Canadian Science Publishing | Canadian Journal of Physiology and Pharmacology

Intricacies of the endothelin system in human obesity: role in the development of complications and potential as therapeutic target

Journal:	*Canadian Journal of Physiology and Pharmacology*
Manuscript ID	cjpp-2019-0651.R1
Manuscript Type:	Review
Date Submitted by the Author:	18-Jan-2020
Complete List of Authors:	Schinzari, Francesca; Policlinico A Gemelli, Internal Medicine Cardillo, Carmine; Università Cattolica del Sacro Cuore, Translational Medicine and Surgery
Is the invited manuscript for consideration in a Special Issue:	ET-16 Kobe 2019
Keyword:	endothelin, adipose tissue, obesity, adipokines

SCHOLARONE™
Manuscripts

Manuscript CJPP-2019-0651-R1

Intricacies of the endothelin system in human obesity: role in the development of complications and potential as therapeutic target

Francesca Schinzari, MD[1], Carmine Cardillo, MD[1,2]

[1]Policlinico A. Gemelli IRCCS and [2]Università Cattolica del Sacro Cuore, Roma, Italy

Draft

Correspondence to:
Prof. Carmine Cardillo
Department of Translational Medicine and Surgery
Università Cattolica del Sacro Cuore
Largo F. Vito 1
00168 Roma
Tel. 06 30159432
Fax. 06 30157232
E-mail: carmine.cardillo@unicatt.it

Abstract

Activation of the vascular endothelin (ET)-1 system is a key abnormality in vascular dysfunction of human obesity, especially in patients developing complications, such as the metabolic syndrome, diabetes and atherosclerosis. Vascular insulin resistance, an increased insulin-stimulated endothelial production of ET-1 combined with impaired nitric oxide availability, is the hallmark of obesity-related vasculopathy, but dysregulated adipokine release from obese adipose tissue may contribute to predominance of ET-1-dependent vasoconstriction. ET-1, in turn, might determine unhealthy obese adipose tissue expansion, with visceral and perivascular adipose tissue changes driving the release of inflammatory cytokines and atherogenic chemokines. In addition, ET-1 might also play a role in the development of the metabolic complications of obesity. Studies have shown inhibition of lipoprotein lipase activity by ET-1, with consequent hypertriglyceridemia. Also, ET-1 in pancreatic islets seems to contribute to beta-cells dysfunction, hence affecting insulin production and development of diabetes. Moreover, ET-1 may play a role in nonalcoholic steatohepatitis. Recent clinical trials using innovative design have demonstrated that antagonism of ET type A receptors protects against some complications of obesity and diabetes, such as nephropathy. These findings encourage further investigation to evaluate whether targeting the ET-1 system could afford better protection against other consequences of the obesity epidemic.

Draft

Key words: endothelin; adipose tissue; adipokines; obesity; prediabetes; NASH; dyslipidemia.

Introduction

The incidence of obesity and type 2 diabetes is still increasing worldwide at an alarming rate, in relation predominantly to lack of regular physical activity and consumption of high fat/sugar diets, and carries a heavy burden in terms of morbidity, mortality and health care-related costs. One direct consequence of obesity is the rising incidence of type 2 diabetes, which occurs when insulin resistance is present and insulin secretion fails to compensate. Another unwanted complication of excess body weight is the development and progression of cardiovascular disease, with multiple, complex mechanisms underlying this relationship. Of note, the rate of obesity-related cardiovascular consequences is higher in those individuals with excessive fat accumulation in the visceral adipose tissue (VAT) that predispose them to the metabolic syndrome, an association of hypertension, disglycemia and lipid abnormalities that occurs as a consequence of insulin resistance (Ahima and Lazar 2013). In contrast with this “metabolically unhealthy” phenotype, obese patients with predominant fat storage in the subcutaneous adipose tissue (SAT) seem to possess a metabolically inert profile, the so called “metabolically healthy obesity”. In these individuals, it is likely that subcutaneous adipose tissue acts as a safe depot for potentially toxic lipids produced in excess, thereby leading to improved metabolic and cardiovascular health due to preserved insulin sensitivity, absence of diabetes and reduction of other risk factors for cardiovascular disease (Lee et al. 2013b; Wildman et al. 2008).

Vascular dysfunction in human obesity: role of the endothelin (ET)-1 system

An important aspect of vascular dysfunction in obesity relates to the physiological actions of insulin in blood vessels and to the consequence of insulin resistance on vascular homeostasis. Physiologically, insulin receptors are present on endothelial cells, where they activate both the phosphatidylinositol (PI) 3-kinase/Akt pathway and the MAP kinase cascade, leading to nitric oxide (NO) and ET-1 synthesis, respectively (Muniyappa et al. 2008; Zeng et al. 2000). Evidence of the concurrent insulin-induced stimulation of both the NO pathway and the ET-1 system in humans

was first collected by us in the forearm circulation of healthy volunteers, where simultaneous blockade of ET_A and ET_B receptors by combined infusion of BQ-123 and BQ-788 was associated with a significant vasodilator response during hyperinsulinemia, but not during saline infusion (Cardillo et al. 1999). Furthermore, during ET-1 receptor blockade, the vasoconstrictor response to NO synthesis inhibition with L-NMMA was significantly higher after insulin infusion than in the absence of hyperinsulinemia, indicating a concurrent increment in NO bioavailability. Under physiological conditions, insulin-induced release of NO may lead to expansion of the available capillary surface area in peripheral tissues, particularly in the skeletal muscle, thus augmenting the delivery of insulin itself, glucose, and other nutrients to the metabolically active tissues (Clark et al. 2003). This functional coupling between the microvascular effects of insulin, muscle perfusion and glucose utilization, however, is impaired in insulin resistant states like obesity and type 2 diabetes (Clark 2008), where a pathway-specific insulin resistance seems to take place at the vascular level. In fact, a pivotal biochemical defect in these patients is an impairment of the PI 3-kinase-dependent signaling cascade, while the MAP kinase pathway is spared (Cusi et al. 2000). Given the compensatory hyperinsulinemia occurring to maintain euglycemia in insulin resistant states, the potential pathophysiological implications of this abnormality become relevant. Thus, hyperinsulinemia overstimulates the normally functioning MAP kinase-dependent pathways, an effect that cannot be balanced by the abnormal PI 3-kinase cascade, hence leading to increased endothelial production of ET-1 and consequent vasoconstriction (Kim et al. 2006). This higher ET-1-dependent tone might decrease muscle perfusion and blunt glucose disposal, thereby contributing to impaired glucose tolerance. Demonstration of enhanced ET-1 activity in human obesity was obtained in our laboratory, when we observed that the vasodilator effect of the selective ET_A receptor blocker BQ-123 is augmented in obese hypertensive individuals as compared to their lean counterpart (Cardillo et al. 2004). Similarly, we later reported that

Draft

enhanced ET_A-dependent vasoconstrictor tone is present in the forearm vasculature of obese patients with the metabolic syndrome, but not in lean subjects (Tesauro et al. 2009). In keeping with our results, Weil et al. have observed heightened vasodilator response to BQ-123 in overweight and obese individuals (Weil et al. 2011); interestingly, blockade of ET_A receptor was able to improve endothelium-dependent relaxation in these patients. The latter finding is in line with a previous observation of Mather et al. (Mather et al. 2004), who noted that antagonism of ET_A by BQ-123 corrects the defect in endothelium-dependent vasodilation in individuals with obesity or type 2 diabetes. Similarly, Lteif at al. reported that BQ-123 improves the defective endothelium-dependent vasodilator response to exogenous insulin in the leg circulation of obese subjects, further underscoring the key role of ET-1 in the pathophysiology of obesity-related vascular dysfunction (Lteif et al. 2007).

Obesity-driven adipose tissue remodeling: potential role of ET-1

In obesity, adipose tissue expands through hypertrophic (increase in adipocyte volume) and hyperplastic (increase in adipocyte number) remodeling, in order to accommodate the fat resulting from surplus of calories. Large prospective studies support the view that the pattern of obesity-dependent adipose tissue remodeling plays a major role in determining the cardiometabolic risk profile, clearly indicating that SAT is the largest and least metabolically harmful storage site for excess fat (Neeland et al. 2012). SAT, however, has limited ability to expand by recruiting new adipose cells (Gustafson and Smith 2012), therefore impaired SAT adipogenesis results in increased VAT and ectopic fat accumulation at different sites.

The plasticity of adipose tissue requires the development of newly formed vascular networks that are crucial for a “healthy” adipose tissue expansion. In fact, angiogenic activity provides oxygens, nutrients, growth factors, and cells that maintain adequate homeostasis of adipose tissue; development of the vascular supply via angiogenesis, therefore, is a rate-limiting

Draft

step in adipose tissue expansion (Sun et al. 2011). A network of pro-angiogenic and anti-angiogenic factors exerts tight control on angiogenesis and subsequent adipogenesis (Hammarstedt et al. 2018). Among the pro-angiogenic forces a key role of vascular endothelial growth factor (VEGF) signaling has been convincingly demonstrated in experimental models (Robciuc et al. 2016). Thus, in sub-optimally vascularized adipose tissue of insulin resistant mice, overexpression of VEGFB induces angiogenesis, reduces inflammation and improves glucose metabolism; in this setting, knock-out of the VEGF receptor 1 (also known as Fms-like tyrosine kinase-1 [Flt-1]), which act as decoy receptor, unleashed the greater angiogenic potential of VEGF interaction with its receptor 2 and resulted in greater stimulation of angiogenesis, thermogenesis and even weight loss. By contrast, here is substantial, though indirect, evidence supporting the view that, in conditions of reduced VEGF activity, up-regulation of the ET-1 system might occur. Thus, switch-on of ET-1 production is known to follow VEGF inactivation by the soluble form of Flt-1 in pre-eclampsia, thereby leading to decreased placental perfusion and hypertension (Verdonk et al. 2015). Similarly, pharmacological tools interfering with the VEGF pathway, such as VEGF receptor inhibitors, soluble VEGF receptors, or anti-VEGF antibodies, are known to result in activation of the ET-1 system (Saleh et al. 2016). Owing to the vasoconstrictor properties of ET-1, it is tempting to speculate that its enhanced activity in obese adipose tissue may contribute to impaired blood perfusion and defective adipogenesis, thereby hinting a potential role of ET-1 receptor antagonism (ERA) to counteract this phenomenon.

Perivascular and epicardial adipose tissue dysfunction in obesity: role of ET-1

One ectopic site of fat accumulation and inflammation in obesity is the perivascular adipose tissue (PVAT), which surrounds large, medium and small vascular beds in disparate circulatory districts. Opposite to the previous view considering PVAT a simple mechanical protection of vascular structures, PVAT has been recently recognized as a critical regulator of vascular function, given its

intimate contact with the vessel wall due to the absence of a physical barrier (Fitzgibbons and Czech 2014). Abundant experimental and clinical evidence has shown that PVAT physiologically exerts vasodilator, anti-contractile and anti-proliferative actions, largely mediated by secretion of protective adipokines (Aghamohammadzadeh et al. 2012). These favorable properties of PVAT, however, are typically lost in the setting of obesity, when decreased production of protective adipokines and increased production of inflammatory cytokines, such as IL-1, IL-6 and TNF-α, impair vascular function (Lastra and Manrique 2015; Lee et al. 2013a). Activation of the renin-angiotensin-aldosterone system, imbalance in immunity, macrophage infiltration and polarization toward an inflammatory M1 phenotype, as well as heightened production of reactive oxygen species, are other vasculotoxic mechanisms in these patients (Lastra and Manrique 2015).

Virdis et al., by use of arterioles isolated from visceral adipose tissue of obese patients undergoing bariatric surgery and challenged in a wire myograph, have elegantly demonstrated that up-regulation of ET-1 by inflammatory cytokines underlies the vasoconstrictor action of obese PVAT (Virdis et al. 2015). Thus, in the presence of PVAT, the relaxing response to ET_A receptor antagonism by BQ-123 was significantly higher in obese vessels than in those taken from lean controls; removal of PVAT, by contrast, the vasorelaxing response to BQ-123 was not different between in vessels obtained from obese patients or lean individuals, indicating that obese PVAT is a source of mediators leading to activation of the vascular ET-1 system. Interestingly, in the presence of PVAT, incubation of obese vessels with the TNF-α-blocking antibody infliximab reduced the vasodilator response to BQ-123, suggesting a key role of this cytokine in their increased ET_A-dependent constriction. This concept was further strengthened by immunofluorescence analysis that revealed in untreated small arteries of obese patients augmented expression of all the components of the ET-1 system, including ET-1, ET_A and ET_B receptors.

Draft

Inflammatory and pro-oxidant changes occurring in obese PVAT seem to involve up-regulation of various pro-inflammatory molecules, such as leptin, resistin, visfatin, angiotensin (Ang) II and chemokines, with concurrent down-regulation of anti-inflammatory substances, including adiponectin and Ang-(1-7) (Xia and Li 2017). It has hence been postulated that these substances might affect vascular function by altering the balance between the two main homeostatic mechanisms, the NO pathway and the ET-1 system.

One of the most widely investigated adipokines with regard to its vascular effects is leptin, which bears complex relationship with insulin sensitivity and is known to oppose the central effects of insulin on food intake. In peripheral tissues, including the vascular endothelium, however, there is a strikingly convergence between insulin and leptin intracellular transduction signaling (Konner and Bruning 2012). Thus, leptin activation of PI 3-kinase/Akt results in stimulation of NOS and increased production of NO (Lembo et al. 2000); activation of MAP kinase, by contrast, may induce increased production of ET-1 (Quehenberger et al. 2002). It would be possible, therefore, that pathway-selective impairment of PI 3-kinase activation in obese vessels might lead to prevalence of the MAP kinase signaling and vascular dysfunction, as suggested by studies showing an association between hyperleptinemia and heightened cardiovascular risk (Wallace et al. 2001). We have tested this mechanism in the human forearm circulation and observed that, in healthy subjects, intra-arterial infusion of exogenous leptin does indeed result in increased bioactivity of both the ET-1 system and the NO pathway; in obese patients, by contrast, it does not elicit any substantial modification of these two vasoactive systems (Schinzari et al. 2013). This suggests that obesity-related leptin resistance (Friedman 2009) also extends to the vascular effects of the peptide and, therefore, hyperleptinemia is unlikely to play a causal role in vascular dysfunction, being rather a marker of hyperinsulinemia and increased adiposity. This notion is indirectly supported by the results of a prospective study and systematic review that

Draft

deemphasizes the pathogenic role of leptin, showing that the association of circulating leptin with cardiovascular risk is largely dependent on BMI (Sattar et al. 2009).

A factor likely contributing to the vasoconstrictor properties of obese PVAT, by contrast, is the decreased expression of Ang-(1-7) (Fang et al. 2017). Ang-(1-7) is one of the components of the renin-angiotensin system physiologically produced by PVAT that diffuses toward the underlying smooth muscle and induces vasodilation (Xia and Li 2017). By infusing exogenous Ang-(1-7) in the forearm circulation of obese patients, we have recently observed that this peptide is able to blunt the vasodilator response to BQ-123, thereby suggesting that defective Ang-(1-7) availability might participate in the increased ET-1-dependent vasoconstriction of these patients (Schinzari et al. 2018).

Another site of ectopic accumulation of excess fat in obesity is the epicardial adipose tissue (EAT). Convincing evidence now demonstrates that changes occurring in obese EAT transduce the deleterious effect of obesity to the heart, hence representing a potential target for therapeutic interventions (Packer 2018). In healthy conditions, EAT has no anatomical boundaries with the underlying myocardial tissue, with which it shares an unobstructed microcirculation that allows facilitated transfer of substances acting in paracrine manner to influence the structure and function of the neighboring tissues. Adipocytes in healthy EAT prevents local inflammation and oxidative stress by combusting fatty acids and by secreting substances that nourish myocytes and minimize inflammation, hypertrophy, and fibrosis. Obese EAT, however, modifies its biological characteristics by adopting an inclination to lipolysis, with release of fatty acids, and a tendency to secrete pro-inflammatory molecules like Ang II and ET-1 (Lewis et al. 2017). All these changes contribute to the development in cardiac myocytes of a biological phenotype predisposing to HFpEF, including abnormal calcium handling, endothelial and mitochondrial dysfunction, and modifications of the isoform expression and phosphorylation of a large sarcomeric protein, titin

Draft

(Lewis et al. 2017). These abnormalities, in turn, result in decreased ventricular distensibility due to cardiac microvascular rarefaction and fibrosis, with consequent abnormalities of diastolic filling, functional capacity and outcomes (Kitzman and Shah 2016).

Given the action of ET-1 to stimulate myocardial hypertrophy and fibrosis characteristic of the HFpEF biological phenotype, treatment with ERAs have been tested in preclinical and clinical studies. In a murine model of HFpEF induced by chronic aldosterone infusion, the dual $ET_{A/B}$ blocker macitentan has been effective in reducing left ventricular hypertrophy independently of blood pressure changes, with no benefit on diastolic dysfunction; interestingly, in the left ventricle of those mice, macitentan improved adverse cardiac remodeling by reducing the expression of the stiffer collagen I and titin n2b isoforms (Valero-Munoz et al. 2016). In a randomized, double-blind, placebo-controlled trial, Zile et al. evaluated the effect of the selective ET_A antagonist sitaxsentan in patients with HFpEF; in these patients, sitaxsentan increased exercise tolerance compared to placebo, but did not significantly modify left ventricular mass, functional class, death, or hospital stay related to heart failure (Zile et al. 2014). Even though the results of these trials have not been entirely favorable and use of ERAs in patients with heart failure has been discouraged by occurrence of fluid retention following ET_A blockade (an effect, however, transitory and manageable with diuretics), the strong pathophysiological role of ET-1 in HFpEF compels additional clinical studies.

Metabolic complications of obesity: c***ontribution of ET-1***

Evidence collected in our laboratory demonstrates that the intravascular activity of the ET-1 system is higher in patients with metabolically unhealthy obesity, defined as the presence of at least one glucose or lipid abnormality characteristic of the metabolic syndrome, than in obese defined as metabolically healthy by the absence of those changes (Schinzari et al. 2015). This observation hints that enhanced ET-1 activity plays a role in the occurrence of the metabolic

complications of obesity, based on the view that ET-1-dependent microvascular constriction contributes to the development of metabolic syndrome by reducing the exposure of circulating triglyceride-containing lipoproteins to endothelial lipoprotein lipase (LPL) (Lind and Lithell 1993). In fact, a direct effect of ET-1 to inhibit LPL has been observed in cultured adipocytes, where LPL activity is inhibited in a concentration-dependent manner by addition of ET-1 and is restored by selective ET_A, but not ET_B, receptor blockade (Ishida et al. 1992). Similarly, ET-1, but not ET-3, has been shown to suppress LPL expression in adipocyte cultures (Uchida et al. 1995). More recently, Briançon-Marjollet et al. have reported that ET-1 is able to modulate adipocyte metabolism, reducing glucose uptake and inducing lipolytic effects, through regulation of the hormone-sensitive lipase phosphorylation; interestingly, these metabolic effects of ET-1 are reversed by ET_A receptor antagonism, either selective (BQ-123) or nonselective (dual ET_A and ET_B blockade by bosentan) (Briancon-Marjollet et al. 2016). In a clinical study, Piatti et al. have found that, in a heterogeneous group of individuals with various degrees of glucose tolerance and insulin resistance, circulating triglycerides correlate linearly and independently with ET-1 plasma levels (Piatti et al. 2000). Finally, a recent re-analysis of data from a previous clinical study has shown that selective ET_A antagonism by sitaxentan for 6 weeks is able to reduce plasma triglycerides and other atherogenic lipid particles in patients with chronic kidney disease (Farrah et al. 2019); of note, treatment with sitaxentan was associated with reduced circulating levels of proprotein convertase subtilisin/kexin type 9 (PCSK9), with a significant linear relationship between PCSK9 reduction and improved lipid profile. Even though sitaxentan has been withdrawn from clinical use due to severe hepatotoxicity, the latter findings suggest that coexistence of increased ET-1 activity and hypertriglyceridemia may not simply be an association due to a common pathophysiological background, but that activation of the ET-1 system plays a mechanistic role in atherogenic

Draft

dyslipidemia; as a consequence, targeting the ET-1 system might provide additional benefits for cardiovascular prevention in these patients.

In recent years, abundant evidence has indicated that the pancreatic islet capillary bed, comprised predominantly of endothelial cells, is a crucial source of signals that affect beta cell structure and function, and may hence play a role in the development and progression of diabetes. Thus, in the absence of diabetes, a number of endothelium-derived growth-factors (hepatocyte growth factor, fibroblast growth factor, connective tissue growth factor, thrombospontin-1) favor beta cells proliferation and survival. Also, balanced secretion of endothelial vasoactive mediators, such as ET-1 and NO, is instrumental in maintaining adequate perfusion of beta cells and insulin secretion. In addition, extracellular matrix components (fibronectin, collagens, laminins) affect insulin expression and release from beta cells (Hogan and Hull 2017). In prediabetic conditions like obesity, however, functional abnormalities of endothelial cells, with dysregulation of their secretory pattern, may lead to reduced perfusion of beta cell and impaired secretion of insulin. Under these conditions, endothelial release of ET-1 seems to play a relevant mechanistic role, given that ET-1 has been shown to reduce the diameter of islet vessels, an effect reversed by ET_A receptor antagonism by BQ-123, but not by ET_B blockade by BQ-788 (Lai et al. 2007). Another important regulator of beta cell perfusion are pericytes that coexist with endothelial cells in islet capillaries. Recent work has indeed demonstrated that application of ET-1 simultaneously activates islet pericytes by increasing cytosolic Ca^{2+} levels and reduces capillary diameter by eliciting a constrictor response (Almaca et al. 2018). Owing to these unfavorable effects of ET-1 in islet capillaries and on beta cell perfusion, it is tempting to speculate that ET_A receptor antagonism might beneficially impact beta cell function and survival, thus preventing or slowing the development of diabetes in obese patients. This notion gains indirectly supported by preclinical evidence demonstrating that targeting another vasoconstrictor system, such as the

Draft

renin-angiotensin system, exerts beneficial effects on beta cell mass and function in rodent models of type 2 diabetes (Shao et al. 2006). Whether these effects could extend to human beta cells in vivo is yet to be determined.

Hepatic steatosis may be another unwanted metabolic sequela of obesity. Hepatic lipid content is regulated by the complex interplay between the delivery of lipids to the liver and the hepatic uptake, synthesis, oxidation and secretion of lipids. In the healthy state, liver triglyceride content is derived in variable percentages from free fatty acids produced by adipose tissue lipolysis, dietary fatty acids, *de novo* lipogenesis, and circulating chylomicrons and VLDL particles. A high-fat diet, obesity and insulin resistance can increase the flux through each of these pathways, leading to increased hepatic lipid uptake and greater accumulation of intracellular triglycerides in hepatocytes. Nonalcoholic fatty liver disease (NAFLD) develops owing to disequilibrium in these processes; in NAFLD, oxidation in the mitochondria is decreased, and lipolysis, triglyceride synthesis, *de novo* lipogenesis and VLDL secretion are all increased (Meex and Watt 2017). These circumstances can induce metabolic stress, oxidative stress, and endoplasmic reticulum-related stress resulting in fatty hepatocytes (lipotoxicity), and, when mechanisms to cope with these stresses become overwhelmed, hepatocytes death. Dying and dead hepatocytes, in turn, release signals to cells that are necessary for the repair of liver damage, such as immune cells, sinusoidal endothelial cells, hepatic stellate cells, and ductal-type cells. The hepatocyte-derived, damage-associated signals cause the repair-related cells to accumulate and launch wound-healing responses, which include inflammation and fibrogenesis, leading to nonalcoholic steatohepatitis (NASH) (Cohen et al. 2011) (Diehl and Day 2017). A number of intrahepatic molecules have been identified as mediators of inflammatory signals, particularly those related to stellate cells activation and fibrosis, such as the farnesoid X receptor [FXR], the chemokine receptors type 2 and 5 [CCR 2/5], apoptosis signal regulating kinase-1 [ASK-1], the peroxisome

Draft

proliferator-activated receptor α/γ/δ [PPARα/γ/δ]) (Friedman et al. 2018). In addition to these molecules, activation of the ET-1 system might importantly contribute to the activation of stellate cells and hepatic fibrosis. Thus, a number of reports demonstrate that ET-1 promote activated stellate cell differentiation from a variety of cellular precursors (Rodriguez-Pascual et al. 2014). Also, precise intracellular signaling pathways involved in the profibrotic aspects of ET-1 have been identified, including action on focal adhesion and integrin-linked kinases (FAK/ILK), downstream activation of the mitogen-activated (MAP) kinases JNK and ERK, up-regulation of the activator protein (AP)-1 transcription factor and induction of a profibrotic program with expression of matrix components like collagens (Rodriguez-Pascual et al. 2014). Recent advances in knowledge of the underlying molecular mechanism has sparked a number of clinical trials, currently in phase 2 or 3, with drugs targeting those pathways (such as FXR agonists, ASK-1 inhibitors, CCR2/5 inhibitors, PPAR α/δ or PPAR γ ligands) to reduce fibrosis and effectively cure NASH before its progression to cirrhosis (Friedman et al. 2018). Notwithstanding the known profibrotic activity of ET-1, there has some been some reluctance to test endothelin receptor antagonists (ERAs) in these patients. This is probably because investigators and sponsors have been discouraged by cases of hepatotoxicity associated in the past with ERAs, especially those with a sulphonamide structure like bosentan and sitaxentan, so that liver injury has been considered for years the Achille's heel of this class of drugs (Hoeper 2009). Yet, some recent preclinical evidence suggest that newer ERAs might indeed provide benefits in NASH. Thus, Okamoto et al. have reported that ambrisentan, a selective ET_A antagonist, is able to reduce the degree of hepatic fibrosis, even with no effect on the amount of hepatic lipid content, in a NASH mouse model (Okamoto et al. 2016). From a clinical standpoint, it is encouraging that ambrisentan is currently under testing in a phase 2 clinical trial to assess its utility in lowering portal hypertension in patients with liver cirrhosis (ClinicalTrials.gov Identifier: NCT03827200).

Draft

Obesity-related complications: role of ET-1 as a possible therapeutic target

Over the last 3 decades, up-regulation of ET-1 system has been implicated in the pathophysiology of a variety of disease conditions, ranging from arterial hypertension to chronic kidney disease, coronary artery disease, pulmonary hypertension, sickle cell disease, autoimmune disease, cancer, and several other (Barton and Yanagisawa 2019). In most of these conditions, the therapeutic benefits of ERA have been demonstrated in clinical trials; in some of them, such as pulmonary hypertension and autoimmune disease (in particular, systemic sclerosis/scleroderma-related digital ulcers), there has been regulatory approval of ERA treatment for this indication. A recently completed phase 3 clinical trial (SONAR, Study of Diabetic Nephropathy with Atrasentan) has indicated a novel way to improve the therapeutic efficacy of ERA, by preliminary identifying subgroups of patients that could benefit most from chronic treatment with this class of drugs (Heerspink et al. 2019). The design of the SONAR trial, in fact, has been deemed critical in determining its favorable outcome: among over 5000 obese patients with mild to moderate diabetic nephropathy that had entered the short-term "enrichment" phase of the trials, only 2648 who were identified as responders (based on a substantial reduction of their albumin-to-creatinine ratio and minimal signs of sodium retention during enrichment) were selected for the randomized phase of the trial with 0.75 mg per day of atrasentan (the lowest effective dose of the drug, determined based on a sub-study of the previous RADAR trial (Koomen et al. 2018). After a mean follow-up of 2.2 years, the SONAR trial demonstrated that, compared to placebo, atrasentan is indeed effective in reducing the progression of nephropathy (as indicated by doubling of serum creatinine or reduction of estimated glomerular filtration rate below 50%) and, of note, also in lowering the incidence of nonfatal stroke, hence suggesting an ancillary protective effect of ERA on cerebral atherosclerosis. It is important to emphasize that the average body mass index of patients participating in the SONAR trial was greater than 30 kg/m^2, thereby supporting the notion

Draft

that ERA may be effective in preventing some disease states associated with obesity. This consideration, in addition to the success of the "personalized medicine" approach applied in that trial, could foster further clinical studies to test novel applications of ERA in those obesity-related pathologies, such as HFpEF, atherogenic dyslipidemia, prediabetes, and NASH, in which activation of the ET-1 system seems to play a relevant pathophysiological role.

As the complexity of the ET-1 system in obesity continues to be revealed, so do the intricacies of its involvement in the regulation of human body adaption and response to excess adiposity (**Table 1**). Thus, up-regulation of the ET-1 system acts at times as the last effector of other changes brought about by caloric overload; at times, it may trigger or enhance further perturbations downstream. Overall, the comprehensive theme is that enhanced ET-1 activity, irrespective of the specific organ or tissue in which it takes place, is deeply involved in the cardiovascular and metabolic derangement associated with obesity. Further clinical research with ERAs, therefore, should be undertaken to fully ascertain the potential of these drugs in preventing or reducing those complications arising from the obesity epidemic. In this regard, it would be desirable to learn from the past and avoid those mistakes that have hampered further clinical development of ERAs. In retrospect, selection of the suitable patients, in terms of both adequate responsiveness and limited side effects, and choice of the right drug dose might have prevented some disappointing results observed in previous ERA trials, some of which had to be discontinued early. A personalized medicine approach, as demonstrated by recent studies and as already successfully applied for other drugs, could help expand the clinical use of ERAs to target various unwanted complications of obesity.

Draft

References

Aghamohammadzadeh, R., Withers, S., Lynch, F., Greenstein, A., Malik, R., and Heagerty, A. 2012. Perivascular adipose tissue from human systemic and coronary vessels: the emergence of a new pharmacotherapeutic target. Br J Pharmacol **165**(3): 670-682. doi: 10.1111/j.1476-5381.2011.01479.x.

Ahima, R.S., and Lazar, M.A. 2013. Physiology. The health risk of obesity--better metrics imperative. Science **341**(6148): 856-858. doi: 10.1126/science.1241244.

Almaca, J., Weitz, J., Rodriguez-Diaz, R., Pereira, E., and Caicedo, A. 2018. The Pericyte of the Pancreatic Islet Regulates Capillary Diameter and Local Blood Flow. Cell Metab **27**(3): 630-644 e634. doi: 10.1016/j.cmet.2018.02.016.

Barton, M., and Yanagisawa, M. 2019. Endothelin: 30 Years From Discovery to Therapy. Hypertension **74**(6): 1232-1265. doi: 10.1161/HYPERTENSIONAHA.119.12105.

Briancon-Marjollet, A., Monneret, D., Henri, M., Hazane-Puch, F., Pepin, J.L., Faure, P., and Godin-Ribuot, D. 2016. Endothelin regulates intermittent hypoxia-induced lipolytic remodelling of adipose tissue and phosphorylation of hormone-sensitive lipase. J Physiol **594**(6): 1727-1740. doi: 10.1113/JP271321.

Cardillo, C., Campia, U., Iantorno, M., and Panza, J.A. 2004. Enhanced vascular activity of endogenous endothelin-1 in obese hypertensive patients. Hypertension **43**(1): 36-40. doi: 10.1161/01.HYP.0000103868.45064.81.

Cardillo, C., Nambi, S.S., Kilcoyne, C.M., Choucair, W.K., Katz, A., Quon, M.J., and Panza, J.A. 1999. Insulin stimulates both endothelin and nitric oxide activity in the human forearm. Circulation **100**(8): 820-825.

Draft

Clark, M.G. 2008. Impaired microvascular perfusion: a consequence of vascular dysfunction and a potential cause of insulin resistance in muscle. Am J Physiol Endocrinol Metab **295**(4): E732-750. doi: 90477.2008 [pii]

10.1152/ajpendo.90477.2008.

Clark, M.G., Wallis, M.G., Barrett, E.J., Vincent, M.A., Richards, S.M., Clerk, L.H., and Rattigan, S. 2003. Blood flow and muscle metabolism: a focus on insulin action. Am J Physiol Endocrinol Metab **284**(2): E241-258. doi: 10.1152/ajpendo.00408.2002

284/2/E241 [pii].

Cohen, J.C., Horton, J.D., and Hobbs, H.H. 2011. Human fatty liver disease: old questions and new insights. Science **332**(6037): 1519-1523. doi: 10.1126/science.1204265.

Cusi, K., Maezono, K., Osman, A., Pendergrass, M., Patti, M.E., Pratipanawatr, T., DeFronzo, R.A., Kahn, C.R., and Mandarino, L.J. 2000. Insulin resistance differentially affects the PI 3-kinase- and MAP kinase-mediated signaling in human muscle. J Clin Invest **105**(3): 311-320. doi: 10.1172/JCI7535.

Diehl, A.M., and Day, C. 2017. Cause, Pathogenesis, and Treatment of Nonalcoholic Steatohepatitis. N Engl J Med **377**(21): 2063-2072. doi: 10.1056/NEJMra1503519.

Fang, Z., Cao, H., Stoffel, E., and Cohen, P. 2017. Role of Perivascular Adipose Tissue in Vascular Physiology and Pathology. Hypertension **69**(5): 770-777. doi: 10.1161/Hypertensionaha.116.08451.

Farrah, T.E., Anand, A., Gallacher, P.J., Kimmitt, R., Carter, E., Dear, J.W., Mills, N.L., Webb, D.J., and Dhaun, N. 2019. Endothelin Receptor Antagonism Improves Lipid Profiles and Lowers PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) in Patients With Chronic Kidney Disease. Hypertension **74**(2): 323-330. doi: 10.1161/HYPERTENSIONAHA.119.12919.

Draft

Fitzgibbons, T.P., and Czech, M.P. 2014. Epicardial and perivascular adipose tissues and their influence on cardiovascular disease: basic mechanisms and clinical associations. J Am Heart Assoc **3**(2): e000582. doi: 10.1161/JAHA.113.000582.

Friedman, J.M. 2009. Leptin at 14 y of age: an ongoing story. Am J Clin Nutr **89**(3): 973S-979S. doi: 10.3945/ajcn.2008.26788B.

Friedman, S.L., Neuschwander-Tetri, B.A., Rinella, M., and Sanyal, A.J. 2018. Mechanisms of NAFLD development and therapeutic strategies. Nat Med **24**(7): 908-922. doi: 10.1038/s41591-018-0104-9.

Gustafson, B., and Smith, U. 2012. The WNT inhibitor Dickkopf 1 and bone morphogenetic protein 4 rescue adipogenesis in hypertrophic obesity in humans. Diabetes **61**(5): 1217-1224. doi: 10.2337/db11-1419.

Hammarstedt, A., Gogg, S., Hedjazifar, S., Nerstedt, A., and Smith, U. 2018. Impaired Adipogenesis and Dysfunctional Adipose Tissue in Human Hypertrophic Obesity. Physiol Rev **98**(4): 1911-1941. doi: 10.1152/physrev.00034.2017.

Heerspink, H.J.L., Parving, H.H., Andress, D.L., Bakris, G., Correa-Rotter, R., Hou, F.F., Kitzman, D.W., Kohan, D., Makino, H., McMurray, J.J.V., Melnick, J.Z., Miller, M.G., Pergola, P.E., Perkovic, V., Tobe, S., Yi, T., Wigderson, M., de Zeeuw, D., Committees, S., and Investigators. 2019. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. Lancet **393**(10184): 1937-1947. doi: 10.1016/S0140-6736(19)30772-X.

Hoeper, M.M. 2009. Liver toxicity: the Achilles' heel of endothelin receptor antagonist therapy? Eur Respir J **34**(3): 529-530. doi: 10.1183/09031936.00094409.

Hogan, M.F., and Hull, R.L. 2017. The islet endothelial cell: a novel contributor to beta cell secretory dysfunction in diabetes. Diabetologia **60**(6): 952-959. doi: 10.1007/s00125-017-4272-9.

Draft

Ishida, F., Saeki, K., Saeki, T., Ishikawa, K., Ihara, M., Kamei, T., and Yano, M. 1992. Suppressive effects of the endothelin receptor (ETA) antagonist BQ-123 on ET-1-induced reduction of lipoprotein lipase activity in 3T3-L1 adipocytes. Biochem Pharmacol **44**(7): 1431-1436. doi: 10.1016/0006-2952(92)90545-t.

Kim, J.A., Montagnani, M., Koh, K.K., and Quon, M.J. 2006. Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation **113**(15): 1888-1904. doi: 113/15/1888 [pii]
10.1161/CIRCULATIONAHA.105.563213.

Kitzman, D.W., and Shah, S.J. 2016. The HFpEF Obesity Phenotype The Elephant in the Room. Journal of the American College of Cardiology **68**(2): 200-203. doi: 10.1016/j.jacc.2016.05.019.

Konner, A.C., and Bruning, J.C. 2012. Selective insulin and leptin resistance in metabolic disorders. Cell Metab **16**(2): 144-152. doi: 10.1016/j.cmet.2012.07.004.

Koomen, J.V., Stevens, J., Mostafa, N.M., Parving, H.H., de Zeeuw, D., and Heerspink, H.J.L. 2018. Determining the optimal dose of atrasentan by evaluating the exposure-response relationships of albuminuria and bodyweight. Diabetes Obes Metab **20**(8): 2019-2022. doi: 10.1111/dom.13312.

Lai, E.Y., Persson, A.E., Bodin, B., Kallskog, O., Andersson, A., Pettersson, U., Hansell, P., and Jansson, L. 2007. Endothelin-1 and pancreatic islet vasculature: studies in vivo and on isolated, vascularly perfused pancreatic islets. Am J Physiol Endocrinol Metab **292**(6): E1616-1623. doi: 10.1152/ajpendo.00640.2006.

Lastra, G., and Manrique, C. 2015. Perivascular adipose tissue, inflammation and insulin resistance: link to vascular dysfunction and cardiovascular disease. Horm Mol Biol Clin Investig **22**(1): 19-26. doi: 10.1515/hmbci-2015-0010.

Draft

Lee, H.Y., Despres, J.P., and Koh, K.K. 2013a. Perivascular adipose tissue in the pathogenesis of cardiovascular disease. Atherosclerosis **230**(2): 177-184. doi: 10.1016/j.atherosclerosis.2013.07.037.

Lee, M.J., Wu, Y., and Fried, S.K. 2013b. Adipose tissue heterogeneity: implication of depot differences in adipose tissue for obesity complications. Mol Aspects Med **34**(1): 1-11. doi: 10.1016/j.mam.2012.10.001.

Lembo, G., Vecchione, C., Fratta, L., Marino, G., Trimarco, V., d'Amati, G., and Trimarco, B. 2000. Leptin induces direct vasodilation through distinct endothelial mechanisms. Diabetes **49**(2): 293-297.

Lewis, G.A., Schelbert, E.B., Williams, S.G., Cunnington, C., Ahmed, F., McDonagh, T.A., and Miller, C.A. 2017. Biological Phenotypes of Heart Failure With Preserved Ejection Fraction. Journal of the American College of Cardiology **70**(17): 2186-2200. doi: 10.1016/j.jacc.2017.09.006.

Lind, L., and Lithell, H. 1993. Decreased peripheral blood flow in the pathogenesis of the metabolic syndrome comprising hypertension, hyperlipidemia, and hyperinsulinemia. Am Heart J **125**(5 Pt 2): 1494-1497.

Lteif, A., Vaishnava, P., Baron, A.D., and Mather, K.J. 2007. Endothelin limits insulin action in obese/insulin-resistant humans. Diabetes **56**(3): 728-734. doi: 10.2337/db06-1406.

Mather, K.J., Lteif, A., Steinberg, H.O., and Baron, A.D. 2004. Interactions between endothelin and nitric oxide in the regulation of vascular tone in obesity and diabetes. Diabetes **53**(8): 2060-2066. doi: 53/8/2060 [pii].

Meex, R.C.R., and Watt, M.J. 2017. Hepatokines: linking nonalcoholic fatty liver disease and insulin resistance. Nat Rev Endocrinol **13**(9): 509-520. doi: 10.1038/nrendo.2017.56.

Draft

Muniyappa, R., Iantorno, M., and Quon, M.J. 2008. An integrated view of insulin resistance and endothelial dysfunction. Endocrinol Metab Clin North Am **37**(3): 685-711, ix-x. doi: S0889-8529(08)00032-7 [pii]
10.1016/j.ecl.2008.06.001.

Neeland, I.J., Turer, A.T., Ayers, C.R., Powell-Wiley, T.M., Vega, G.L., Farzaneh-Far, R., Grundy, S.M., Khera, A., McGuire, D.K., and de Lemos, J.A. 2012. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. JAMA **308**(11): 1150-1159. doi: 10.1001/2012.jama.11132.

Okamoto, T., Koda, M., Miyoshi, K., Onoyama, T., Kishina, M., Matono, T., Sugihara, T., Hosho, K., Okano, J., Isomoto, H., and Murawaki, Y. 2016. Antifibrotic effects of ambrisentan, an endothelin-A receptor antagonist, in a non-alcoholic steatohepatitis mouse model. World J Hepatol **8**(22): 933-941. doi: 10.4254/wjh.v8.i22.933.

Packer, M. 2018. Epicardial Adipose Tissue May Mediate Deleterious Effects of Obesity and Inflammation on the Myocardium. Journal of the American College of Cardiology **71**(20): 2360-2372. doi: 10.1016/j.jacc.2018.03.509.

Piatti, P.M., Monti, L.D., Galli, L., Fragasso, G., Valsecchi, G., Conti, M., Gernone, F., and Pontiroli, A.E. 2000. Relationship between endothelin-1 concentration and metabolic alterations typical of the insulin resistance syndrome. Metabolism **49**(6): 748-752. doi: 10.1053/meta.2000.6257.

Quehenberger, P., Exner, M., Sunder-Plassmann, R., Ruzicka, K., Bieglmayer, C., Endler, G., Muellner, C., Speiser, W., and Wagner, O. 2002. Leptin induces endothelin-1 in endothelial cells in vitro. Circ Res **90**(6): 711-718.

Robciuc, M.R., Kivela, R., Williams, I.M., de Boer, J.F., van Dijk, T.H., Elamaa, H., Tigistu-Sahle, F., Molotkov, D., Leppanen, V.M., Kakela, R., Eklund, L., Wasserman, D.H., Groen, A.K., and Alitalo, K.

Draft

2016. VEGFB/VEGFR1-Induced Expansion of Adipose Vasculature Counteracts Obesity and Related Metabolic Complications. Cell Metab **23**(4): 712-724. doi: 10.1016/j.cmet.2016.03.004.

Rodriguez-Pascual, F., Busnadiego, O., and Gonzalez-Santamaria, J. 2014. The profibrotic role of endothelin-1: is the door still open for the treatment of fibrotic diseases? Life Sci **118**(2): 156-164. doi: 10.1016/j.lfs.2013.12.024.

Saleh, L., Danser, J.A., and van den Meiracker, A.H. 2016. Role of endothelin in preeclampsia and hypertension following antiangiogenesis treatment. Curr Opin Nephrol Hypertens **25**(2): 94-99. doi: 10.1097/MNH.0000000000000197.

Sattar, N., Wannamethee, G., Sarwar, N., Chernova, J., Lawlor, D.A., Kelly, A., Wallace, A.M., Danesh, J., and Whincup, P.H. 2009. Leptin and coronary heart disease: prospective study and systematic review. J Am Coll Cardiol **53**(2): 167-175. doi: 10.1016/j.jacc.2008.09.035.

Schinzari, F., Iantorno, M., Campia, U., Mores, N., Rovella, V., Tesauro, M., Di Daniele, N., and Cardillo, C. 2015. Vasodilator responses and endothelin-dependent vasoconstriction in metabolically healthy obesity and the metabolic syndrome. Am J Physiol Endocrinol Metab **309**(9): E787-792. doi: 10.1152/ajpendo.00278.2015.

Schinzari, F., Tesauro, M., Rovella, V., Di Daniele, N., Mores, N., Veneziani, A., and Cardillo, C. 2013. Leptin stimulates both endothelin-1 and nitric oxide activity in lean subjects but not in patients with obesity-related metabolic syndrome. J Clin Endocrinol Metab **98**(3): 1235-1241. doi: 10.1210/jc.2012-3424.

Schinzari, F., Tesauro, M., Veneziani, A., Mores, N., Di Daniele, N., and Cardillo, C. 2018. Favorable Vascular Actions of Angiotensin-(1-7) in Human Obesity. Hypertension **71**(1): 185-191. doi: 10.1161/Hypertensionaha.117.10280.

Shao, J., Iwashita, N., Ikeda, F., Ogihara, T., Uchida, T., Shimizu, T., Uchino, H., Hirose, T., Kawamori, R., and Watada, H. 2006. Beneficial effects of candesartan, an angiotensin II type 1 receptor blocker,

Draft

on beta-cell function and morphology in db/db mice. Biochem Biophys Res Commun **344**(4): 1224-1233. doi: 10.1016/j.bbrc.2006.04.011.

Sun, K., Kusminski, C.M., and Scherer, P.E. 2011. Adipose tissue remodeling and obesity. J Clin Invest **121**(6): 2094-2101. doi: 10.1172/JCI45887.

Tesauro, M., Schinzari, F., Rovella, V., Di Daniele, N., Lauro, D., Mores, N., Veneziani, A., and Cardillo, C. 2009. Ghrelin restores the endothelin 1/nitric oxide balance in patients with obesity-related metabolic syndrome. Hypertension **54**(5): 995-1000. doi: 10.1161/HYPERTENSIONAHA.109.137729.

Uchida, Y., Irie, K., Tsukahara, F., Ohba, K., Ogawa, A., Fujii, E., and Muraki, T. 1995. Endothelin-1, but not endothelin-3, suppresses lipoprotein lipase gene expression in brown adipocytes differentiated in culture. Eur J Pharmacol **291**(1): 33-41. doi: 10.1016/0922-4106(95)90186-8.

Valero-Munoz, M., Li, S.P., Wilson, R.M., Boldbaatar, B., Iglarz, M., and Sam, F. 2016. Dual Endothelin-A/Endothelin-B Receptor Blockade and Cardiac Remodeling in Heart Failure With Preserved Ejection Fraction. Circ-Heart Fail **9**(11). doi: ARTN e003381 10.1161/CIRCHEARTFAILURE.116.003381.

Verdonk, K., Saleh, L., Lankhorst, S., Smilde, J.E., van Ingen, M.M., Garrelds, I.M., Friesema, E.C., Russcher, H., van den Meiracker, A.H., Visser, W., and Danser, A.H. 2015. Association studies suggest a key role for endothelin-1 in the pathogenesis of preeclampsia and the accompanying renin-angiotensin-aldosterone system suppression. Hypertension **65**(6): 1316-1323. doi: 10.1161/HYPERTENSIONAHA.115.05267.

Virdis, A., Duranti, E., Rossi, C., Dell'Agnello, U., Santini, E., Anselmino, M., Chiarugi, M., Taddei, S., and Solini, A. 2015. Tumour necrosis factor-alpha participates on the endothelin-1/nitric oxide imbalance in small arteries from obese patients: role of perivascular adipose tissue. European Heart Journal **36**(13): 784-794. doi: 10.1093/eurheartj/ehu072.

Draft

Wallace, A.M., McMahon, A.D., Packard, C.J., Kelly, A., Shepherd, J., Gaw, A., and Sattar, N. 2001. Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). Circulation **104**(25): 3052-3056.

Weil, B.R., Westby, C.M., Van Guilder, G.P., Greiner, J.J., Stauffer, B.L., and DeSouza, C.A. 2011. Enhanced endothelin-1 system activity with overweight and obesity. Am J Physiol Heart Circ Physiol **301**(3): H689-695. doi: 10.1152/ajpheart.00206.2011.

Wildman, R.P., Muntner, P., Reynolds, K., McGinn, A.P., Rajpathak, S., Wylie-Rosett, J., and Sowers, M.R. 2008. The obese without cardiometabolic risk factor clustering and the normal weight with cardiometabolic risk factor clustering: prevalence and correlates of 2 phenotypes among the US population (NHANES 1999-2004). Arch Intern Med **168**(15): 1617-1624. doi: 10.1001/archinte.168.15.1617.

Xia, N., and Li, H. 2017. The role of perivascular adipose tissue in obesity-induced vascular dysfunction. Br J Pharmacol **174**(20): 3425-3442. doi: 10.1111/bph.13650.

Zeng, G., Nystrom, F.H., Ravichandran, L.V., Cong, L.N., Kirby, M., Mostowski, H., and Quon, M.J. 2000. Roles for insulin receptor, PI3-kinase, and Akt in insulin-signaling pathways related to production of nitric oxide in human vascular endothelial cells. Circulation **101**(13): 1539-1545.

Zile, M.R., Bourge, R.C., Redfield, M.M., Zhou, D., Baicu, C.F., and Little, W.C. 2014. Randomized, Double-Blind, Placebo-Controlled Study of Sitaxsentan to Improve Impaired Exercise Tolerance in Patients With Heart Failure and a Preserved Ejection Fraction. Jacc-Heart Fail **2**(2): 123-130. doi: 10.1016/j.jchf.2013.12.002.

Draft

Table. Mechanisms underlying increased ET-1 activity and consequences of up-regulation of the ET-1 system in obesity

Site	Mechanisms	Consequences
Blood vessels	Insulin resistance	Imbalance between NO and ET-1: defective vasodilation, increased vasoconstrictor tone
Adipose tissue (SAT, VAT)	Defective VEGF signaling Inhibition of LPL Activation of HSL	Impaired AT expansion Hypertriglyceridemia Decreased glucose uptake; increased lipolysis
PVAT EAT	Dysregulated adipokines; increased inflammatory cytokines; oxidative stress; lower Ang-(1-7) secretion	Premature atherosclerosis HFpEF
Pancreatic islet	Capillary endothelial dysfunction and pericyte contraction Arteriolar constriction	Beta cell hypoperfusion, dysfunction and death: impaired insulin secretion
Liver	Stellate cell activation in response to NAFLD Fibrosis	NASH

Draft

ET-1, endothelin-1; NO, nitric oxide; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; VEGF, vascular endothelial growth factor; LPL, lipoprotein lipase HSL, hormone-sensitive lipase; PVAT, perivascular adipose tissue; EAT, epicardial adipose tissue; Ang, angiotensin; HFpEF, heart failure with preserved ejection fraction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.