytes (LT)

Can be differentiated into subpopulations, presenting a characteristic pattern of cytokine secretion.

LT CD8+

These are cytotoxic and mediate an immune response after activating. The lymphocyte's antigen receptors recognize a family of cell-surface molecules on APCs that are collectively known as major histocompatibility complex (MHC) I or II determinants.

LT CD4+

T helper lymphocytes (LTh) characterized by expressing the CD4+ cell membrane protein, coordinate the adaptive immune response, modulating the formation of antibodies by B lymphocytes (LB), cytotoxic LT activation and growth, and the macrophages activity. When activated, they specialize, differentiating themselves in effector lymphocytes, distinguished by their cytokines type production. There are several subtypes: Th1, Th2, Th17 and others, that are the most involved in inflammation [2].

LT regulators (LTreg)

Treg cells are characterized by expressing a FOXP3 transcription factor able to suppress the innate and adaptive immune response and appears essential for tissue self-tolerance. Interleukin 10 (IL-10) secretion has been proposed among the molecular mechanisms that would explain its protective effect [3].

B lymphocytes (LB)

These cells also play an important role in organ damage producing immunoglobulins G (IgG).

Innate Immunity

Its most important cells are neutrophils, APC and macrophages, which are the first at the scene of an environmental breach. One of the most significant features of the immune response is its ability to retain a memory of previous infections. This immunity recognizes via pattern recognition receptors (PRRs), damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) which are endogenous biomolecules that can initiate and/or perpetuate an inflammatory and/or neoantigen response, and thus excites the inflammatory reaction and starts the defense mechanism [4].

The development of a specific response requires that cells of the monocyte-macrophage system, antigen-presenting (APCs), interact with either LTCD4+ or “naive” LTCD8+ [5]. This interaction promotes the LT differentiation and proliferation, towards "effectors". Monocyte-macrophage system cells also have a pathogenic role.

Macrophages play an important role in the induction of inflammation in many different tissues through production of pro-inflammatory cytokines and chemokines such as interleukins (IL) -1, -6, -8, Tumoral Necrosis Factor alpha (TNF-α and monocyte chemoattractant protein-1 (MCP-1), free oxygen radicals or Reactive oxygen species (ROS), proteases (such as cathepsins) and tissue-degrading enzymes such as metalloproteinases (MMP) [6].

Monocyte/macrophages (MMc)

The central nervous system (CNS) plays an integral role in synchronizing macrophage mobilization from immune reservoirs and their chemotaxis to compromised tissues/organs.

Macrophages have a lot of plasticity, and their phenotype has been characterized as M1 (pro-inflammatory) and M2 (immunomodulator). Polarization in the presence of

interferon-gamma (IFN-γ) and/or Aldosterone induces differentiation to M1, while in IL-4 or IL-21 presence, it differentiates to M2. The salt rich diet promotes macrophage differentiation towards proinflammatory phenotype (M1), decreasing differentiation towards reparative phenotype and suppressor of the function of LT effectors (M2). ROS, which decrease the bioavailability of nitric oxide (NO), may be a product of M1, which is also associated with proinflammatory cytokines secretion including: TNF-α IL-1β, IL 6, 12, 18 and 23. This profile favors the development of Th1 and Th17 lymphocytes (especially IL-6 and IL-23). The M2 cytokine profile includes tumor growth factor beta (TGF-β) that induces the differentiation and activation of Treg and IL-10 [7].

Dendritic cells (Dc)

Cells derived from the bone marrow, its role being to present antigens to T cells. There are 4 subtypes. However, can also be classified by surface markers. These cells patrol the vessels and organs even in their immature form. They maintain the immunological tissues tolerance, but in pathological situations such as arteriosclerosis, chronic kidney disease or pulmonary hypertension, are activated through chemokines and induce T lymphocytes activation. Dc orchestrate the innate and adaptive immune response and have the ability to capture, process and present antigens in MHCI and MHCII context, for lymphocyte activation and polarization [8].

Oxidative stress

In addition to inflammation, an increase in oxidative stress has been observed in patients, which generates early vascular aging. These subjects show a chronic condition of oxidative stress that is demonstrated by high levels of malonyldialdehyde and F-8 isoprostanes due to the low antioxidant capacity of plasma and enzymes such as superoxide dismutase, catalase and glutathione peroxidase in red blood cells and glutathione stores [9]. ROS can increase due to a decrease in the activity of antioxidant enzymes. Its molecules, which include xanthine oxidoreductase, uncoupled NO synthase, NADPH, xanthine oxidase, and mitochondrial respiratory enzymes, play a role in the development of hypertension and lipidic oxidation.

THE IMMUNE SYSTEM AND OBESITY

The individual approach in the management of obesity should improve the quality of life, avoid early mortality, and reduce cardiovascular risk, the progression to T2D and cancer incidence. The concept of obesity has gone from being considered, rather than a risk factor, to a primary disease, a process that has not been without discussion. There have been numerous publications in which international societies invite to identify it as a disease. In 2008, The obesity society (TOS) published a position paper defining obesity as a disease. Subsequently, in 2013, the American medical association (AMA) recognized obesity as a disease, followed shortly by other organizations and societies, such as the World health organization (WHO), Food and drug administration (FDA) of the United States of America, National institute of health (NIH), American Association of clinical endocrinologists (AACE), Internal revenue service (IRS) and recently Warranty of fitness (WOF), all of which also position obesity as a disease [10].

Expansion of adipose tissue in obesity promotes inflammation:

1. At the population level, obesity is associated with hypertension (HT), T2D, cancer and other pathologies. An increase in body mass index (BMI) is one of the most important risk factors for its development, and represents an immuno-metabolic vascular disease state [11]. The adipose tissue expansion induces a dysfunction in the adipocytic hormones production, known as adipokines (Leptin, Adiponectin, Resistin, Retinol binding protein 4, and Secreted frizzled-related protein 5, IL-6, TNF-α, among others) which mediate metabolic communication

between adipose tissue and other tissues with functions in the systemic metabolism [12].

2. In obesity, the pro-inflammatory adipokines secretion such as TNFα, IL-6 and MCP-1 increases, which are also produced by myeloid and lymphoid cells that infiltrate adipose tissue. Thus, the expansion of adipose tissue contributes to the development of a chronic sub-inflammatory state with tissue damage [13].

Increased activity of the renin-angiotensin-aldosterone system (RAAS) is associated with the adipokines alteration, that would depend of the local renal adipose tissue effect and/or aldosterone secretion by the adipose tissue itself, activation of the sympathetic system and hemodynamic overload, which also will act as proinflammatory factors [14].

Under physiological conditions, adipose tissue has practically the entire spectrum of immune cells [13]. The expansion of adipose tissue leads to an increase in the number and activity of macrophages, mast cells, neutrophils, T and B lymphocytes associated with a reduction of regulatory cells like LTh2 , LTreg and other subtypes of lymphocytes [15].

Macrophages are the most abundant immune cell component of adipose tissue and a primary effect of obesity is their increase, from approximately 4% of visceral fat cells in lean, rise to 12% in the visceral fat of obese patients [16,17]. Most of this increase is explained by the cellular influx from the periphery, which correlates with the increase in the expression of adipokines, pro-inflammatory cytokines, adipocyte size and BMI [18,19]. Besides, unlike the immunomodulatory phenotype of macrophages in lean adipose tissue (classically M2), obesity shows a proinflammatory profile (M1) [20,21]. On the other hand, the rich fat diet and/or the positive caloric balance, increase the amount of DCs in adipose tissue, inducing presenter's molecules, necessary to orchestrate the immune response in the context of the major histocompatibility complex II (MHC-II). In obesity, the activity of DCs promotes LTh17 and LTh1 infiltration and polarization, together with the decrease of LTreg, enhancing macrophage differentiation towards the M1 phenotype [22].

Adipose tissue in obesity also shows an increase in LTCD8$^+$ and natural killer cells (NKTs), which represent an important source of proinflammatory cytokines. Studies have shown that different subsets of T cells are present in the adipose tissue, affecting macrophage accumulation and - when the CD8$^+$ T cells were depleted by using a neutralizing antibody, M1 macrophage accumulation was significantly reduced, whereas M2 macrophages were not affected [23].

In addition, increased LB has been shown, particularly IgG producers [24]. Further, the proinflammatory molecules release from adipocytes and immune cells that infiltrate adipose tissue into the circulation, it has been proposed that perivascular adipose tissue - a particular compartment of visceral adipose tissue that surrounds most of the blood vessels - has a negative effect on vascular function and remodeling, directly promoting HT in obesity [25,26]. Several studies show that it would contribute to the development of: A) Increased ROS and endothelial dysfunction; B) Hyper reactivity and hypertrophy of vascular smooth muscle, remodeling of the tunica media, increasing the extracellular matrix and stiffness of the arterial wall; C) Perivascular fibrosis and accumulation of immune cells.

The available evidence from experimental studies indicates that this pattern of perivascular adipose tissue changes can be recognized in high circulating levels of angiotensin II (AngII) and obesity [26].

3. The role of the gut microbiota in obesity. Inflammatory and hypertensive inducing mechanisms.

The intestinal microbiota (includes bacteria, viruses and fungi living in the intestine) that changes according to the composition of the diet and caloric balance, modulates the local and systemic immunity, particularly of the visceral adipose compartment. The action of the microbiota is explained in part by antigens (lipopolysaccharides and peptidoglycans) that enter the portal circulation from the intestinal lumen and trigger an endotoxemic sub-acute inflammatory reaction [27,28]. Experimental models of hypertensive rats induced by AngII or spontaneously hypertensive rats show an increased intestinal permeability, particularly through a paracellular route, which would favor the entry of antigens from the intestinal microbiota and the generation of a sub-acute inflammatory state [29]. In contrast, the products of bacterial fermentation of dietary fiber, especially short-chain fatty acids (butyrate, propionate, acetate) have demonstrated anti-inflammatory effects [30]. Treatment with short-chain fatty acids reduces rodent blood pressure, attenuates AngII-induced hypertension, decreases systemic inflammation, endothelial dysfunction, cardiac and vascular damage [31,32].

Various studies have shown that the transplantation of the intestinal microbiota from hypertensive to normotensive animals causes increases in blood pressure. In hypertensive patients, a change in the pattern of the microbiota is observed, with reduction in number of species, and shows a predominance of clostridiales and bacteroidales, which would have a lower production of short-chain fatty acids [32]. T2D patients had gut microbiota dysbiosis and a reduction in the butyrate-producing bacteria [33]. In addition, the increased intake of NaCl alters the composition of the microbiota, favoring the activation of immunity. In particular, LTh17 activity is rapidly modulated by dietary changes that affect the intestinal microbiota [34]. Increased NaCl intake in murines causes decreased intestinal Lactobacillus, associated with increased LTh17 activity, while supplementation with Lactobacillus with a rich salt diet prevents its increase. A rich salt diet (13.6 grams/day) supplied to healthy volunteer's causes an intestinal Lactobacillus decrease, which is associated with higher Th17 activity and increased blood pressure [35]. In murines as in humans, increased salt intake increases the Firmicutes abundance, proteobacteria and bacteria of the prevotella genus, which are associated with increased blood pressure (BP) in humans and a predisposition in the development of inflammation and HT with suppressor doses of AngII in mice. These responses would be mediated by intestinal DCs, which would orchestrate the development of a chronic sub-inflammatory state, by mechanisms that also imply the ROS increase and the intestinal neoantigens generation [36].

Although supplementation with probiotics has been conceptualized as a strategy to correct intestinal dysbiosis, studies shows that diets rich in probiotics have a modest modulating effect on BP in humans [37].

THE IMMUNE SYSTEM AND HYPERTENSION

T Lymphocytes (LT)

LTCD8+

Their absence in mice confers protection to the development of HT against the supply of Angiotensin II+ Mineralocorticoids and NaCl [38]. When they infiltrate the myocardium, are activated and, although eliminating them do not prevent the BP increase and the left ventricle cardiomyocytes hypertrophy, it does significantly reduce the development of fibrosis, macrophages infiltration and a myocardial pro-inflammatory cytokines increase [39]. Studies shows that although $LTCD4^+$ and LTCD8 accumulate in HT target tissues, only the $LTCD8^+$ are activated by antigen [40]. The specific deletion of the mineralocorticoid receptor (MR) in $LTCD8^+$, decreases the INF-γ production preserving endothelial function and reducing the BP increase when infusing AngII. Conversely, its overexpression induces the production of

INF-γ. Thus, the benefit of anti-aldosterone drugs in HT could involve endothelial function protection and decreased reabsorption of sodium in the renal tubule by inhibiting LTCD8^{+} activity [41].

LTCD4+

In HT, they play a pathogenic, proinflammatory role, exacerbating tissue damage in inflammatory and autoimmune diseases and, in experimental HT increase their activity, damaging target organs [42]. Hypertensive patient's serum shows increases in proinflammatory cytokines and, its expression in experimental HT, showing a predominant tisular pattern of LTh1 and LTh17. Non-dippers or hypertensive patients with carotid plaque, frequently have this pattern [43].

LTreg

Studies have shown that Treg attenuates hypertension. They are protective in angiotensin-induced hypertension experimental studies, blocking it by adding Treg transfer factor, and decreasing oxidative stress or increasing the nitric oxide production available in the vasculature [44]. The molecular mechanism proposed of its protective effect is the secretion of IL-10 that counteracts the action of AngII. Its genetic deficiency causes increased BP in mice and potentiates the hypertensive action of AngII, while infusing them decreases this response, relating to better endothelium-dependent relaxation and decreasing arterial parietal remodeling [45]. At the renal level, increasing IL-10 expression stimulated by the AngII receptor or its circulating levels, protects against the damage associated with hypertension and obesity. The protective IL-10 action would depend on reducing NADPH oxidase activity, increasing endothelial nitric oxide synthase (eNOS) activity and greater NO bioavailability [46].

B Lymphocytes (LB)

They play an important role in HT and target organ damage. Like the Ig-G produced, are crucial for HT development and AngII-induced vascular remodeling in rat experiences [47].

The immunological mechanism postulated is an adaptive immune response development, triggered by antigens generated by DAMPs, produce as result or -in association with-the development of increased BP [48,49].

The antigens must be presented to the LT by antigen-presenting cells, such as macrophages or DC cells by molecules of the MHC I or II and also would have a pathogenic role of increasing PA [5].

Monocyte/Macrophages (MMc)

Monocytes in peripheral blood are activated in patients with hypertension and have a proinflammatory phenotype compared to normotensive ones [50]. Rats with experimental HT by AngII show increased aorta infiltration and renal tissue by monocytes, DC and macrophages with activated TNF-α. During HT this is associated with a monocyte STAT3 cytoplasmic transcriptional activation by vascular endothelium subjected to greater stretching [51].

It is proposed that the absence of MMc protects vascular function favoring greater bioavailability of endothelial NO against pro-hypertensive stimuli [52].

M1/M2 Ratio

It seems to be associated with the pathophysiology of HT. Studies show that the decrease in the ratio (higher denominator) normalizes hypertension in spontaneously hypertensive rats. On the contrary, if M1 increases, hypertension develops, specially that induced by AngII [53].

Dendritic Cells (DC)

Surface markers can also classified them; for example it has been postulated that cardiac DCs change their characteristics if they are in the vessels or the heart. DC expresses in a 67% a fractalkine receptor (CX3CR1) that is protective for the invasion of inflammatory cells that can develop hypertension. This expression is much more than macrophages or T cells [54].

Hypertension is associated with increased production of superoxide via NADPH oxidase and the protein modification by highly reactive isolevuglandins (IsoLGs). These IsoLGs are produced from lipid peroxidation via isoprostanes and mediated by free radicals that can potentially act as neo-antigens to be presented to T cells [55].

Elimination of DCs prevents the development of a chronic sub-inflammatory state, protecting from cardiac hypertrophy, decreased natriuretic capacity and decreased pressure natriuresis, as seen in states of increased circulating AngII levels. In addition, this elimination in animals with already established HT for two weeks, causes a decrease in BP less than 24 hours. This shows that DCs modulate kidney function rapidly, although adaptive immunity mechanisms are already triggered. Its action would imply a localized effect on kidney tissue, but it would also include actions in the CNS, in areas related to the control of blood pressure and sympathetic tone [56]. Thus, by removing myeloid cells (microglia) from these areas, BP increase would be partially protected by AngII in animals with salt-sensitive HT [57].

Oxidative Stress

There is an increase in oxidative stress in hypertensive patients, whith early vascular aging. Furthermore, it has been known for years that AngII increases oxidative stress mediated by NADP/NADPH oxidative systems [58].

An acute rise in blood pressure induces a self-limited production of superoxide anion, which rapidly inactivates the NO derived from the endothelium, thus losing its vasodilatory capacity. The use of antioxidants has shown variable and not sustainable results over time [59]. Angiotensin II Receptor Antagonists (ARAIIs) have shown antioxidant capacity by decreasing superoxide anion and reducing endothelial dysfunction [60].

THE IMMUNE SYSTEM AND DIABETES TYPE 2 (T2D)

T2D is the result of an increase in the generation of glucose in the liver and a decrease in the emission and activity of insulin. In T2D, a poor-quality part is communicated in tissues associated with digestion control, such as the liver, adipose and muscle tissues. A metabolic inflammation is characterized by moderate cytokine generation, including IL-6, IL-1, or TNF-α, which adversely influence cell insulin flags and prompt insulin resistance and T2D. Low-grade inflammation starts with increased weight. Some researchers report that the gut microbiota is a significant independent factor in the improvement of T2D. In type 1 diabetes, the adhesion proteins inside the intestinal epithelium, prompt a more significant immune response that may result in the destruction of pancreatic β cells by LTCD8+, as well as increased articulation of IL-17, which is associated with autoimmunity [61].

These proinflammatory cytokines and chemokines activate various stress pathways inside the cells, such as the Jun kinase (JNK) and the NF-κB signaling pathways. Activation of these pathways leads to serine phosphorylation of insulin receptor substrate-1 (IRS-1) by the intracellular kinases involved, that is, JNK and IκB kinase (IKK), respectively. The phosphorylation of IRS-1 leads to inactivation of the insulin receptor signaling pathway [62].

TNF-α has also been shown to cause lipolysis in the adipose tissue, which produces free fatty acids accumulation leading to decreased insulin sensitivity by interference with insulin signaling pathway via activation of protein kinase C (PKC) [63]. When the excessively amount of these cytokines increases, they leak out of the tissue and cause endocrine effects on distant organs such as liver and muscle. This cascade of events finally results in systemic insulin resistance [64]. Lipotoxicity caused due to lipolysis in obesity can function as a primary insult to the pancreas and lead the release of auto-antigens. These are then taken up by antigen-presenting cells and presented to LTCD4+ cells in the pancreatic lymph nodes, driving to their recruitment to the pancreatic islets and production of proinflammatory cytokines such as IFN-γ leading to a mild β cell loss, which exacerbates T2D.This again points toward an autoimmune aspect in T2D [65].

In Studies comparing pancreatic islets from diabetic and non-diabetic patients, B cells were found to be significantly elevated in diabetic islets by up to 2.2 times. It is suggest that the B cells functions as antigen-presenting cells, are involved in T cell activation in the islets. Pancreatic islets have also been shown to be sites of macrophage recruitment in diabetic patients and mice with diet-induced obesity [66,67].

T2D must be considered as an auto-immune disorder based on the available evidence this last years, and might lead to exploration of new treatment strategies.

PHARMACOLOGICAL THERAPY CONSIDERATIONS

Obesity

In obese mice, thalidomide administration induced a reduction in adiposity accompanied by a reduction of TNF-α, leptin and MCP-1 adipose tissue production, macrophage infiltration and JNK activation. TNF-α and leptin serum levels were also reduced [68].

Hypertension

AngII has been described to induce inflammation, so therapies with Angiotensin II receptor blocker (ARA II) would reduce it and also oxidative stress [69].

Several immune cells (LT, DC, and macrophages) express AT1-R receptors. By binding, AngII determines the differentiation of immune cells and the subsequent production of proinflammatory cytokines, such as IL-6, IFN-g and TNF-α. This last one determines the increase of the angiotensin-converting enzyme (ACE), which contributes to hypertension mediated inflammation [70].

Conventional cardiovascular drugs (statins, calcium channel blockers, and ACEI/ARAII) have shown additional anti-inflammatory effects [71]. First-line antihypertensives with action on RAAS, have shown anti-inflammatory effects. Their mechanisms are blocking AT1 receptors antagonizing AngII and, allowing activation of AT2 receptors that can increase NO production [72].

Amlodipine would have anti-inflammatory effects similar than ARA II and ACE inhibitors, lowering serum levels of pro-inflammatory cytokines in hypertensive patients [73]. Matrix metalloproteinases (MMPs) are endopeptidases secreted by myocardial fibroblasts and inflammatory cells, that remodel the myocardium induced by pressure overload in hypertensive patients. Experimental studies with hypertensive rats treated with Amlodipine and / or statins reduce MMPs [74].

Statins down regulate angiotensin II type 1 (AT1R) receptors, increase NO production through positive regulation of NO synthase [75,76] and inhibit endothelin-1 synthesis and proinflammatory cytokine production by blocking the NF-κB pathway [77].

Recently, the use of Neprilysin inhibitor Sacubitril alone or associate with Valsartan (ARA II) has demonstrated

that the high expression of IL-6, MMP-8 and MCP-1 provoked by oxidized LDL cholesterol *in vitro* is suppressed [78].

Immunosuppressive drugs such as mycophenolate lower blood pressure levels or may prevent the development of hypertension [79], but other immunosuppressive drugs in immuno-mediated diseases such as Systemic lupus erythematous, Psoriasis and Rheumatoid Arthritis (RA), like Adalimumab (anti TNF-α) and Ustekinumab (anti IL-12 and 23) in psoriatic patients, doesn´t produce changes in BP levels [80]. Infliximab (anti TNF-α) reduces systolic and mean arterial pressure in hypertensive fed fructose rats [81]. Etanercept (central TNF-α blocker) reduces AngII-induced hypertension [82].

However other immunosuppressants can cause HTA [83].

T2D

Regarding to T2D there´s none experience in treating diabetes with immunosuppressants (IMS) drugs when reviewing the literature.

Immunosuppressants like mTOR inhibitors, used as anticancer agents (everolimus, temsirolimus) increase significantly the risk for new-onset diabetes and induce a 5-fold increase in the risk for severe hyperglycemia [84]. Other IMS drugs have the same effect.

Black tea consumption correlated with significantly reduced glycated hemoglobin (HbA1c) levels, with increased regulatory T cells (an immunosuppressive phenotype), reduced pro-inflammatory cells [85].

A study in RA, the incidence of T2D was higher, but the use of antirheumatic drugs shows that the hazard ratio for diabetes was significantly reduced in patients receiving TNF inhibitors, compared to patients treated with non-biologic drugs. Hydroxychloroquine, methotrexate and use of other biologic drugs had a numerically reduced risk [86].

Empagliflozin a sodium-glucose cotransporter (SGLT2) inhibitor shows reduced M1-polarized macrophage accumulation while inducing the anti-inflammatory M2 phenotype of macrophages within the white adipose tissue and the liver, lowering plasma TNFα levels and attenuating obesity-related chronic inflammation [87].

Dapagliflozin treatment, another SGLT2 inhibitor, has showed favorable effects on glucose and fat metabolism, partially reverse the formation of atherosclerosis, inhibited macrophage infiltration, and enhanced the stability of lesion. Also, reduced production of ILs, NLRP3 protein, and mitochondrial ROS in the aortic tissues [88].

Finally it will be necessary to have more clinical studies that can establish an immuno-anti-inflammatory therapy to treat these pathologies.

CONFLICT OF INTEREST

I declare no interest conflict, and none external financing.

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