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Review

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Impact of Obesity-Related Inflammation on Cardiac Metabolism and Function

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ABSTRACT

This review focuses on the role of adipose tissue in obese individuals in the development of metabolic diseases, and their consequences for metabolic and functional derangements in the heart. The general idea is that the expansion of adipocytes during the development of obesity gives rise to unhealthy adipose tissue, characterized by low-grade inflammation and the release of proinflammatory adipokines and fatty acids (FAs). This condition, in turn, causes systemic inflammation and elevated FA concentrations in the circulation, which links obesity to several pathologies, including impaired insulin signaling in cardiac muscle and a subsequent shift in myocardial substrate oxidation in favor of FAs and reduced cardiac efficiency. This review also argues that efforts to prevent obesity-related cardiometabolic disease should focus on anti-obesogenic strategies to restore normal adipose tissue metabolism.

Keywords: Visceral adipose tissue; Inflammation; Lipid metabolism; Heart; Oxygen consumption

INTRODUCTION

Obesity causes adverse metabolic effects and is a major risk factor for metabolic diseases, such as type 2 diabetes and fatty liver disease, which increase the risk of coronary heart disease (CHD) and ischemic stroke. Obesity is a growing health problem in both developed and developing countries, and in the last 20 years the world has witnessed an alarming increase in obesity.[1] Obesity has nearly tripled worldwide since 1975, and according to the World Health Organization, more than 1.9 billion adults (18 years and older) were overweight in 2016.[2] Of these, over 650 million were obese (defined as a body mass index above 30 kg/m^2). It should also be noted that 38 million children under the age of 5 were overweight or obese in 2019. In China, the world's most populous country, obesity has also increased at an alarmingly rapid rate, and during the past decade the prevalence of obesity in the country has tripled, while that of abdominal obesity has increased by more than 50%.[3] These numbers are expected to rise in the future unless effective actions are taken to prevent such a development.[2] The current rise in human obesity is primarily linked to increased energy intake and decreased energy expenditure, resulting in excess fat deposition in adipose tissue.[4]

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ADIPOSE TISSUE: AN ENERGY RESERVOIR WITH THE CAPACITY TO CHANGE ITS DIMENSIONS IN RESPONSE TO NUTRITIONAL STATUS

Storage of extra energy obtained during food abundance in adipose tissue is an essential physiological activity in living organisms, especially in free-ranging animals who have to deal with marked seasonal alterations in food availability.[5] Fat storage is also important in humans in order to maintain metabolic homeostasis during the post-prandial period, and even more importantly, in humans undergoing extended periods of starvation. The adipose tissue is distributed throughout the body and has a large capacity to expand to accommodate excess energy in the form of lipids. White adipose tissue comprises two major depots, subcutaneous and visceral adipose tissue, the latter of which is found within the abdominal cavity and stored around important internal organs. Anatomically, it is further subdivided into mesenteric, omental, perirenal, and peritoneal depots.[6,7] Although adipose tissue historically has been regarded as an energy storage depot, research over the last few decades has revealed that adipose tissue also acts as an endocrine organ. Thus, several cytokines, hormones, and peptides secreted by adipocytes, collectively termed as "adipokines" (e.g. leptin, resistin, adiponectin, tumor necrosis factor alpha [TNF-α], and interleukin [IL]-6) have been identified and intensively investigated to elucidate their roles in the control of energy homeostasis.[8,9]

Subcutaneous adipose tissue is the largest fat depot in the body. The expansion of subcutaneous adipose tissue occurs through the recruitment and differentiation of adipose precursor cells, resulting in healthy adipose tissue.[10] However, when the storage capacity of the subcutaneous depot is exceeded, excess energy intake leads to fat accumulation in undesirable locations, such as the intra-abdominal depots, as well as in ectopic tissues such as the liver, skeletal muscle, and heart. Over time, this situation creates a condition commonly referred to as "lipotoxicity," as described in more detail below.

LOW-GRADE INFLAMMATION IN OBESE ADIPOSE TISSUE

Adipose tissue is considered to be a pathogenic site of obesity-induced insulin resistance.[11] This is due to the fact that adipose tissue in obese individuals, particularly those with abdominal obesity, is associated with a chronic, local low-grade inflammatory response involving the production of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) and chemokines.[4,12-14] Numerous studies have shown that cellular stress is a major factor contributing to inflammation in adipose tissue.[4,15] Thus, in response to nutrient excess, adipocytes expand and become hypertrophic. At the same time, the distance between blood-bearing vessels increases and oxygen diffusion becomes insufficient,[16] leading to local hypoxia, which triggers the increased secretion of inflammatory markers.[17] Characteristically, the adipose tissue of obese individuals shows lower blood flow, higher vasoconstriction, and lower capillary density than adipose tissue in non-obese individuals.[15]

Macrophage infiltration is another characteristic of adipose tissue in obese individuals. After initial rolling and attachment of monocytes to activated endothelial cells, monocytes then extravasate through the endothelial cell layer and differentiate into macrophages. It has been reported that monocyte chemoattractant protein-1 (MCP-1) secretion is markedly enhanced locally and in the plasma of obese rodents and humans.[18,19] At the onset of an inflammatory

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process, the macrophages that are usually present in the adipose tissue switch from an anti-inflammatory (M2) state to a pro-inflammatory (M1) state.[20] More than 90% of M1-type macrophages are localized to dead adipocytes and form so-called "crown-like structures," which are a characteristic component of the immuno-histological picture of adipose tissue in both obese mice and humans.[16] Cross-talk between adipocytes, macrophages, and endothelial cells may enhance the inflammatory state by increasing the secretion of pro-inflammatory cytokines and chemokines, which in turn can develop into local and/or systemic insulin resistance in a paracrine and/or endocrine fashion.

Sun et al.[17] documented increased interstitial fibrosis in white adipose tissue during the development of obesity, which may reduce extracellular matrix flexibility and decrease the tissue plasticity, ultimately leading to adipocyte dysfunction. Abnormal collagen deposition, which characterizes fibrosis development in adipose tissue, is paralleled by the infiltration of macrophages and other immune cells.[21] Under these conditions, fibrotic response genes are markedly up-regulated, and classically activated pro-inflammatory M1 macrophages are attracted by dead adipocytes,[17] reinforcing the inflammatory process and altering adipose tissue metabolism. Thus, the development of hypertrophic adipose tissue (in response to excess energy intake), macrophage infiltration, and fibrosis are major factors initiating the local low-grade inflammatory response in adipose tissue. On the molecular level, this process includes activation of the c-Jun N-terminal kinase (JNK) and IκB kinase (IKK) β/nuclear factor kappa light chain enhancer of activated B cells inflammatory signaling pathways,[22] which in turn regulate protein phosphorylation and cellular transcriptional events leading to the secretion of proinflammatory cytokines (TNF-α, IL-6, and IL-1β) and chemokines, such as MCP-1.[23]

INFLAMMATION AND LIPID OVERLOAD CAUSE DYSREGULATION OF MYOCARDIAL METABOLISM AND VENTRICULAR FUNCTION

Low-grade inflammation in abdominal adipose tissue also contributes to hepatic inflammation due to portal delivery of abdominal fat—derived cytokines and lipids.[11,16] Thus, TNF-α and IL-6 originating from adipocytes, as well as from macrophages, in adipose tissue and the liver[22] create systemic inflammation and subsequent dysregulation of insulin action in peripheral tissues, such as skeletal and cardiac muscle[24] (**Fig. 1**).

Although the role of inflammation in the etiology of myocardial insulin resistance is limited, Ko et al.[25] reported that high-fat feeding of rats caused increased macrophage infiltration in myocardial tissue from these animals, as well as increased cytokine and suppressor of cytokine signaling proteins levels in cardiomyocytes. These observations were associated with reduced myocardial insulin sensitivity and glucose metabolism. It was proposed that cytokines from macrophages and cardiomyocytes activate their receptors and associated signaling pathways to increase serine phosphorylation of insulin receptor substrate 1 (IRS-1). This eventually leads to insulin resistance via inhibition of protein kinase B/Akt and reduced glucose transporter type 4 (GLUT4) translocation.[26]

Increased uptake of fatty acids (FAs) also plays a central role in the development of cardiac insulin resistance in obesity. Increased FA uptake is catalyzed, in part, by the translocation of FA transporters (FAT/CD36) to the sarcolemma.[27-29] However, not all FAs entering the cell are

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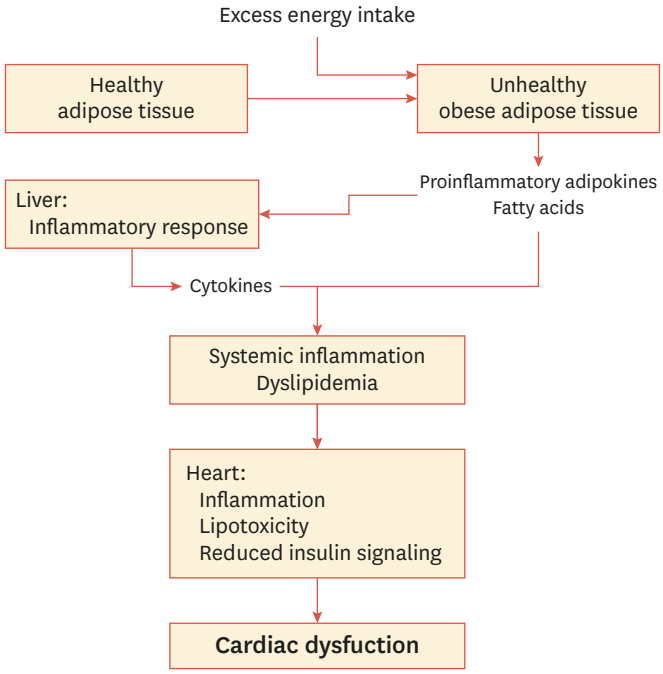

Fig. 1. Increasing visceral obesity causes inflammatory responses and metabolic dysregulation in fat and liver tissue. This condition involves infiltration of monocytes and macrophages and subsequent secretion of pro-inflammatory adipokines and elevated release of free fatty acids, leading to systemic inflammation, which promotes insulin resistance in several organs, including the heart. In addition, an elevated supply of lipids (free and esterified fatty acids) exceeds the fatty acid oxidation capacity and causes lipotoxicity in the myocardium, eventually leading to cardiac dysfunction.

utilized for oxidative purposes, and long-chain FAs in the form of acyl-CoA provide substrates for nonoxidative processes such as triglyceride, diacylglycerol, and ceramide synthesis.[30,31] The accumulation of these substances is known to activate kinases, including JNK, IKK, and protein kinase C, which down-regulate insulin signaling[32,33] via serine phosphorylation of IRS-1.[27,34] Besides its adverse effects on insulin signaling and glucose metabolism, excessive lipid accumulation may also have direct lipotoxic effects on cardiomyocytes.[30,35]

The mismatch between FA uptake and oxidation by cardiomyocytes[27,28] and the consequent myocardial lipid accumulation and insulin resistance may have serious cardiac consequences that ultimately lead to compromised cardiac mechanical function.[35,36] Thus, reduced left ventricular (LV) systolic function has also been demonstrated in several animal models of obesity,[37-39] except for some studies in diet-induced obese rats that showed unchanged or mildly reduced systolic function.[40,41] FA binding protein 4, an intracellular lipid-binding protein involved in the transportation of FAs, has been suggested to be strongly associated with inflammation, obesity, diabetes, and cardiovascular diseases (CVD).[42] Cardiac-specific overexpression of this protein in mice resulted in greater cardiac hypertrophy following transverse aorta constriction than in wild-type controls.[43] Furthermore, transgenic mice expressing mutated lipoprotein lipase (GPI-anchored human LPL) in cardiomyocytes developed dilated cardiomyopathy with lipid accumulation within myocytes.[44] Mice with cardiomyocyte-restricted knockout of the insulin receptor also exhibited reduced heart size and mildly impaired contractile function, indicating that insulin signaling is an important physiological regulator of growth and function.[45,46]

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Many studies have demonstrated that obesity (isolated or co-existing with hypertension) in humans is associated with abnormal diastolic function,[47-49] whereas impairment of systolic function is not consistently observed.[50] Obesity-related dysfunction includes left heart remodeling (i.e., left atrial dilatation and LV hypertrophy) as well as abnormalities in LV contractile and relaxation functions (i.e., LV stiffness and impaired relaxation).[47,51-53] This condition can ultimately progress to cardiac hypertrophy and/or systolic dysfunction when lipotoxicity and/or local perfusion heterogeneities result in cell death and fibrosis.[36,54-56]

OBESITY-INDUCED ALTERATIONS IN MYOCARDIAL SUBSTRATE UTILIZATION: LOSS OF METABOLIC FLEXIBILITY

Approximately 50%–70% of the energy (ATP) requirement of the healthy heart is produced by oxidation of long-chain FAs, which are bound to albumin or esterified in circulating triglycerides, whereas carbohydrates, lactate, and to some extent also ketone bodies and amino acids account for the rest of overall ATP production.[57,58] Although the normal heart seems to prefer FAs for the production of energy, it has the ability to change to other substrates for the generation of ATP to ensure that its energy demands are met. The contribution of individual substrates to ATP production depends on substrate availability, hormonal status, and energy demand, and the capacity of the heart to switch between the different energy substrates is referred to as "metabolic flexibility." In the 1960s, Sir Philip Randle performed landmark studies showing how metabolic products of increased FA oxidation can inhibit glucose uptake in muscle.[59] This mechanism, subsequently known as the Randle cycle, is the basis of metabolic flexibility in healthy individuals, which allows energy-requiring organs such as heart and skeletal muscle to switch between fuels, depending on nutrient composition and intake, as well as variations in insulin signaling. As mentioned above, the substrate transporters GLUT4 (for glucose) and CD36 (for FAs), play a central role in this dynamic balance of substrate utilization.[60] CD36 plays a central role in facilitating cellular long-chain FA uptake across the plasma membrane, acting in concert with other membrane proteins, such as FA-binding protein.[61] With the development of insulin resistance, however, the metabolic flexibility of the heart (as well as skeletal muscle) deteriorates,[55] so that myocardial energy production becomes primarily dependent on FA oxidation. As a consequence, accumulation of the intermediates of FA metabolism in cardiomyocytes results in a state of lipotoxicity (as discussed above),[30,56] causing cellular oxidative stress, impaired cytosolic and mitochondrial calcium homeostasis, and mitochondrial dysfunction.

ACUTE AND SUSTAINED ELEVATIONS OF THE FA SUPPLY LEAD TO INCREASED MYOCARDIAL OXYGEN CONSUMPTION (MVO_2) AND IMPAIRED ENERGETICS

A study conducted in the beginning of the 1970s[62] using a canine model reported that MVO_2 increased markedly in response to acute elevations in the plasma concentration of FA. In addition, higher FA oxidation and MVO_2 were reported in obese relative to non-obese young women.[63] It has been suggested that uncoupling of oxidative phosphorylation and induction of energy-wasting triglyceride-FA[64,65] and Ca^{2+} cycling[66] could contribute to this elevation in MVO_2. Moreover, it was proposed that an excess substrate supply might result in impaired transcriptional regulation of proteins involved in the pathways of cardiac energy

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metabolism.[67] Thus, it was reported that patients undergoing coronary artery bypass graft surgery exhibited elevated plasma FA concentrations, which were associated with higher expression of cardiac mitochondrial uncoupling proteins.[67] Moreover, an impaired cardiac energy reserve in patients with type 2 diabetes mellitus (as reflected by a lower myocardial phosphocreatine [PCr]/ATP ratio) was correlated with fasting plasma FA concentration,[68] a finding that is also in line with increased mitochondrial uncoupling. Cardiac PCr/ATP ratios have also been documented during catecholamine stress[69] or exercise[70] in people with obesity and insulin resistance, although this response is not always observed.[55] Whether a lower myocardial PCr/ATP ratio in diabetic cardiomyopathy is a cause or effect of the progression to heart failure is currently unknown.[71]

Cardiac efficiency is characterized by the relationship between the mechanical performance and energy consumption of the heart in the form of ATP utilization or oxygen consumption. The development of the pressure-volume conductance catheter enabled calculation of the total work performed by the heart during the cardiac cycle as the pressure-volume area (PVA), and the relationship between MVO_2 and PVA can be used to calculate the oxygen used for mechanical activity versus the oxygen consumed for basal metabolism and excitation-contraction coupling. Oxygen consumption for the latter 2 processes is achieved by extrapolating the MVO_2-PVA relationship to zero work and is referred to as unloaded MVO_2.[72] Around the turn of the 21st century, Korvald et al.[73] showed, for the first time, that the MVO_2-PVA relationship was significantly influenced by changes in myocardial substrate metabolism in pigs. Thus, a change in myocardial metabolism from glucose towards higher FA oxidation shifted the *in vivo* MVO_2-PVA relationship upward in a parallel manner, reflecting that hearts exposed to high levels of FAs used more energy, independent of the workload. This elevation in MVO_2 was ascribed to a higher unloaded MVO_2 (i.e., the use of more oxygen for basal metabolism and excitation-contraction coupling), and the increased ratio between MVO_2 and work was translated into decreased cardiac efficiency. Similar observations were reported by How et al.[74] using isolated perfused working mouse hearts exposed to different workloads. In the same manner as in pigs, elevation of the FA concentration in the perfusion buffer shifted the MVO_2-PVA relationship upward, producing a near 30% increase in unloaded MVO_2. It should be noted that the FA-induced elevation in MVO_2 can by no means be explained by the switch in metabolism from glucose to FAs, since the difference in the phosphorylation-to-oxidation (P/O) ratios between FA and glucose oxidation (2.33 vs. 2.58, respectively) could account for a maximum increase in oxygen consumption of 11%. Other mechanisms, such as uncoupling of oxidative phosphorylation in the mitochondria and induction of futile cycles, as discussed above, could explain the high MVO_2 during predominant FA utilization. In line with this notion, Cole et al.[75] reported a lower mitochondrial maximal respiratory capacity and efficiency (P/O ratio) in high-fat–fed rats and suggested that decreased respiratory coupling can contribute to the impaired cardiac efficiency observed following obesity.

CHANGES IN CARDIAC METABOLISM AND FUNCTION IN OBESE AND DIABETIC ANIMALS RESULT IN REDUCED CARDIAC EFFICIENCY

Over the years, our laboratory has studied energy metabolism and cardiac performance of *ex vivo* perfused hearts from type 2 diabetic (*db*/*db*) as well as diet-induced obese mice. In accordance with other researchers,[76,77] we have demonstrated repeatedly that hearts from

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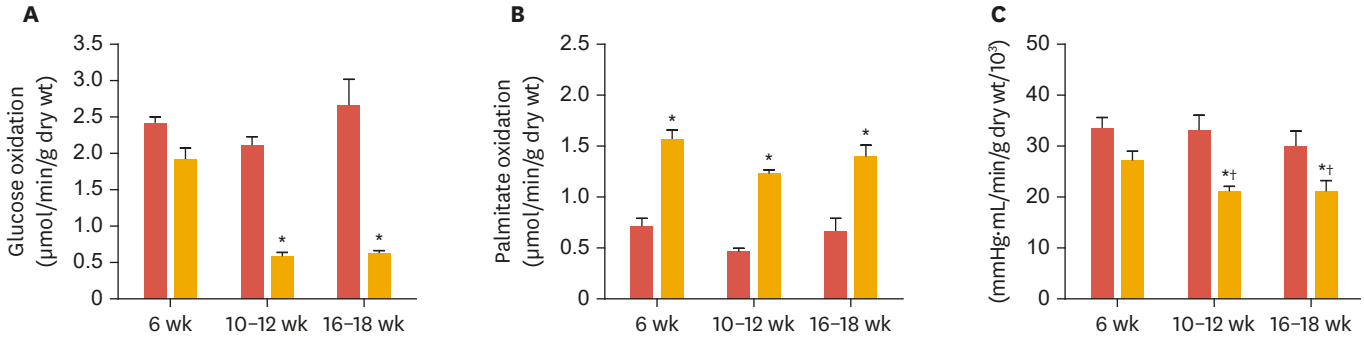

Fig. 2. Age-dependent changes in myocardial substrate oxidation and ventricular function in control (*db*/+, red columns) and type 2 diabetic (*db/db*, yellow columns) mice. (A) Reduction of glucose oxidation in *db/db* hearts after 10–12 weeks, while fatty acid oxidation had already significantly increased at 6 weeks (B), preceding the decline of left ventricular function (C), measured as PSP times CO. Modified from Aasum et al.[51]
PSP, peak systolic pressure; CO, cardiac output.
*p<0.05 vs. *db*/+; †p<0.05 vs. 6 week.

these mice exhibit altered substrate metabolism, characterized by an over-reliance on FAs for cardiac energy production and low contribution of glucose.[51,52,78] Aasum et al.[51] made the important observation that changes in cardiac metabolism in *db/db* mice preceded the development of cardiac dysfunction (**Fig. 2**) (including increased susceptibility to ischemia-reperfusion), indicating a causal relationship between altered cardiac metabolism and the development of ventricular dysfunction in diabetes.

Later studies demonstrated ventricular dysfunction, not only in *db/db* hearts, but also in hearts from diet-induced obese mice.[51,52,78-80] As mentioned above, these hearts show metabolic shifts towards predominant FA utilization, and the MVO_2-PVA relationships obtained from these hearts were also lifted upward relative to those of normal mouse hearts[53,79] (**Fig. 3A**). These results therefore demonstrate that not only acute elevation in myocardial FA oxidation (as discussed above), but also chronic elevation of FA oxidation, results in decreased cardiac efficiency (i.e. the ratio between MVO_2 and cardiac work). Furthermore, by unloading and chemically arresting hearts, it was shown that the increased oxygen consumption of hearts in diet-induced obese mice was due to increases in both excitation-contraction coupling and basal metabolism (**Fig. 3B**).[53]

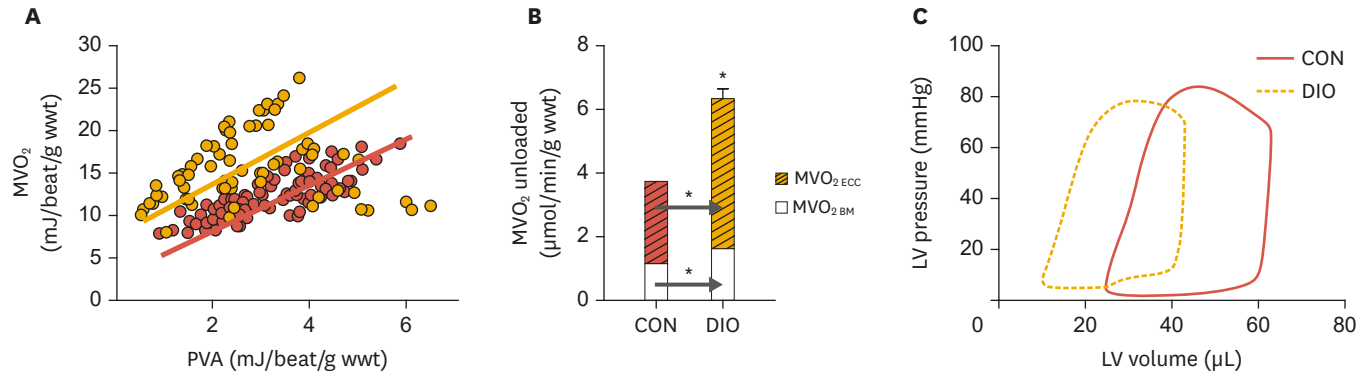

Fig. 3. Increased myocardial oxygen consumption and ventricular dysfunction in DIO mice. (A) Relationship between MVO_2 and total cardiac work (measured as PVA) in isolated perfused hearts from lean CON (red line) and DIO mice (yellow line). (B) The increased oxygen consumption of the DIO hearts is explained by increased oxygen cost for excitation-contraction coupling as well as for basal metabolism. (C) Leftward shift of the pressure-volume loop of DIO heart relative to control, indicating concentric remodeling and ventricular stiffness. Modified from Hafstad et al.[53]
MVO_2, myocardial oxygen consumption; PVA, pressure-volume area; CON, control; DIO, diet-induced obese; LV, left ventricular.
*p<0.05 vs. CON.

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Further examination of ventricular function in hearts from both diabetic and obese mice by pressure-volume analysis clearly revealed diastolic dysfunction, both in hearts from *db*/*db* mice[74] and in hearts from diet-induced obese mice[53] This change in LV function was reflected in a marked leftward shift in the pressure-volume loop (**Fig. 3C**), indicative of the development of concentric remodeling.[79,81,82] In accordance with previous studies on diabetes-induced cardiac remodeling, the hearts exhibited increased fibrosis, impaired metalloproteinase expression, and elevated oxidative stress.[83,84] Park et al.[85] also reported that chronic high-fat feeding and obesity in mice impaired myocardial glucose metabolism, which was associated with ventricular hypertrophy and cardiac dysfunction. The same group reported that diet-induced obesity in mice led to increased macrophage and cytokine levels in the heart, which was associated with significant reductions in AMPK phosphorylation and down-regulation of glucose metabolism.[25]

In summary, the healthy heart is characterized by a high degree of metabolic flexibility, allowing optimal matching of metabolic supply and demand. During conditions of insulin resistance and diabetes, the cardiac muscle is not able to switch effectively from FAs to glucose metabolism in the post-prandial state. As a consequence, the heart becomes metabolically less flexible and ineffective in adapting its fuel preferences to altered energy supply and demand. When relying primarily on FA oxidation for energy production, the heart uses more oxygen for a given workload, compared with a heart oxidizing a mixture of FAs and glucose. The FA-induced elevation in MVO_2 is due to increased oxygen use for non-contractile processes (i.e., basal metabolism and excitation-contraction coupling). The development of both ventricular dysfunction and mechanoenergetic impairments in diabetes/obesity is clearly multifactorial and complex and, in addition to alterations in myocardial substrate utilization, the involvement of Ca^{2+} handling, oxidative stress, mitochondrial dysfunction, and structural remodeling has been proposed.[49,50,65,86-88] Diabetes is also associated with impaired myocardial Ca^{2+} handling, including increased ryanodine receptor 2 Ca^{2+} leak,[88,89] which most likely contributes to the increased oxygen consumption demonstrated herein and in previous studies.[75,79,80,90,91]

TREATMENT STRATEGIES

The obvious solution to prevent adipose tissue inflammation and the accompanying metabolic and cardiovascular complications is to apply strategies for the targeted reduction of this particular fat store in obese individuals. Lifestyle interventions, including changes in diet and physical activity, remain the cornerstone of treatment for obesity and insulin resistance. Both reduced calorie intake and increased calorie expenditure via daily exercise should result in weight loss, but these interventions have not been effective in achieving lasting weight loss. A major part of lost weight is regained within 1 year following the end of treatment, and almost all weight is regained within 5 years.[92,93] The pharmaceutical industry has therefore developed a number of anti-obesogenic medications, including some developed for maintenance of insulin sensitivity. However, several of these agents have been withdrawn from the market due to safety concerns.[93] A new class of anti-diabetic drugs, sodium-glucose cotransporter-2 inhibitors,[94] could hold promise for combatting the obesity epidemic in the future. Although their main effects are to inhibit glucose reabsorption in the renal proximal tubular cells and to reduce blood glucose levels through increased glycosuria, some of these drugs (dapagliflozin and canagliflozin) have been shown to reduce body weight through reductions in fat mass, including both visceral fat and subcutaneous fat.[36,95] Liraglutide

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(Saxenda) is a glucagon-like peptide-1 receptor agonist that was developed for the treatment of type 2 diabetes. It turned out, however, that liraglutide is also an effective treatment for obesity,[96] in part through its actions in the limbic system of the brain,[97] regulating appetite and calorie intake. Pharmacotherapies to prevent obesity will not be further discussed in this review, however, and readers should refer to sources such as the comprehensive review by Van Gaal and Dirinck.[93]

In the final section, we will briefly focus on the use of marine omega-3 FAs in the control of energy homeostasis and their potential role in weight management due to their anti-inflammatory and insulin-sensitizing effects. Long-chain omega-3 polyunsaturated FAs (PUFAs) from fish oil are considered to have beneficial health effects.[98] Thus, treatment of severely obese non-diabetic patients with eicosapentaenoic acid and docosahexaenoic acid was shown to reduce adipose tissue mass and systemic inflammation.[99] A recent meta-analysis of 13 randomized controlled trials, which included over 120,000 participants, confirmed that PUFA supplementation reduces the risk for CHD and CVD, myocardial infarction, and death due to CHD and CVD.[100,101] A systematic review and meta-analysis by Natto et al.[102] also concluded that PUFA consumption may be associated with lower plasma levels of inflammatory biomarkers in patients with diabetes. However, results regarding the effects of PUFAs on glucose metabolism, insulin resistance, and type 2 diabetes are less clear,[103] most likely due to differences in the choice of PUFA preparation, dosage, and intervention.[104] Although the benefits of PUFA intake remain controversial for some diseases and conditions, the anti-inflammatory effects of these compounds are well accepted.[105]

We have previously reported that dietary supplementation with a small amount of oil from the marine crustacean, *Calanus finmarchicus*, reduced both intra-abdominal and hepatic fat deposition, while simultaneously exerting a strong anti-inflammatory action in adipose tissue during high-fat feeding in male C57bl/6J mice.[13] Recently, we also reported[106] that dietary supplementation with *Calanus* oil was able to prevent the obesity-induced decline in myocardial glucose utilization in hearts from high-fat–fed mice. More importantly, post-ischemic recovery of these hearts was significantly better than that of hearts from mice on a non-supplemented high-fat diet, indicating the cardioprotective properties of the *Calanus* oil in obesity. Of note, this effect was achieved with a much lower dose (2%, w/w) than was used in similar experiments in the past.[107] It should be emphasized that the above study included female mice, and in contrast to results obtained with male mice that obesity impaired the recovery of cardiac function after an ischemic insult,[53,78,80] we observed that the post-ischemic recovery of ventricular function in hearts from high-fat—fed female mice was not impaired relative to hearts from mice receiving normal chow. This result confirms previous observations by Edland et al.,[108] who reported that cardioprotection was afforded by long-term feeding of an obesogenic high-fat diet in hearts from female mice. In addition to other possible sex differences, mRNA expression of TNF-α and IL-6 in adipose tissue was hardly detectable in response to high-fat feeding in the female mice, in contrast to previous results with male mice.[12,13] The low inflammatory status could probably be explained by the finding that high-fat feeding induced only a relatively mild degree of adiposity in the female mice, so that the signal for adipokine secretion[17] was missing. In addition, it has been reported that the genes involved in inflammation are more highly up-regulated in males than in females.[109] Still, dietary *Calanus* oil resulted in less deposition of intra-abdominal fat than in untreated high-fat–diet mice. The underlying mechanism is not clear, but increased adipose tissue lipolysis and/or decreased lipogenesis, as well as increased hepatic drainage of FAs from the abdominal fat stores, are possibilities that could be further investigated. Although clinical

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studies are sparse, recent studies in elderly untrained overweight participants[110] suggested that a combination of moderate exercise and intake of oil from *C. finmarchicus* may promote fat loss. It was also shown that wax ester—bound PUFAs from *Calanus* oil were significantly incorporated into the membranes of red blood cells, thereby increasing the omega-3-index.[111]

CONCLUSION

Adipose tissue appears to act as a priming tissue that initiates inflammation in obesity in response to excess energy intake. Thus, obesity-induced dysfunction of visceral and ectopic adipose tissue, including the release of proinflammatory cytokines and FA, is a major contributor to potential pathogenic mechanisms leading to insulin resistance and type 2 diabetes. Preclinical studies have demonstrated that these conditions are associated with a marked shift in myocardial metabolism towards predominant FA utilization for energy production. Over time, this switch in myocardial metabolism leads to a lipotoxic milieu and subsequent metabolic and functional derangements in the heart. Prevention of obesity-related cardiometabolic disease should therefore focus on anti-obesogenic strategies to restore normal adipose tissue metabolism, and understanding the inflammatory responses in adipose tissues of obese individuals is therefore of clear clinical importance.

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