REVIEW ARTICLE

Update on Obesity: Induced Inflammation to Cause Cardiometabolic Diseases

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Abstract

BACKGROUND: Obesity incidence has risen dramatically during the last 50 years, reaching epidemic proportions. Obesity's growing prevalence, as well as its numerous metabolic and cardiovascular problems, poses a danger to human health and lifespan across the world.

CONTENT: Numerous studies have shown that obesity causes inflammation, and suggest that inflammation may have a causal role in the development of insulin resistance, defective insulin secretion, and energy homeostasis disturbance. Obesity-induced inflammation is different from other inflammatory models because it includes tonic activation of the innate immune system, which has a long-term influence on metabolic balance. Inflammation can cause tissue damage by causing maladaptive responses such as fibrosis and necrosis. Obesity-induced inflammation is unique since it affects a variety of organs, including the adipose tissue, pancreas, liver, skeletal muscle, heart, and brain. These characteristics of obesity-induced inflammation make it difficult to decipher the underlying processes and how they affect metabolic systems.

SUMMARY: The disruption of energy homeostasis caused by a positive energy balance is most likely the first trigger of metabolic inflammation, and the initial adaptive response aim to relieve the anabolic pressure caused by obesity. However, over time, this adaptive reaction becomes maladaptive, and the persistence of inflammation shows that the initial response has failed. The inflammation affects so many organ systems during obesity, and to develop novel treatment methods, a greater knowledge of the process was needed.

KEYWORDS: obesity, inflammation, diabetes mellitus, non-alcoholic fatty liver disease, cardiovascular diseases, heart failure

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Introduction

Obesity has roughly quadrupled globally since the 1970s, making it a global epidemic. In 2016, over 1.9 billion individuals were overweight, accounting for 39% of the global adult population, and over 650 million were obese. (1,2) Obesity-related complications such as type 2 diabetes (T2DM), cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), musculoskeletal disorders, and some cancers have a significant impact on morbidity, quality of life (QoL), and mortality in this disease.(3) Obesity may also result in decreased QoL, unemployment, lower productivity, and social disadvantages. Obesity-related osteoarthritis, for example, is one of the primary causes of disability and early retirement. Obesity has been classified as a chronic progressive disease by the World Obesity Federation and other organizations, including the American and Canadian Medical Associations.(3)

After two decades, many studies focusing on the etiology of obesity with insulin resistance and diabetes found a strong association between nutritional excess and innate immune system activation in most organs involved in energy balance.(4) The exact causes of obesity-related inflammation are unknown, and they may have different arrangement in different tissues. While elevated inflammatory markers in the liver, adipose tissue (AT), skeletal muscle, pancreatic islets, and brain are all linked to obesity, the specific timing correlations between these processes in rodents or obese humans are still unclear.

Multiple data suggesting that the disturbances in both the brain and the periphery contribute most of the obesity complex disorders. The crosstalk between AT and immune cells on obesity happens both in the central nervous system (CNS) and peripheral after induced by many factors such as high-fat diets (HFDs), lack of physical activity which related to less energy expenditure, and adipocyte expansion.(4)

Obesity is simply caused an energy imbalance between calories taken and calories expended. Many weight reduction strategies at individual level aiming at lowering calorie intake and increasing energy expenditure, somehow are ineffective in the long term.(5) Although behavioural changes, such as changes in food and exercise habits, appear to be the personal responsibility, they are result of the social environment. In the absence of supportive policies in areas such as health, agriculture, transportation, urban planning, environment, food processing and marketing, education, and others, such behavioral changes may be unsuccessful. (6) As a result, the World Health Organization recognizes that should be policies and actions in communities that encourage healthy diet and increased physical activity among the whole population.(7,8). In this review, we update the current knowledges on how inflammation become the main cause of obesity comorbidities especially on cardiovascular system, and how we can develop a better strategy to manage this problem.

Inflammation, Metaflammation, and Insulin Resistance

Most metabolic disorders including obesity and its comorbidities, T2D, and NAFLD are characterized by low-grade inflammation, known as ‘metabolic inflammation’. (9) These conditions aggravate atherosclerosis, which is a primary cause of cardiovascular morbidity and death. As a result, some investigations have linked these disorders to higher levels of acute phase proteins in the blood, such as C-reactive protein (CRP), fibrinogen, haptoglobin, serum amyloid A, cytokines, and chemokines.(10)

In experimental and clinical settings, various non-infectious variables, such as nutrition and specifically excess dietary lipid species, have emerged as causal factors for metabolic inflammation.(11) Lipotoxicity affects organs involved in lipid metabolism, such as the liver, muscle, and AT. As a result, lipid metabolism and oxidative activities known to have an influence on metabolic inflammation. In metabolic dysregulation, unresolved endoplasmic reticulum (ER) stress and oxidative stress, for example, are primary causes of an inflammatory response.(12) Hypoxia may also trigger inflammatory responses and suppress the production of antiinflammatory adipokines (such as adiponectin) while AT is expanding.(13-15) AT expanding can happens in two ways, hypertrophy where adipocytes expand by increasing their size until their maximum capacity, and hyperplasia where the preadipocyte differentiate into new adipocytes and the cell number are increased.(16) Adipocyte hypertrophy relates to low adipogenic capacity and adipocyte hyperplasia related to high adipogenic capacity and smaller adipocites.(17)

AT dysfunction is also characterized by immune cell infiltration and changes in adipose-derived inflammatory cytokines. In summary, we now know that AT homeostasis includes intricate interactions between a variety of immune cell types, including B cells, natural killer (NK) and regulatory T (Tregs) cells, eosinophils, and innate lymphoid cells, in addition to macrophages.(18) There are two types of inflammation depends on which cells they activate. Type 1 inflammation is referred to as "proinflammation" or "inflammation." Type 2 inflammation, on the other hand, is sometimes referred to as "anti-inflammation".(19) Each type of inflammation will promote different stream of inflammatory molecules and transcription factors, thus perform different tasks in type 1 and type 2 inflammation. (20,21)

Healthy AT homeostasis is linked to a type 2 inflammatory, while obesity with insulin resistance, is linked to type 1 inflammation in AT. Many data suggest that insulin resistance play a role in AT inflammation (22), while on the other hand most research still suggest that inflammation is the cause of insulin resistance. Inflammation and insulin resistance can worsen each other after they've started. Like a loop, the autocrine effect of inflammatory cells secreted by AT can impair insulin signaling and adipocytes metabolism, while their endocrine effect affect the neighbour tissues such as muscle and liver. Long term positive energy balance can induce fat spill over from AT to skeletal muscle and

liver, termed as ectopic fat deposition and this will lead to systemic insulin resistance and T2DM.(23)

Inflammation is involved in AT remodelling in a variety of ways. Adipocyte inflammation, extracellular matrix remodelling, and angiogenesis is required for healthy AT growth, and that adipocyte inflammation suppression leads to AT malfunction and systemic metabolic illness. (24) Macrophages may have a role in AT remodelling in a variety of ways, including generating vascular endothelial growth factor (VEGF) to induce angiogenesis, matrix metalloproteinases (MMP) and MMP-1 at the terminals of developing AT for extracellular matrix remodeling. Several cytokines released by macrophages, like as TNF-α and IL-8, have proangiogenic properties, suggesting that they may contribute to healthy AT growth and remodelling. (25) During AT remodelling, M2-like macrophages may aid adipogenesis.(26) In obesity, macrophages repress adipogenesis but increase AT fibrosis by secreting cytokines like TNF-α and transforming growth factor(TGF)-β or producing macrophage-inducible C-type lectin, which is thought to contribute to AT dysfunction.(26) Multiple immune cells are found in adipocyte depots, which work cooperatively to monitor and maintain adipocyte integrity and hormone sensitivity. Th2 or type 2 manage tissue integrity and metabolism to keep resident macrophages in an M2-polarized by generating a cascade of cytokines and modulate the activity of subsets of T lymphocytes.(27) M2-polarized macrophages, in turn, release interleukin (IL)-10 and maybe other cytokines that help adipocytes maintain insulin sensitivity.(28)

We now know that inflammation is strongly associated to insulin resistance, and can be suppressed by knocking down important pathways, such as components of the fuclear factor kappaB (NF-κB), and c-Jun N-terminal kinase (JNK) pathways (Figure 1) (29), or other proinflammatory signaling molecules, scaffolding proteins, and cytokines in obese mice can break the relationship between obesity and insulin resistance directly or indirectly.(30) Adipocytes release the arachidonic acid-derived product leukotriene B4 (LTB4), which recruits macrophages to AT and may also inhibit insulin signaling in myocytes and hepatocytes, for example by releasing galectin-3.(31)

The involvement of the innate immune response has been the focus of most of the research relating inflammation

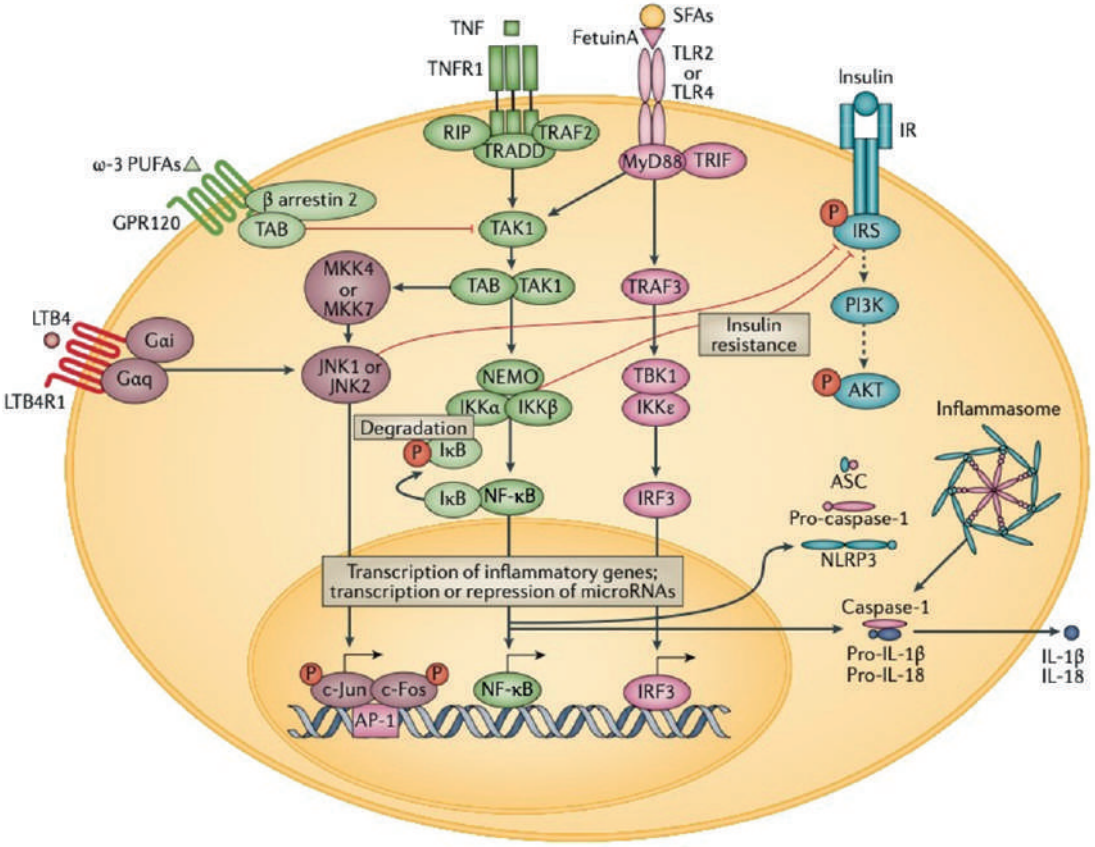

Figure 1. Inflammatory signalling pathways involved in the development of insulin resistance.(7) (Adapted with permission from Macmillan Publishers Limited).

and metabolic illness. Obese mice has more mast cells compare to non-obese mice, and is linked to insulin insensitivity. Elastase production by neutrophils has been proven to promote insulin resistance.(32) Dendritic cells (DCs) are antigen-presenting cells (APCs) that serve as a bridge between the innate and adaptive immune systems. They are involved in the development of naive $CD4^+$ T cells into Th1, Th2, or Th17 cells, as well as Tregs. When compared to lean control participants, more activated DCs were found in the AT of obese non-diabetic adults and people with T2DM. Antiinflammatory cytokines IL-4 and IL-13 are produced by eosinophils in murine visceral adipose tissue (VAT), promote macrophage development into alternatively activated M2-polarized cells. Innate lymphoid type 2 cells (ILC2s) produce IL-5 and IL-13, which aid in the maintenance of eosinophils and metabolic balance in VAT. Recent research found that IL-5 deficiency increased insulin resistance and obesity, and removal of ILC2s resulted in lower eosinophil and alternatively activated macrophage accumulation in VAT.(33)

While most studies of inflammation, obesity, and insulin resistance have focused on macrophages, current research suggests that the adaptive immune system plays an essential role. T and B lymphocytes use antigen recognition to form various populations of immune cells that are either proinflammatory or regulatory in nature. Several investigations have found that proinflammatory T and B cell phenotypes are strongly linked to illness development and severity. T cells, B cells, NK cells, NKT cells, and ILC2s are lymphocytes that make up up to 10% of non-adipocyte cells in human AT.(34) CLSs around necrotic adipocytes contain T and B lymphocytes, as well as macrophages.(35,36)

ILCs are a family of innate immune cells resident in VAT that mirror T cells. ILC2s play a crucial role in metabolic homeostasis regulation. In response to IL-33 and IL-25 activation, ILC2s are a key source of the Th2-associated cytokines IL-5 and IL-13. To maintain glucose homeostasis, ILC2s stimulate the formation of eosinophils and alternatively activate macrophages by producing IL-5 and IL-13. Furthermore, activated ILC2s have recently been discovered to have a role in AT beiging by generating methionine-enkephalin peptides thus enhance the amount of beige adipocytes in white adipose tissue (WAT) (37), while another research found that activated ILC2s cause adipocyte precursor proliferation and subsequent beige lineage commitment via ILC2- and eosinophil-derived IL-4 and IL-13 (38). Many studies in animal models suggest that inflammation in AT and the gut may appear to play important roles in the development of insulin resistance.

Dietary Fatty Acid, Adipokines and Lipokines in Obesity

Fatty acids is a strong causative factor in T2DM and its complication. Diets rich in saturated fat and calories cause insulin resistance and β-cell malfunction quickly. Intravenous (IV) fat infusion is potentiating glucose-stimulated insulin secretion, and consistently linked to the development of insulin resistance, regardless of β-cell malfunction.(39) High fat diets (HFDs) often result in lower blood glucose and improved cardiovascular risk profiles compared to isocaloric high-carbohydrate diets. This demonstrates the intricacy of the metabolic pathways that relate dietary fatty acid (DFA) consumption to the development of T2DM especially the effect of gender, and altered postprandial DFA metabolism (IV vs oral intake) amongst people to diabetes. (40,41)

The DFA type consumed has an impact on their absorption and distribution rate, digested emulsified triglycerides, absorption, and carried into the systemic circulation rate.(42) In the gut, all DFAs are mainly esterified into triglycerides, while stearate (C18: 0) and linoleate (C18: 2) contribute more to phospholipid production than palmitate (C16: 0).(43,44)

A large amount of DFA from a single meal is stored in enterocytes, where it is released into circulation after successive meals, and directly increased by dietary carbs. (45) As a result, DFA from a particular meal can enter the circulation for at least 16 hours.(46) Long-chain fatty acids (LCFA) kinetics like digestion, absorption, assembly into CM-triglycerides, and secretion is much affected by gastric emptying and intestinal peristalsis. Some data showed that insulin and glucagon-like peptide (GLP)-1 slowing the secretion of intestinal CM particles, while high circulating non-esterified fatty acid (NEFA) and GLP-2 speeding it up.(47-49) However, it is uncertain if these variables impact DFA intestinal metabolism and secretion in isolation from CM-apo-B48.

DFA storage in abdominal subcutaneous and visceral (perirenal) AT was reduced per AT volume because of postprandial NEFA levels. Thus, in prediabetes, reduced abdominal adipose tissue DFA storage efficiency is tightly linked to increased postprandial NEFA spillover. Abdominal obesity is the key factor of inefficient abdominal AT DFA storage.(50)

Increased cardiac fatty acid delivery has negative implications (51,52), as does energy deficit of the oxidative

route in metabolic cardiomyopathies (*e.g.*, lower energetic efficiency). These findings imply that a shift in cardiac fatty acid metabolism from nonoxidative to oxidative, as well as an increase in cardiac DFA absorption, may compromise left-ventricular performance. It's unclear how this increase in cardiac DFA uptake in prediabetes affects postprandial intramyocardial fatty acid metabolism in people. The intricacy of DFA metabolisms is unappreciated, and it is probable that it explains at least some of their disparate impacts on cardiometabolic health.(53)

AT in obese mice secretes TNFα, a proinflammatory cytokine normally generated by immune cells, and that adipocyte-derived TNF-α is involved in obesity-induced insulin resistance.(54) Following TNF-α, it was shown that AT generates a variety of cytokines and chemokines, including IL-6 and monocyte chemoattractant protein-1 (MCP1), that affect systemic glucose and lipid metabolism either positively or negatively. Because certain adipokines have cytokine-like properties or control inflammatory responses, these two families of adipocyte-derived substances are commonly referred to as 'adipocytokines.'

Leptin, which now recognized as a “satiety hormone” and play a primary role in hypothalamus to promote neuropeptides and neurotransmitters to signal nutritional status in our body, means that to control the food intake. (55,56) Leptin shares the same janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway as Class I helical cytokines and is regulated by the same receptor. Endotoxin or the cytokine TNF-α can cause leptin expression. Oppositely, leptin enhances T helper 1 cell differentiation by increasing thymic production of acute-phase reactants and TNF-α. Leptin stimulates the production of a wide range of cytokines in T cells, macrophages, and other immune cells.(57) This proinflammatory activity of leptin might contribute to its overall effects on body weight management, given the significance of many cytokines in boosting energy expenditure and lowering food intake. (58) Inflammation generated by metabolic stress adversely affects leptin signaling. Leptin has also been linked to a number of immune system problems. Leptin, for example, has been hypothesized as a metabolic connection to multiple sclerosis, and has been shown to counteract starvation-induced immunosuppression.(59)

Ceramidase activity linked with adipoR1 and adipoR2 has recently been discovered to modulate a range of downstream effects of the adiponectin receptor. Adiponectin is an anti-inflammatory cytokines, which contribute to its obesity-related metabolic stress protection. In obese mice, adiponectin inhibits TNF-α production, and adiponectin-deficient animals have high TNF-α levels in AT. In humans, low plasma adiponectin levels are linked to CRP.(60) Adiponectin facilitates the opsonization and absorption of apoptotic cells by macrophages, enhancing their clearance. (61) Some of adiponectin's anti-atherogenic actions are mediated by its function in suppressing inflammatory responses. Adiponectin reduces monocyte adherence to endothelial cells via inhibiting NF-κB activation and its downstream adhesion molecules. Furthermore, adiponectin has vascular-protective properties by inhibiting endothelial cell apoptosis.(62)

RBP4 is a retinol transport protein that is primarily generated by the liver but also expressed in white adipocytes in systemic circulation. RBP4 first discovered in Glut4-deficient mice AT and known to promote insulin resistance. Clinical research in obese human also indicate the role of RBP4 in the early stage of metabolic syndrome.(63)

The anti-inflammatory adipocytokine secreted frizzled-related protein 5 (Sfrp5) was recently discovered. (64) Sfrp5 is significantly expressed in lean mice's AT but is downregulated in obese mice's. When mice were given an HFD, a targeted mutation of Sfrp5 produced insulin resistance, glucose intolerance, and hepatosteatosis.(64) Sfrp5 stimulates JNK1 via noncanonical Wnt signaling, causing inflammatory cytokines to rise and insulin action to be blocked.(64) However, the authors postulated a totally different mode of action for Sfrp5 when a second independently created Sfrp5 mutant mice line was shown to exhibit distinct symptoms.

Adipocyte Protein 2 (aP2) is the first adipokine whose production is highly influenced by lipolysis-released fatty acids, indicating that it may serve as a lipid sensor in adipocytes and transport particular lipids from the plasma to specific organs or cells. As a result, released aP2 might possibly work on other critical organs such as the central nervous system (CNS) or heart to control other elements of metabolic balance, similar to other well-studied adipocytokines. As a result, a full endocrine network of organ connections in nutrition sensing and metabolic equilibrium is quite likely to emerge in the near future. Such an organ crosstalk roadmap would have a huge influence on the development of successful obesity and metabolic illness medicines.(65)

Adipose secretome is a rich supply of endocrine chemicals as a communication tools between adipose and other tissues. Aside from traditional polypeptide adipokines, adipose-secreted endocrine lipids, such as LPA, palmitoleate, FAHFAs, oxylipins, and N-acyl amino acids, are an important class of adipose-derived chemical

messengers. Pharmacological and genetic research have revealed that these lipid molecules have endocrine activities in facilitating cross talk with the pancreas, liver, and muscle. This type of lipid-mediated signaling might be part of a broader endocrine mechanism for interorgan metabolic communication.(66)

"Lipokines" refer to the latter category of adipose-secreted blood-borne bioactive lipids. Lipokines have been postulated to operate as endocrine mediators of adipose cross talk to other tissues such as the pancreas, liver, and muscle via a variety of cell-surface and intracellular modes of action due to their presence in blood plasma. Furthermore, because these hydrophobic molecules are biochemically linked to intracellular fatty acid metabolic pathways, they are ideally positioned to convey adipocyte energy status to nonadipocyte cell types. Direct lipid pharmacological research, as well as genetic modification of their production or secretion routes in AT, have emerged as key tools for determining their functional involvement in intercellular signaling. These investigations have uncovered a fascinating and surprisingly fruitful realm of adipose cross talk and systemic metabolic integration mediated by adipose-derived endocrine lipids (Figure 2).(67)

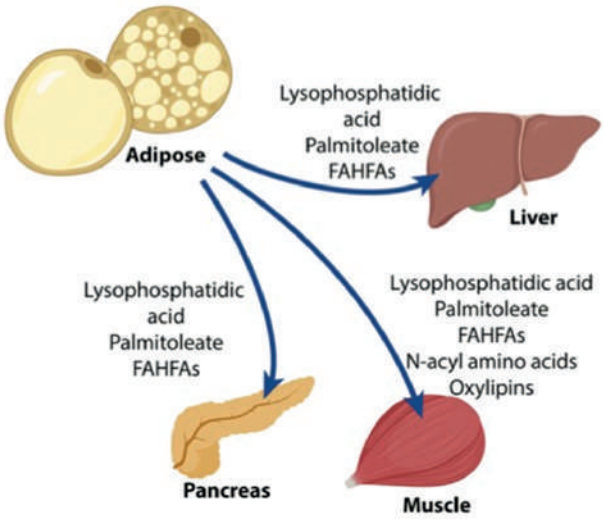

Figure 2. Schematic of adipose-derived endocrine lipids that mediate crosstalk from adipose to other peripheral metabolic tissues.(67) (Adapted with permission from the American Diabetes Association).

Obesity Metaflammation in Adipose Tissue, Skeletal Muscle, Liver, Pancreas Islet, Intestine, and Brain

The processes behind obesity-related inflammation are unknown, and they may differ depending on tissue type and location. The primary component of AT inflammation may be immune cell recruitment, contacts, and activation, which releases inflammatory chemicals. Inflammation and recruitment of immune cells, mostly type 1 inflammatory cells, begin early in the development of obesity in AT.(32) During obesity development in mice, however, increases in macrophages occur before increases in T cells in intermuscular adipose tissue (IMAT)/perimuscular adipose tissue (PMAT).(68) After 3 days on the HFD, neutrophils in the VAT of mice begin to grow.(32,69) T cell increases appear to occur before and contribute to macrophage increases in VAT of mice with diet-induced obesity.(70)

The predominant resident cells in AT, adipocytes, were first blamed for the inflammation. Adipocytes can become inflamed and release inflammatory moleculs.(71) Since macrophages were found in AT (72,73), macrophages and other immune cells have been shown to be the predominant inflammatory cells in AT of obese animals and people.(74) One of the characteristics of obesity-related inflammation in AT is higher number of macrophages.(75) Macrophages are most abundant immune cell population in AT with established obesity, including VAT and subcutaneous AT (SAT). They dwell in AT under lean circumstances and gradually increase as obesity progresses.(76)

T cells are similarly elevated in AT of obese mice and people, with a higher number in VAT than in SAT, and are strongly linked to systemic inflammation in humans. In HFD given mice increases in AT T cells may precede and contribute to increases in AT macrophages. αβT cells appear to have larger increases in obese AT compared to γδT cells. In AT of obese mice, $CD8^+$ T cells exhibit larger increases than $CD4^+$ T cells within αβT cells (74,77).

By modulating macrophage population and activity in epididymal fat, NK cells is responsible for inflammation and insulin resistance in obese (Figure 3). In obesity, adipocyte NK cells may operate as an upstream regulator of adipocyte macrophages.(77,78)

Adipose group 1 innate lymphoid cells (ILCs) and tissue-resident ILC1 consist of immature and mature NK cells. Diet-induced obesity promotes adipose-resident ILC1s to selectively concentrate in adipose depots and generate interferon (IFN)-γ in response to IL-12 release, contributing to M1 macrophage polarization and insulin resistance.(79) Far before impaired glucose tolerance develops in T2DM subjects, β-cell function has already started to deteriorate. (80,81) Immune cell infiltration, amyloid deposition, cell

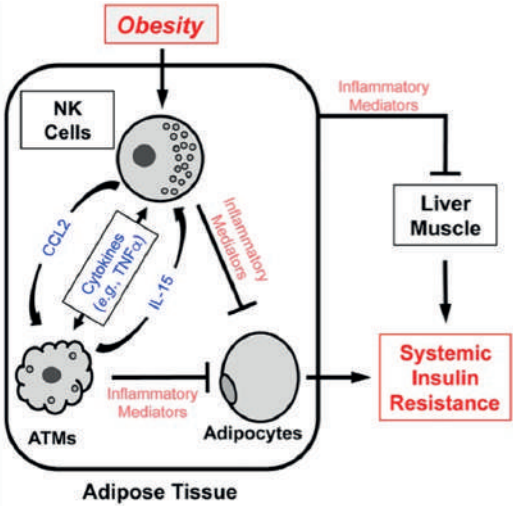

Figure 3. A high-fat diet increases both NK cell numbers and activation in epididymal fat. Epididymal adipose NK cells regulate ATM inflammation in obesity, and adipose NK cells regulate the development of obesity-induced insulin resistance. (77) (Adapted with permission from Elsevier).

death, and fibrosis are all seen in the islets of T2DM patients. (82,83) These studies demonstrate that inflammation has a role in β-cell dysfunction, although there is variety degree of severity.(83)

IL-1β release can induce β-cell dysfunction in rats, and humans.(84,85) Human islet amyloid polypeptide (hIAPP), palmitate, and endocannabinoid stimulate islet macrophages to release IL-1β *in vivo*. Other immune cell types may be implicated in T2DM islet inflammation; whereas one research found an increase in the number of β-cells (86), other studies have shown no changes in the number of immune cell types such as neutrophils, lymphocytes, and mast cells (87). It has also been proposed that certain T2DM patients acquire islet autoimmunity as the condition progresses, contributing to cell dysfunction. (88) Islet cells, such as β-cells, are critical in the onset of islet inflammation because they can recognize stimuli and release chemokines and hIAPP, which activate macrophages. According to most studies, macrophages are the primary source of proinflammatory cytokines in islets. IL-1β, a proinflammatory cytokine produced by M1-like macrophages, is important in the beginning and progression of islet inflammation. M2-like macrophages, on the other hand, are required for both islet formation and β-cell proliferation in adults.(89)

The molecular linkages between fat, insulin resistance, and T2D include chronic inflammation in AT including their endocrine manner.(76) Furthermore, disruption of preadipocyte/adipocyte activities speeds up fat spill over from AT to skeletal muscle and liver, resulting in ectopic fat deposition and insulin resistance in these tissues, which contributes to systemic insulin resistance and T2D.(90) Skeletal muscle is the most essential organ for maintaining whole-body glucose homeostasis, accounting for around 80% of insulin-stimulated whole-body glucose absorption and disposal under normal circumstances.(91) Insulin resistance in skeletal muscle is the most common cause of T2D (91), and it is therefore important to T2DM and systemic insulin resistance.

Skeletal muscle myocytes, like adipocytes, produce and release a variety of cytokines, mostly when we do exercises including IL-6, IL-8, and IL-15, as well as additional myokines such fibroblast growth factor (FGF)21, irisin, myonectin, and myostatin.(92,93) Most proinflammatory adipokines involved in obesity-related metabolic dysfunction development (74-76), while most myokines counteract the adipokines negative effects. That's how doing exercise give benefit on glucose, lipid metabolism, and inflammation.(94,95)

Obesity-related inflammation in AT is characterized by increased immune cell infiltration.(96,97) Immune cells, macrophage and T cell numbers have been shown to increase in skeletal muscle and may be the primary inflammatory cells in skeletal muscle in obese people. (68) In fact, in healthy adults, a short-term high-fat, high-calorie meal or overfeeding with insulin resistance elevated macrophage markers in skeletal muscle.(98,99) Obesity and insulin resistance generated by HFD were consistently linked to an increase in immune cells such as macrophages and T lymphocytes in skeletal muscle in mice.(100) The immune cells infiltration mostly located in muscle adipose depots (IMAT/PMAT), and may be the major cause of skeletal muscle inflammation in obesity because theytend to polarize into proinflammatory phenotypes.(101)

Because the liver is involved in lipid and glucose metabolism, liver inflammation is linked to metabolic diseases such NAFLD, which affects up to 40% of Western adult populations.(102,103) NAFLD refers to a group of illnesses caused by the ectopic fat accumulation in the liver. It characterizes by inflammation, cellular damage, and fibrosis (which can develop to cirrhosis). Increased *de novo* lipogenesis, reduced β-oxidation, and decreased very-low-density lipoprotein (VLDL) secretion cause steatosis in hepatocytes, which can lead to lipotoxicity. The saturated free fatty acids palmitate and stearate are cytotoxic. Palmitate can cause the production of ceramide and lysophosphatidylcholine (LPC), which may cause extracellular vesicle (EV) release by activating

proapoptotic signaling.(104,105) C16:0 ceramide generated from palmitate has been linked to insulin resistance and steatohepatitis (106), and it can also cause EV release. Exosomes, microvesicles, and apoptotic bodies (107), among other EVs, include payloads such effector proteins and miRNAs that allow cells to communicate. Through macrophage activation or chemotaxis, TRAIL, C-X-C motif chemokine ligand 10 (CXCL10), and sphingosine-1-phosphate in EVs from damaged hepatocytes may play a role in the pathogenesis of NASH.(104,108) Furthermore, CD40L and miRNAs (let7f, miR-29a, and miR-340) have been detected in EVs and have been linked to an alcoholic liver damage mouse model.(109,110) Although EVs have been shown to have a harmful impact in cultured cells, demonstrating an *in vivo* involvement for EVs in the pathogenesis of NASH is difficult.

Inflammation of the liver is mediated by Kupffer cells, the resident macrophages that dwell in the liver sinusoids' lumen and account for around 30% of sinusoidal cells. (111) Kupffer cells get activated and produce cytokines and signaling molecules in response to hepatocyte damage. Additionally, depending on the signals they get from their surroundings, activated Kupffer cells express markers of M1-like macrophages or M2-like macrophages. The proportion of proinflammatory M1 Kupffer cells and antiinflammatory M2 Kupffer cells in the liver controls the level of inflammation.(112) Kupffer cells are exposed to a variety of substances via the portal circulation, including nutrients and gut-derived bacterial metabolites, and they use pattern-recognition receptors to detect and eliminate pathogens and danger compounds (PRRs). Toll-like receptors (TLRs) and nuclear oligomerization domain-like receptors (NLRs) are two different groups of sensor proteins that recognize danger signals such as pathogen-associated chemical patterns and alarmins. TLRs identify bacterial compounds generated from the gut microbiota, such as LPS and peptidoglycan. In granulomatous liver disease, ischemia/reperfusion liver damage, NASH, and alcoholic liver disease, Kupffer cells react to LPS via TLR4 and generate inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-12, IL-18, and chemokines.(113) As a result, several of these mediators become activated, worsening insulin resistance and metabolic syndrome.(114)

Immunologic tolerance to commensal bacterial and food antigens is maintained by the gut immune system. The intestinal barrier is maintained by innate and adaptive immune systems positioned throughout the intestinal epithelial surface and lamina propria. The innate immune system including mucus, antimicrobial peptides (AMPs), intestinal epithelial cells (IECs), microfold cells, paneth cells, lILCs, and other rapid-response immune cells. Adaptive immune system including T cells, B cells, and plasma cells, along with their produced antibodies, such as IgA. The gut-associated lymphoid tissue (GALT), is the largest mass in lymphoid tissue consists of Peyer's patches (distal ileum), isolated lymphoid follicles, and mesenteric lymph nodes, together with T and B cells. Sensing of microbe-associated molecular patterns (MAMPs) generated by commensal gut flora or pathogens triggers reactions in the intestinal immune system. In IECs and immune cells, MAMPs are identified by PRRs such as TLRs, NLRs, and retinoic acid-inducible gene I (RIG-I) like receptors.(115)

Dietary variables have a big influence on the immune system in the intestine. Ligands for the aryl hydrocarbon receptor (AHR) transcription factor can be found in fruits, nuts, and vegetables. Intestinal lymphoid tissue growth is decreased in mice missing AHR or eating fruits and vegetables, as well as the quantity and function of intraepithelial lymphocytes (including CD8 T cells and T cells) and RORt+ ILCs.(116) ILC-derived IL-22 responses, which increase intestinal barrier integrity, are likewise dependent on AHR activity.(117) Western diet lack in vegetables and fruits is synergize with dysbiosis to promote impaired barrier integrity, as happens in obesity too, may increase the lack of such protective effects on the intestinal barrier. As a result, during diet-induced obesity, the intestinal immune system works as a major hub, amplifying systemic inflammation and the metabolic implications that follow. Manipulation of this mechanism might lead to novel metabolic illness treatments.(118)

Hypothalamic inflammation currently known to be associated in the development and progression of obesity and its complications in recent years, and it has emerged as a key cause of disturbed energy balance, and a contributor to obesity-related insulin resistance via altered neurocircuit functioning. The hypothalamus is in charge of a number of neuroendocrine activities that maintain energy balance and integrate metabolic feedback.(119,120) Early lesion trials demonstrated that changes in the hypothalamus portion of the brain affected eating behavior and energy consumption.(121,122) The melanocortin system consist of the orexigenic neuropeptides agouti-related peptide (AgRP) and neuropeptide Y (NPY), and the functionally antagonist which are the anorexigenic peptides proopiomelanocortin (POMC) and cocaine and amphetamine regulated transcript (CART). The circulating signals were integrated by arcuate nucleus (ARC) of the mediobasal hypothalamus (MBH). (123) Both of these neuronal groups have high numbers of

hormone receptors and hence respond to metabolic signals to govern food intake and expenditure, depending on the body's energy balance.(123-125) Insulin and leptin levels in the blood, which are proportional to nutritional status and AT storage, block AgRP neurons and activate POMC neurons, resulting in lower calorie intake and higher energy expenditure.(126) The majority of data suggests that diet-induced inflammation and gliosis in the hypothalamus cause uncoupling of food intake and energy expenditure. Early inflammation due to obesogenic diet affect hypothalamus first before reach the peripheral organs.(127)

Gut Microbiota and Metaflammation

Recent research suggests that changes in gut microbial flora and gut peptide levels after consuming an HFD may promote low-grade systemic inflammation, which may precede and predispose to obesity, metabolic problems, and T2D.(128) This theory is interesting because the gastrointestinal system is the initial point of contact with nutrients, and so may be the first link in the chain of events leading to obesity-related systemic inflammation.(129)

Pathogen-associated molecular patterns (PAMPs) and metabolites are produced by a variety of microorganisms, particularly bacteria, in the gastrointestinal system. PAMPs interact with the host via eliciting responses from membrane-bound PRRs like TLRs, as well as cytoplasmic PRRs like NOD-like receptors and RIG-I-like receptors. (130) Healthy people have a varied intestinal microbiota and an intact intestinal barrier, which prevents bacteria and their mediators from penetrating and spreading throughout the body.(131) Metabolic impairment such as obesity, T2DM and NAFLD correlated with gut microbiota functional and compositional changes, known as dysbiosis (132), and a weakened and defective intestinal barrier (133,134), makes the gut bacteria and endotoxins leak to the circulation and cause low-grade inflammation (135). Dysbiosis does not always lead to systemic inflammation; rather, but commonly linked to a growth of might be harmful commensals (so-called pathobionts).(136)

Various mechanisms that support a tolerogenic immune response maintain segregation between the host gut epithelium and the microbiome at equilibrium including PRRs, antimicrobial peptides, secretory immunoglobulin A (IgA), the immune milieu that comprises a cytokine environment such as IL-33, IL-10, and TGF-β, and some cells like $CD103^+$ dendritic cells and regulatory T cells, achieve this in the small intestine. A thick continuous mucus layer also helps compartmentalize the big intestine. (137,138) The intestinal barrier is altered anatomically and functionally as a result of HFD eating and obesity.

In mice, an HFD enhanced intestinal inflammation, which preceded the initiation of weight gain, indicating that dietary composition, particularly fat-rich nutrition, might influence intestinal permeability.(139,140) In the presence of dietary lipids, *in vitro* and animal studies showed that chylomicrons transport the LPS across the epithelial barrier by chylomicrons through the transcellular route, and not the traditional paracellular pathway.(141,142) Similarly, a study in patients with severe obesity found that jejunal permeability increased in response to a lipid challenge compared to healthy controls (143), while jejunal epithelial T cell densities was linked to low carbohydrate and HFD in obese (144), suggesting that factors other than obesity may be to blame for the discrepancies in human trials. In animal models, several probiotic therapy have been shown to reduce intestinal permeability. In a mouse model of alcoholic liver illness, *Akkermansia muciniphila* supplementation was found to increase mucus thickness and tight junction expression, as well as protect against gut leakiness.(145) Figure 4 shows some gastrointestinal problems that contribute to metabolic diseases.(146)

In mice, *Lactobacillus rhamnosus* GG supernatant reduced intestinal leakage, endotoxemia, and liver toxicity caused by alcohol.(147) While *Lactobacillus reuteri* alleviated metabolic syndrome symptoms in mice by producing aryl hydrocarbon receptor ligands.(148) Supplementing fibre-deficient diet mice with *Bifidobacterium longum* NCC 2705 and inulin improved mucus development and decreased mucus permeability, respectively, but no change in metabolic parameters.(149) *Parabacteroides distasonis* can reduce body weight, improve hyperglycemia and hepatic steatosis by increased lithocholic acid and ursodeoxycholic acid (UDCA) in the bile of HFD-fed mice and ob/ob mice, upregulating ileal tight junction protein expression and reducing endotoxaemia.(150) Finally, treating obesity with *Bifidobacterium adolescentis* IVS-1, *Bifidobacterium lactis* BB-12, or the prebiotic galactooligosaccharides enhanced intestinal permeability in humans, while no changes in endotoxaemia indicators occurred.(151) Prebiotic, probiotic, and postbiotic therapy in combination have shown potential in improving gut barrier integrity to prevent metabolic inflammation in animals; however, human data is still limited.(152) In preclinical settings, the gut microbiota–metabolism axis has gained traction, opening an interesting new route for doctors that may also become significant in other disorders (for example, neurological).(153,154)

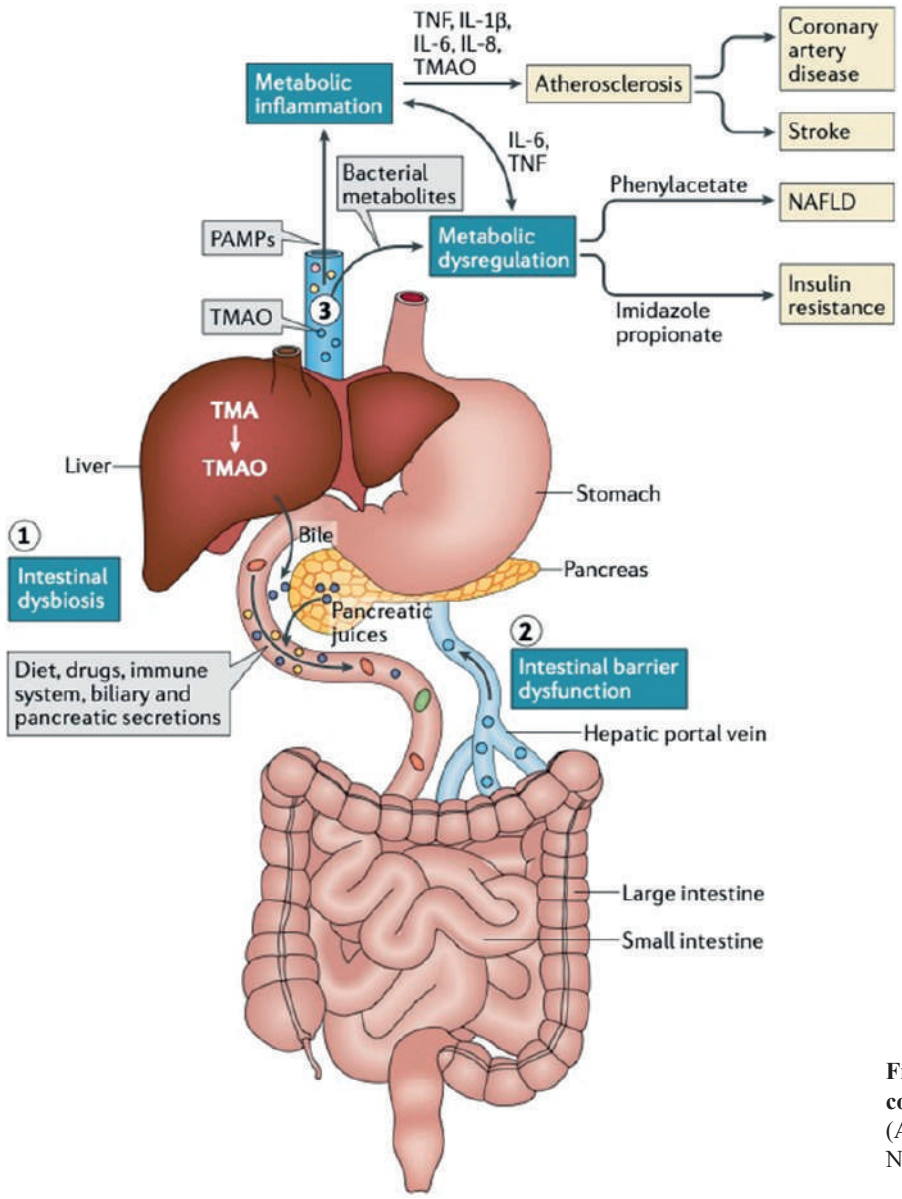

Figure 4. Multiple 'gastrointestinal hits' contribute to metabolic diseases.(146) (Adapted with permission from Springer Nature).

Adipose Tissue Dysfunction: Inflammation, Fibrosis, and Impaired Angiogenesis

AT remodelling need a coordinated response of adipocytes, immunological cells, endothelial cells, and fibroblasts. Adipocytes store diverse lipid species in lipid droplets when nutritional availability is abundant. It can increase in size and surpass the diffusional limit of oxygen. The resulting hypoxia is minimal, but it triggers a stress response that promotes angiogenesis and ECM remodeling, allowing AT to expand further and reducing hypoxia. This "healthy" AT growth can be considered of as an acute consequence. However, throughout AT's evolutionary history, the need to expand and store lipids was only temporary, with periods of fasting or hunger insuring weight loss. Unresolved AT hypoxia is on the rise as a result of the present widespread situation of chronic overnutrition. When AT reached its maximum capacity of angiogenesis, it will result in persistent hypoxia, fibrosis, cellular senescence, and necrotic adipocyte death. These will lead to unhealthy AT expansion and further promote metabolic impairment such as obesity and T2D. Thus, we can say that AT dysfunction basically rooted from the trinity of inflammation, extracellular matrix (ECM) remodeling, and angiogenic potential problems, as described in Figure 5.(46)

Today, we have more understanding about many type 2 cytokines function in host immunity and inflammatory illness. Type 2 immunity act as either a host protector or

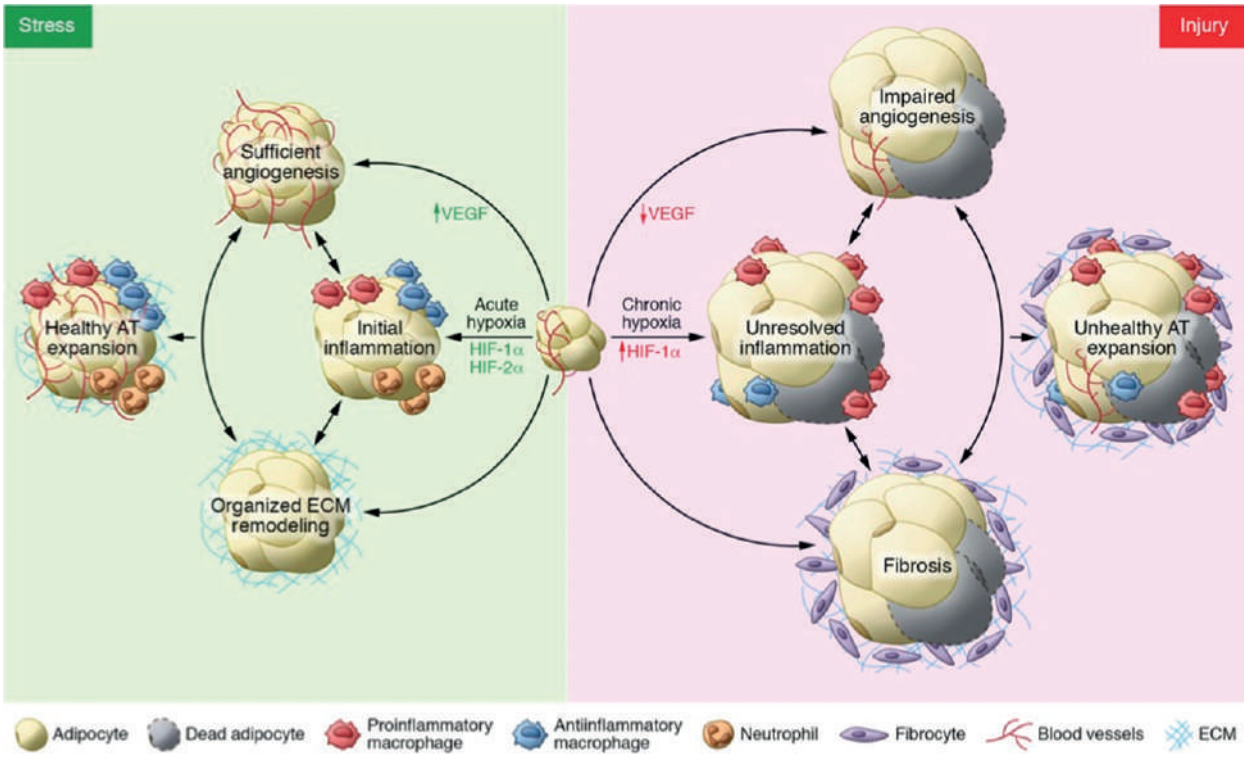

Figure 5. Angiogenesis, inflammation, and fibrosis all play a role in healthy and pathological AT growth.(46) (Adapted with permission from American Society for Clinical Investigation).

a pathogen depending on the situation.(155) It is involved in tissue regeneration after injury, to restore tissue homeostasis.(156) Somehow, it can also lead to the formation of pathological fibrosis but the clear mechanism in unknown.(77)

IL-25, which was first discovered as a T cell derived cytokine.(157) It triggers type 2 cytokines including IL-4, IL-5, and IL-13. Epithelial expression of ACT1 (which encodes TRAF3 interacting protein 2 and is also known as TRAF3IP2) enhance IL-25 signaling via a non-lymphocyte, non-NK cell, non-granulocyte lineage known as ILC2s. (158)

Around the same time, epithelial cell-derived thymic stromal lymphopoietin (TSLP) was shown to activate local DCs, causing them to produce CCL22 and CCL17, increasing TH2 cell development and spreading type 2 allergic inflammation. IL-33, a third alarmin, has been discovered as a TH2 cell-promoting cytokine (159), that signals on mast cells and TH2 cells via IL-1 receptor-like 1 (IL-1R-L1; also known as protein ST2); nevertheless, it has now been revealed that IL-33 has essential T cell-independent immunological effects.(160)

Monocytes and macrophages are important regulators of the beginning, maintenance, and resolution of wound healing, determining whether wounds heal effectively or develop to pathological fibrosis in response to the environment immediate signals. This result in significant functional alterations in the surrounding cells and extracellular matrix.(77,161) These parameters are crucial in deciding whether the injured microenvironment favors continued inflammation, regeneration, or fibrosis. Macrophages use l-arginine changes drastically during macrophage polarization. IFNγ-activated macrophages create nitric oxide and citrulline by activating inducible nitric oxide synthase, while IL-4 and IL-13-activated macrophages use arginase, the basic ingredient of to make ornithine, polyamines, and proline which were needed to construct collagen.(162) As a result, competition for l-arginine can have a direct impact on fibrosis advancement by reducing the substrates available for collagen synthesis. By managing matrix disintegration and regulating local inflammation, macrophage produced MMPs govern the course and resolution of fibrosis.(163)

Senescent and another programmed cell death such as apoptosis, necroptosis, or pyroptosis, are associated to low-grade chronic inflammation and play important roles in fibrosis initiation process.(164) The demand for oxygen is high during chronic HFD's metabolic strain, but the

capacity to produce new blood vessels is low. The result is chaotic and pathologic angiogenesis, although the processes behind it are yet unknown. Long-term HFD causes improper VEGF-A expression regulation; not only do VEGF-A levels fall in the AT of obese mice and humans (165), but there is also evidence that VEGF may impede the control of neovascularization and vessel normalization in obese mice (166). The sort of angiogenesis that develops during long-term obesity is one possible predictor of vessel density and integrity. We can assume that in obese AT, myofibroblast activation leads to the formation of new vascular networks by intussusception, or the splitting of existing arteries. While rapid angiogenesis like this may be advantageous on wound healing, but it can trigger fibrosis in AT and lead to vascular dysfunction.(167)

Monocytes and macrophages undergo significant phenotypic and functional changes after tissue damage, and they play key roles in the initiation, maintenance, and resolution phases of tissue healing. These complex mechanism of wound healing can result in a state of persistent injury and promote the development of pathological fibrosis if there is failure in cells communication such as macrophages, epithelial cells, endothelial cells, fibroblasts, and progenitor cells, or the inflammatory mediators and growth factors production is uncontrolled, anti-inflammatory macrophages generation is insufficient.(77) Inflammatory response happens in two phases: initiation and resolution. Initiation phase is marked by accumulation and coordinated activation of cytokines and pro-inflammatory lipid mediator in those immune effector cells rich milieu. Inflammation is induced quickly as the host's response to infection and damage, but it must be resolved quickly to restore tissue homeostasis, minimizing tissue harm and preventing the onset of a chronic inflammatory state.(168) Inflammation resolution now is known as an active and dynamic process involving endogenously produced mediators like cytokines and lipids.(169,170) Thus we understand that the key cause of diseases is unresolving inflammation.

The specialized pro-resolving lipid mediators (SPMs), which comprise LXs, resolvins (Rvs), protectins (PDs), and macrophage mediator in resolving inflammation, are a class of endogenously generated pro-resolving lipid mediators derived from the metabolism of PUFAs (MaRs). LXs (Lipoxygenase interaction products) were discovered in a human leukocyte (171), and identified as derivatives of arachidonic acid, a 6 fatty acid (20:4, n-6). The first resolution phase interaction products discovered was Rvs (172), Protectin D1s (PDs) or neuroprotectin D1 in neurons, glial cells, and brain stroke (173), and MaRs in 2009 (174). Rvs, PDs, and MaRs are all 3 fatty acid derivatives: Rvs can come from either the EPA (20:5, n-3) [RVs E-series] or the DHA (22:6, n-3) [RVs D-series], but PDs and MaRs can only come from DHA. All of these compounds are classed as PUFAs because of their precursors' anti-inflammatory and immunoregulatory properties.(175)

Chronic unresolved low-grade inflammation promotes the establishment of atherosclerotic lesions with large necrotic cores, thin fibrous crowns, and thrombosis. There is an imbalance between SPMs and proinflammatory lipid mediators in advanced atherosclerosis, resulting in persistent leukocyte influx into lesions, inflammatory macrophage polarization, and decreased efferocytosis. Restoration of SPMs slows plaque formation in animal models of advanced atherosclerosis by decreasing inflammation, boosting efferocytosis, and encouraging a rise in collagen cap thickness.(176) Non-resolving inflammation causes both resident and invading cells to secrete pro-fibrotic cytokines and other inflammatory mediators, causing fibroblast proliferation and epithelial cell de-differentiation. Inflammation is at the center of these processe. Therefore, targeting inflammation with appeling adjuvant for treating chronic metabolic diseases such as T2D seems to be promising.(177)

Obesity, Diabetes, and Cardiovascular Disease

Obesity is associated to a wide range of cardiac alterations, from minor myocardial abnormalities to serious heart failure. Changes in cardiac energy metabolism have been hypothesized as a primary contribution to cardiac dysfunction associated with obesity and diabetes. The distribution of excess adiposity appears to be a major predictor of cardiovascular risk, with visceral and ectopic adiposity conferring a substantially greater risk than subcutaneous adiposity.(178) One of the probable processes contributing to obesity-related heart illness is altered myocardial metabolism (179), resulting in increased fatty acid oxidation and decreased glucose oxidation (180). These will result in aberrant cardiac substrate use, reduced cardiac efficiency, and lower energy production, as well as functional repercussions connected to an increased risk of heart failure.(181) There are also a number of smaller visceral adipose depots, such as epicardial AT (EAT) and intermuscular AT (182), that may perform specific activities in relation to their neighbour tissues (183). EAT volume has recently been found to be positively and independently

linked with coronary artery calcium score (184), also being able to predict coronary reserve in normal arteries (185).

TLRs binding can activate innate immunity inside EAT, resulting in NF-κB translocation into the nucleus and production of inflammatory mediators.(186) As a result, EAT from CAD patients had increased levels of all of which indicate macrophage recruitment and activation factors. (186) A recent study employing next-generation sequencing technology found bacterial DNA in EAT near sick coronary arteries, suggesting that EAT is prone to microbial colonization and, as a result, may contribute to eliciting a proinflammatory response.(94) Compared to subcutaneous fat, EAT secretes higher levels of proinflammatory markers and soluble intercellular adhesion molecules (ICAMs) (187,188), elevated expression of IL-6, leptin, resistin, TNF-α, and visfatin, and release higher level of mRNA levels of secretory type II phospholipase A2 (sPLA2-IIA), which promotes LDL and phospholipid products in the artery wall to be more atherogenic.(185)

The amount of food consumed was linked to changes in cardiac morphology and function in obese patients.(189) Although these changes might be attributed to obesity-related hemodynamic abnormalities, low-grade inflammation, or oxidative stress (190,191), there is mounting evidence that EAT may have a direct role in their development. Activin A was shown to be one of the key possible mediators of the profibrotic action of the EAT secretome on the atrial myocardium among the EAT-secreted factors.(192) The concentration of activin A in the EAT secretome is very varied, with larger levels in atrial arrhythmia-predisposing situations such as heart failure, obesity, and T2DM.(193) In T2DM mice, EAT promote the development of insulin resistance and cardiomyocytes impairment, suggest that EAT link the T2DM to cardiomyopathy.(193) The cross talk between EAT, myocardium and coronary vessels is shown in Figure 6.(194)

Fat infiltration in cardiomyocyte strongly correlated with the development of ventricular arrhythmias, arrhythmogenic right ventricular cardiomyopathy and myotonic dystrophy (195), suggests that EAT also play a role in the pathogenesis of ventricular arrhythmias (191).

Diabetic Cardiomyopathy

Increases in aging, obesity, and diabetes mellitus are all contributing to an alarming rise in heart failure and accompanying morbidity and death. Diabetic cardiomyopathy is characterized by abnormal cardiac structure and performance while having no other cardiac risk factors such coronary artery disease, hypertension, and severe valvular disease, mostly find in hyperglycemia condition. Diabetic cardiomyopathy has a concealed preclinical phase that encompasses morphological and functional problems such as left ventricular (LV) enlargement, fibrosis, and cell signaling abnormalities in its early stages. These pathophysiological alterations in cardiac fibrosis and stiffness, as well as accompanying subclinical diastolic dysfunction, frequently progress to heart failure with a normal ejection fraction, followed by systolic dysfunction and heart failure with a lower ejection fraction. (196)

In the early stages of diabetic cardiomyopathy, it is frequently asymptomatic. The most common symptoms at these stage are LV hypertrophy with poor LV compliance, impaired early diastolic filling, increased atrial filling, and prolonged isovolumetric relaxation. Following the onset of systolic dysfunction, LV dilatation and clinical heart failure

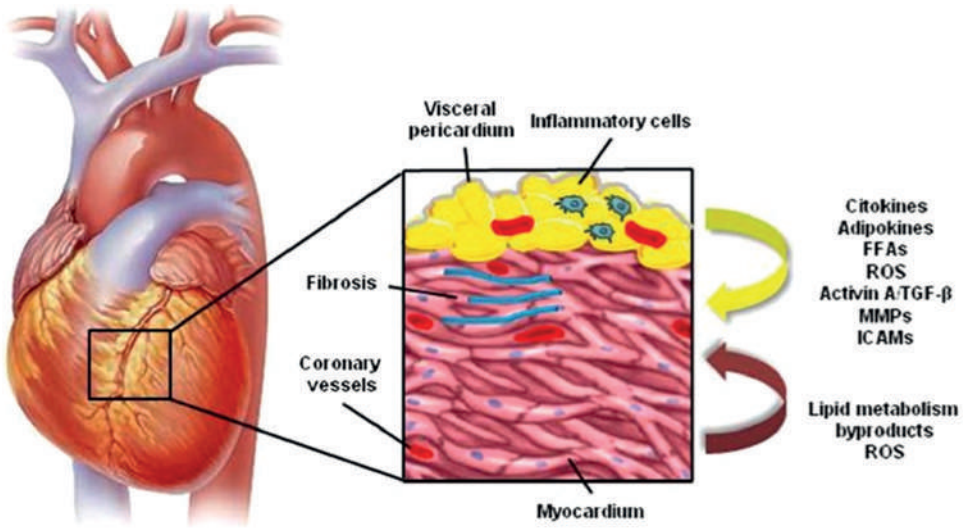

Figure 6. Potential signalling pathways mediating the cross talk between EAT, myocardium and coronary vessels.(194) (Adapted with permission from Springer-Verlag Italia).

emerge.(197) Indeed, our latest findings back up the idea that diastolic dysfunction is linked to poor cardiac insulin metabolic signaling in rodents, as seen by cine magnetic resonance imaging.(198) This cardiac anomaly is caused by cardiomyocyte stiffness and enlargement, as well as myocardial fibrosis.

Cardiovascular Health Study discovered that diabetes patients had thicker ventricular septal and left posterior myocardial wall thicknesses than nondiabetic patients in a cohort of 5201 men and women, and that this was linked to systolic and diastolic dysfunction.(199) Diabetic cardiomyopathy's pathogenesis was mainly underlined by hyperglycaemia, systemic and tissue inflammation, oxidative stress, increased free fatty acid (FFA), and activation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system.(197) Functional phenotype is showed by higher fibrosis and stiffness, lower early diastolic filling with higher atrial filling and enlargement, higher LV end-diastolic pressure.(200)

Reduced Ca^{2+} pump activity resulted in inadequate sarcoplasmic reticulum sequestration. Ca^{2+} is thought to have a key role in the development of heart diastolic dysfunction. (201) The second stage will show some clinical symptoms of heart failure such as LV hypertrophy, progressive cardiac diastolic dysfunction, cardiac remodelling, but still with normal ejection fraction.(197)

ROS plays a significant role in diabetes inflammatory condition. Indeed, a negative feed-forward loop in which increased ROS causes inflammatory cytokines and vice versa is hypothesized to fuel this highly proinflammatory milieu.(202) Both T1DM and T2DM patients have systemic inflammation, as seen in circulating cytokines, chemokines, immune cells, and other inflammatory indicators level, which is thought to be a significant factor in the advancement of peripheral illness in numerous organ systems (*e.g.*, liver, pancreas, kidney, and vasculature).(203)

Increased cytokines, chemokines, and different leukocyte populations in human diabetic myocardium suggests that myocardial inflammation has a role in the development of cardiomyopathy in diabetes individuals. (204) Induction of proinflammatory genes and proteins (TNF-α, IL-1β, IL-6, TGF-β, IFNγ, and NF-κB) in the LV of T1DM and T2DM diabetic mouse models has also been documented.(205) In this scenario, damage-associated molecular pattern molecules (*e.g.*, S100A8/S100A9), infiltration of other inflammatory cells (*e.g.*, T cells, B cells, neutrophils, dendritic cells, and mast cells), and TH1/TH17 immune responses might all play a role in cardiomyopathy. (203,206)

As a result, it's plausible that unresolved inflammation contribute to diabetes-induced heart damage by macrophage infiltration. Therefore targeting macrophage polarization toward an M2-like state, or enhancing heme-oxygenase-1 (downstream of Nrf2), were expected to control the T2DM induction to myocardium dysfunction.(205,207) As a result, there is a lot of interest in developing new pro-resolving medicines to treat a variety of inflammatory illnesses. Diabetes mellitus and its accompanying cardiomyopathy might be a good candidate for this treatment.(208)

In a nutshell, the myocardial metabolic response to diabetes is a local reaction to systemic circumstances. This is due to the normal heart's vital need to oxidize a range of substrates via mitochondrial oxidative phosphorylation to create virtually all of the ATP it requires (≈98%). Fatty acid oxidation provides for 60-90% of mitochondrial ATP synthesis under normal circumstances, with carbohydrate metabolism (glucose and lactate) to pyruvate providing the remainder. The health of cardiac myocytes is dependent on many acute adjustments in substrate selection and metabolism which modulate myocardial fatty acid β-oxidation and glycolytic pathways.(209,210) The heart is the primary organs for ketone bodies' metabolism.(211,212) Ketone metabolism also produces ATP more effectively per molecule of oxygen consumed than glucose or fatty acids, making it a potentially appealing alternative fuel. The established improvement in heart function in patients with diabetes mellitus in response to therapy with sodium-glucose transport protein 2 (SGLT-2) inhibitors, which is accompanied by a rise in plasma ketone body levels, is driving this interest.(213)

Mitochondria play an important role in the integration of redox signals and metabolic flux.(214,215) Mitochondrial dynamics are disrupted in T2D patients, and mitochondrial ROS production surpasses endogenous scavenging capability, resulting in heart oxidative stress and inflammation.(216) In diabetic human myocardium, an imbalance in fission/fusion quality control due to cardiac mitochondrial fragmentation and mitofusin-1 reduced expression, This makes the development of diabetic cardiomyopathy is more complicated.(217)

Apoptosis, autophagy, and necrosis are three types of cell death seen in the diabetic heart in both T1DM and T2D models (216), show that the diabetic myocardium also experience an increase in cardiac cell death. Increased circulating troponin concentrations (detected by very sensitive tests) in persons with T2DM and prediabetes have long been noted in epidemiological research as indication of subclinical myocardial damage.(218)

Obesity and Non-Alcoholic Fatty Liver Disease

NAFLD is becoming more common over the world, with the illness possibly affecting 25% of the adult population.(102) Other non-communicable illnesses, such as T2DM, CVD, obesity-associated and T2DM-associated malignancy, and advanced liver disorders such as hepatic cirrhosis and hepatic cancer, are growing in incidence alongside NAFLD. (219) The rise in cardiometabolic illnesses, malignancies, and NAFLD is linked to poor lifestyles, notably an unhealthy diet.(220)

NAFLD is a heterogeneous disease, thus determining how much the liver phenotype contributes to cardiometabolic risk in NAFLD is critical. NAFL and NASH are two histological classifications for NAFLD. NAFL marked by >5% of hepatic steatosis without hepatocyte ballooning, while NASH marked by >5% hepatic steatosis, inflammation, hepatocyte damage, and fibrosis. The severity in liver damage known to strongly correlate with the cardiometabolic risk, thus it is important to develop a non-invasive tools to diagnose NAFL and NASH (221,222), such as liver ultrasonography. It is the ready tool for the diagnosis of hepatic steatosis, and it is a fairly reliable approach with an overall sensitivity of 85% and specificity of 94%.(223)

The plasma level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) often cannot predict the disease's.(224) Once non-invasive procedures have been used to detect hepatic steatosis, the actual problem is determining the severity of the condition by demonstrating the existence of steatohepatitis, particularly moderate-to-severe fibrosis (fibrosis stage of at least F2). As a result, the most specific test for determining the nature and severity of liver disorders is a liver biopsy. Circulating amounts of cytokeratin-18 fragments have been postulated as one of the most accurate predictors of NASH in patients with NAFLD, among other biomarkers. However, cytokeratin-18's clinical value is restricted by a number of factors, including its low ability to differentiate NAFLD from NASH or to evaluate the degree of NASH fibrosis.(225)

Stender and colleagues found that obesity increases the genetic risk of NAFLD from steatosis to hepatic inflammation to cirrhosis, supporting the theory that genetics is primarily a moderator of disease severity.(226) Somehow, genetic testing's exact significance in diagnosing NAFLD is unknown, and it is presently not recommended by European (227) or US (228) clinical practice recommendations. Nonetheless, genetic testing seems to be useful to predict the upcoming risk.

Precision Lifestyle Medicine

Obesity causes poor cardiometabolic health and raises the risk of cardiovascular events through a variety of pathways. (229) Obesity must be effectively treated in order to lessen the related consequences of diabetes, CVD, and mortality. Despite growing evidence of positive cardiovascular outcomes from obesity therapies, only a tiny percentage of obese people receive optimal treatment.(230) Many indicators of cardiovascular risk improve in response to dietary weight loss via calorie restriction in obese people in different rates. Several studies have incorporated fat restriction in addition to total calorie restriction, and also included exercise.(231)

Our different diet, exercises, habits, comorbidities, gut microbiota, all interact with our genes. Therefore it's impossible to apply one single prescription for all individuals including in managing cardiometabolic risk. Nonetheless, dietary habits can influence cardiometabolic risk in ways that go beyond calorie intake. Many personalized diet such as Low sodium and 'Food Approaches to Stop Hypertension' were developed currently to manage participants' blood pressure and stable weight.(232) While a more simple diet like Mediterranean was now combined with nutrient measurement using diet diaries (233), or a scoring system (234), and showed better inflammation markers level as well as better endothelial function besides controlling body weight.

Recent research has found links between food content and the innate immune system. A high-sucrose/saturated fat diet non-obese mice for four weeks showed the inflammatory markers were increased, and reverting the diet can switched back the monocytes, somehow the enhanced TLR responses developed and persist. This showed that diet train the innate immunity phenotype in monocytes epigenetically and can be last for months.(235)

Personalizing nutrition advice based on empirical and subjective data appears to be becoming increasingly practical and impactful in the future. For example, there is some evidence that baseline glycemic status might assist predict weight reduction effectiveness with a low-carbohydrate/HFD diet.(236) A range of mechanisms on energy balance may relate the microbiome, particularly gut bacteria, to

cardiometabolic risk. Furthermore, the microbiome's makeup varies in response to dietary changes, sometimes quickly.(237) Correcting our microbiome composition, or the metabolites associated with it may moderate obesity and the cardiometabolic risk.(237)

Exercise reflects voluntary energy expenditure, reductions in cardiometabolic risk indicators appear to be similar whether weight loss is accomplished by increased sustained aerobic activity or dietary changes. Adding exercise in your regimen is a beneficial addition to weight reduction (and especially weight maintenance efforts (133), as well as providing a variety of cardiovascular advantages that are independent of weight loss (230).

Dietary change is an important part of weight loss. At its most basic level, weight reduction necessitates creating a negative energy balance. The ideal approach to achieve this balance is a highly debated topic that ultimately hinges on developing a long-term strategy that individuals can stick to. Calorie restriction with various macronutrient compositions, avoidance (or intake) of certain foods, and dietary patterns are all options for those looking to lose weight. Dietary treatments may target different processes for weight loss, and diet characteristics might make adherence more or less challenging. Understanding these pathways might aid in the optimization and tailoring of obesity treatment diets.

A conceptual framework includes physiological, psychological, behavioral, and sociocultural/environmental processes to impact dietary adherence and weight loss. Based on Blundell and others' Satiety Cascade Framework, modieied by (238), and relevant behavioural adherence schemata (134), the adherence (satiety) will be affected by components of the prescribed diet, as well as the mechanisms that initiate eating (initiation), finish an eating episode (satiation), and reduce hunger between meals (135,239). They proposed that food choice, satiation, and satiety (*e.g*., insulin) are a lot affected by sensory (*e.g*., recognition), cognitive (*e.g*., what they believe and how they associate it with will anticipate the reward and pleasure), post-ingestive (*e.g.*, texture, gastric stretch, and appetite-related hormones), and postabsorptive signals. There is no one-size-fits-all strategy for obesity treatment. One of the most crucial components in obesity therapy is sticking to a diet that creates an energy deficit in order to lose weight and then maintain it forever, regardless of whatever diet is used. This is not easy to keep a long-term weight management. Interindividual diversity in responding to the diet also influence this adherence. Thus behavioural and metabolic phenotypes among dieters based on features like habitual hunger and satiation should be identified to formulate a precise recommendation for obesity therapy. We may be able to find dietary treatments that aid weight loss attempts if we better understand the characteristics of people who are attempting to reduce weight.(240)

Precision prevention was coined by Khoury and Evans to emphasize the benefits of precision medicine—increased efficacy and efficiency—before illness start, as well as for secondary and tertiary prevention.(241) Traditional lifestyle intervention techniques must be transformed since lifestyle behaviors cause the biggest share of death and disability globally.(242) The problem in contemporary lifestyle interventions is that the lifestyle intervention strategy cannot easily adapt in different settings, they cannot target the right individuals who can have benefit of the regiment, and they cannot effectively engaging and retaining a diverse patient population. Communities, healthcare systems, and other environments differ in terms of resource availability, existing knowledge, and policies that encourage lifestyle interventions. Furthermore, when it comes to lifestyle treatments, one size does not fit all for individuals.

A precision medicine approach leads in a 50-year-old lady being sent to a diabetes preventive program based on her individual genetic and clinical risk factors.(241) Using this woman as an example, a precision lifestyle medicine approach would provide her with a diabetes preventive program suited to her baseline features (*e.g*., socioecologic and psychobehavioral), as well as adjustments depending on her progress toward intervention objectives over time (*e.g*., weight and physical activity trajectories). To tailor to baseline characteristics, the big data approach will need a large amount of individuals data to be analysed and result in an effective roadmap of individual lifestyle therapies in various populations and settings which can predict individual biology, life course, behavior, and environment throughout time.(243)

Precision lifestyle medicine must be scalable and sustainable in order to achieve optimum population health benefits.(244) Rapid advancements and acceptance of technology like electronic health records, mobile health apps, and wearable devices and sensors can help identify and reach patients, personalize tactics, track progress, and titrate dose. These technologies will make universal scalability and sustainability much easier.

Precision lifestyle medicine differs from traditional lifestyle intervention approaches, inspires the development of new approaches and mechanism-driven techniques. Traditional public health preventative strategies, such as population-wide policy and environmental interventions, should remain an essential aspect of a holistic strategy.

Precision lifestyle medicine, which complements these techniques, helps a wide range of people adopt and maintain healthy lives. Precision medicine has the potential to transform medicine's intrinsically individualized approach to ensuring optimal health for individual people. Similarly, precision lifestyle medicine has a lot of promise to help with current public health preventative initiatives including promoting population health, controlling healthcare costs, and eliminating health inequities. Precision lifestyle medicine, as a subspecialty of precision medicine, has the potential to upend existing healthcare paradigms in order to address the present burden of chronic disease and alter population health in the twenty-first century.(245)

Conclusion

Over the last 40 years, significant progress has been made in understanding the biology of obesity. While previously the understanding was limited to energy balance, *i.e*., intake *vs.* output, now we realize that it has much more complex interactions involving the environment and behaviour such as the food choices, availability, food process, the advertisements, the physical activities as the environment permission, socioeconomic and also psychosocial issues. It's predictable. However, traditional clinical intervention studies that focus on the individual rather than the individual's living environment have had poor long-term effectiveness. Large studies including person and environmental data are being conducted in the hopes of designing and evaluating community treatments that will target not only individuals but also aspects of their living surroundings and communities.

Obesity increased the systemic inflammation especially type 1, and affect diverse innate and adaptive immune cells. Diet, tissue niches, and gut bacteria, may all have a role in tissue inflammation initiation and maintenance. In a long time this will develop obesity-linked insulin resistance and T2DM. Thus, combating obesity and the comorbidities cannot aim on individual or population level, but need a support from a higher level regulations and policies.

Authors Contribution

AM was involved in the drafting and editing the manuscript, AW was involved in supervising and the concepting the topic of the manuscript. All authors were contributing in giving critical revision of the manuscript.

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