applied sciences

MDPI

Review

Perivascular Adipose Tissue Inflammation: The Anti-Inflammatory Role of Ghrelin in Atherosclerosis Progression

Sorin Nicolae Peiu [1], Radu Florin Popa [1,*], Fawzi Akad [2,3], Iustina S. Cretu-Silivestru [2,3], Bogdan Mircea Mihai [4], Anatolie Visnevschi [5,6], Lorina Vudu [7], Bogdan Tamba [8], Teodor Oboroceanu [3], Daniel Timofte [9,10,*] and Veronica Mocanu [2,3,*]

1 Department of Vascular Surgery, "Grigore T. Popa" University of Medicine and Pharmacy, 16, Universitatii Street, 700115 Iasi, Romania; sorin-nicolae.peiu@umfiasi.ro
2 Department of Morpho-Functional Sciences II (Pathophysiology), "Grigore T. Popa" University of Medicine and Pharmacy, 16, Universitatii Street, 700115 Iasi, Romania; fawzy-h-akad@d.umfiasi.ro (F.A.); iustina-silvia.gs.silivestru@d.umfiasi.ro (I.S.C.-S.)
3 Center for Obesity BioBehavioral Experimental Research, 16, Universitatii Street, 700115 Iasi, Romania; teodor.oboroceanu@yahoo.com
4 Department of Medical Sciences II (Diabetes, Nutrition, and Metabolic Diseases), "Grigore T. Popa" University of Medicine and Pharmacy, 16, Universitatii Street, 700115 Iasi, Romania; bogdan.mihai@umfiasi.ro
5 Department of Laboratory Medicine, "Nicolae Testemitanu" State University of Medicine and Pharmacy, 165, Bd. Stefan cel Mare si Sfant, MD-2004 Chisinau, Moldova; anatolie.visnevschi@usmf.md
6 Research Center of Adipose Tissue Biology, "Nicolae Testemitanu" State University of Medicine and Pharmacy, 165, Bd. Stefan cel Mare si Sfant, MD-2004 Chisinau, Moldova
7 Department of Endocrinology, "Nicolae Testemitanu" State University of Medicine and Pharmacy, 165, Bd. Stefan cel Mare si Sfant, MD-2004 Chisinau, Moldova; lorina.vudu@usmf.md
8 In Vivo Metabolic Research Center, "Grigore T. Popa" University of Medicine and Pharmacy, 16, Universitatii Street, 700115 Iasi, Romania; bogdan.tamba@umfiasi.ro
9 Department of Surgery, "Grigore T. Popa" University of Medicine and Pharmacy, 16, Universitatii Street, 700115 Iasi, Romania
10 Bariatric Surgery Center, Clinical Emergency County Hospital "St. Spiridon", 1, Independentei Street, 700111 Iasi, Romania
* Correspondence: radu.popa@umfiasi.ro (R.F.P.); daniel.timofte@umfiasi.ro (D.T.); veronica.mocanu@umfiasi.ro (V.M.)

check for updates

Citation: Peiu, S.N.; Popa, R.F.; Akad, F.; Cretu-Silivestru, I.S.; Mihai, B.M.; Visnevschi, A.; Vudu, L.; Tamba, B.; Oboroceanu, T.; Timofte, D.; et al. Perivascular Adipose Tissue Inflammation: The Anti-Inflammatory Role of Ghrelin in Atherosclerosis Progression. *Appl. Sci.* **2022**, *12*, 3307. https://doi.org/10.3390/app12073307

Academic Editor: Jongsung Lee

Received: 4 February 2022
Accepted: 23 March 2022
Published: 24 March 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: Perivascular adipose tissue (PVAT) and its adipokines engage in bidirectional crosstalk with the vascular wall. Atherosclerosis disrupts this interaction through inflammation, rupture-prone plaques, and subsequent thrombosis. The cardioprotective effects of ghrelin are in contradiction to its adipogenic properties. The concurrent research of anti-/pro-atherogenic mechanisms of ghrelin and PVAT-derived adipokines provides a better understanding of atherosclerosis progression in metabolic disorders. In-depth coverage of the characteristic features of PVAT concerning vascular dysfunction, with a survey of ghrelin-induced anti-inflammatory effects on adipose tissue macrophage infiltration and the inhibitory activity of ghrelin on the proinflammatory adipokine secretion, show that the impact of ghrelin on the endothelial function should be studied in relation to PVAT.

Keywords: perivascular adipose tissue; ghrelin; vascular disease; atherosclerosis; coronary heart disease; endothelium

1. Introduction

The absence of atherosclerosis in myocardial bridges, which have no surrounding fat, led to the misleading hypothesis of a causal role of perivascular adipose tissue (PVAT) in atherosclerosis. PVAT is attached straight to the vascular wall and its adipokines can act directly upon the vascular wall, which for its part modifies PVAT secretome in bidirectional crosstalk. PVAT is neither a mere sustainer of the vascular system nor a risk

factor for atherosclerosis. It exerts various protective vasodilatory, anti-inflammatory, and antioxidative effects.

PVAT-derived adipokines release anti-atherogenic factors, such as adiponectin, hydrogen sulfide, omentin, IL-10, IL-19, adipose-derived relaxing factor (ADRF), nitric oxide, hydrogen sulfide, and methyl palmitate. PVAT-derived adipocytokines with a vascular impact include adiponectin, leptin, nicotinamide phosphoribosyltransferase (NAMPT), omentin, chemerin, and resistin, with the first having the most detrimental impact. Adiponectin was shown to inhibit NADPH oxidase-mediated release of reactive oxygen species and to increase endothelial nitric oxide (NO) bioavailability. The anticontractile relaxing action is achieved by PVAT-released angiotensin (1–7), by potassium (K^+) channel opening in the plasma membrane of smooth muscle cells, by norepinephrine uptake through the organic cation transporter 3 (OCT-3), and the release of adiponectin mediated by the β3-adrenoceptor [1,2].

Human ghrelin ($C_{149}H_{249}N_{47}O_{42}$) is the endogenous ligand for growth-hormone secretagogue receptor (GHS-R), GHS-R1a being its functional form. Ghrelin is a 28 amino acid peptide secreted by the P/D1 cells, lining the stomach fundus. Human ghrelin differs from rat only in amino acids in position 11 and 12. In order to be recognized by the GHS-R1a receptor and to stimulate growth hormone release from the pituitary gland, the ghrelin's serine at position 3 is acylated by a fatty acid, the n-octanoic acid, near its N-terminal region, before secretion. Ghrelin acylation is triggered by an enzyme known as ghrelin O-acyl transferase (GOAT) [3]. The non-modified ghrelin is called desacyl ghrelin and circulates as a free peptide, whereas acyl ghrelin is bound to lipoproteins. Plasma levels of desacyl ghrelin are about four or five times higher than those of acyl ghrelin in non-pathological states [4].

Ghrelin is a hormone that stimulates appetite and increases the volume of white adipose tissue. Ghrelin reduces insulin secretion and suppresses the production of adiponectin. Ghrelin plasma concentrations decrease after glucose and carbohydrate intake, but a high-fat diet does not reduce ghrelin concentrations [3]. It is most abundantly expressed in specialized cells of the oxyntic glands of the gastric epithelium, but it is also present in both vascular and cardiac tissues [4–6]. Ghrelin inhibits cytokine release (IL-1β, IL-6, and TNF-α) in endothelial cells by inhibiting the activation of NF-κB [7]. Vasodilatory effects of ghrelin on arteries are induced by the antagonistic action of ghrelin on the vasoconstrictor effect of endothelin-1 (ET-1). This vasodilatory response is associated with an increase in endothelial nitric oxide synthase production. The imbalance between the vasodilating NO and vasoconstricting ET-1 is solved by synthetic ghrelin administration in humans. The arterial infusion of ghrelin (200 ng/min) in humans mitigated the vasoconstrictive effects of ET-1 and stimulated NO-dependent vasodilation by increasing NO bioavailability [7].

In obese individuals, PVAT also increases in volume and this adipocyte hypertrophy provides less vasoprotective factors and more pro-inflammatory adipokines, such as leptin and resistin, pro-inflammatory cytokines (TNF-α, IL-6, GM-CSF), angiogenic factors (vascular endothelial growth factor—VEGF) and chemokines (RANTES or CCL5, MCP-1 or CCL2). PVAT-derived TNF-α and IL-6 stimulate ROS production and liver synthesis of C-reactive protein (CRP), which reduces NO production by decreasing the expression of eNOS [8].

The increased local inflammation and hypoxia suppress the cardioprotective properties of PVAT. Obese patients with metabolic syndrome (MS) have low levels of circulating ghrelin [9] and a compromised NO bioavailability associated with increased ET-1-mediated vasoconstriction [10]. This makes obese and MS patients a suitable model for investigating the impact of ghrelin on vascular dysfunction.

2. Characteristics of PVAT

Obesity causes the dispersal of a visceral adipose tissue affected by systemic insulin resistance, dyslipidemia, with increased levels of proinflammatory cytokines and modified secretome. PVAT seems to share its origin with vascular smooth muscle cells and not with visceral or subcutaneous adipose tissue. PVAT consists of adipocytes, stromal cells with

pre-adipocytes, fibroblasts, stem cells, inflammatory cells (macrophages, lymphocytes, and eosinophils), nerves, and vascular cells [2]. In rodents, PVAT shows many similarities with brown adipose tissue due to its well-vascularized structure and adipose morphology, whereas in humans PVAT resembles visceral adipose tissue [11]. Extrapolation of rodent studies to humans is frequently deceptive in the research of either adipose tissues or inflammatory responses [12]. Insufficient data on the appearance of PVAT is caused by these disparities between human and animal models. The shortage of human studies on PVAT has been caused by the lack of proper tools, but the advance of imaging techniques has already begun to change that [11].

The inflammation caused by obesity changes the appearance of PVAT. As the macrophages of the adipose tissue turn from anti-inflammatory (M2) into pro-inflammatory (M1), the PVAT of obese individuals shows higher levels of M1 polarized macrophages than in lean individuals. Therefore, PVAT has smaller adipocytes and lower levels of intracellular lipid accumulation.

Obesity induces a whitening of brown adipose tissue in some vascular segments, such as thoracic periaortic adipose tissue [2,11]. Aortic coarctation models in rats show a decreased number of adipocyte progenitor cells, with lower adipocyte formation and lipid accumulation. Differences in arterial pressure modify the adipogenic potential and stress relaxation in aortic PVATs [13].

PVAT surrounding different blood vessels has a heterogeneous density and appearance, resembling endothelial cells and smooth muscle cells from different vascular beds. In human coronary arteries, PVAT has diverse-shaped and smaller adipocytes with decreased adipogenic differentiation [14]. In patients with abdominal aortic aneurysm, adipocytes are larger than in healthy individuals [15].

In atherosclerosis, the amount of PVAT correlates directly with the size of atherosclerotic plaque found in the corresponding vascular wall. In coronary artery disease, enlarged PVAT as measured on CT imaging or in post-mortem human coronary artery samples has higher volume near coronary artery segments with an atherosclerotic plaque as compared with no plaque areas. Plaque composition is also relevant for the structural changes of PVAT. Plaque with a lipid core and calcification was shown to be associated with an increased PVAT mass and macrophage infiltration in PVAT [16].

3. The Anti-Inflammatory Role of Ghrelin in Adipose Tissue Macrophage Infiltration in Atherosclerosis

PVAT surrounding arteries may be involved in building up atherosclerotic plaque from outside the artery through infiltration of macrophages and proinflammatory factors. However, the reciprocal may be also true, and atherosclerosis may be the cause of inflammation in PVAT, as an expression of the bidirectional crosstalk between PVAT and the vascular wall. Adipocytokines secreted by PVAT may diffuse into the vascular wall and draw macrophages. The PVAT on the atherosclerotic segments of the aorta has more macrophages as compared to atherosclerosis-free arteries in the same patient. In the epicardial adipose tissue of patients with coronary atherosclerosis, the number of pro-inflammatory M1 macrophages is more pronounced than in controls. The inflammation of PVATs is correlated with adventitial inflammation and atherosclerosis [16]. In coronary artery disease (CAD), secretion of adipocytokines is higher in PVAT near non-stenotic than near stenotic coronary artery segments in patients undergoing coronary artery bypass graft surgery. PVAT macrophages are associated with atherosclerosis in the adjacent artery, but the anti-inflammatory M2 macrophages are more abundant, which suggests desensitization of the inflammatory response in PVAT in advanced CAD [17]. In perivascular adipocytes, the secretion of the MCP-1/CCL2 protein, with an important role in the pathogenesis of atherosclerosis, is up to 40-fold higher than in perirenal and subcutaneous adipocytes. Again, anti-inflammatory factors, such as adrenomedullin, are also synthesized by PVAT, suggesting a simultaneous protective role for the PVAT on the adjacent vessels [14]. This balance between protective and detrimental effects exerted by PVAT on atherosclerosis could be disturbed by gut-derived antigens such as lipopolysaccharides, dietary lipids,

hypoxia, or mechanical stress, which have a direct impact on inflammation and the accumulation of proinflammatory macrophages in adipose tissues. In vivo animal models have shown that in obesity proinflammatory signaling in perivascular mesenchymal cells has a key role in chronic inflammation of white adipose tissues. TLR4 signaling in perivascular stromal cells mediates proinflammatory macrophage accumulation. Fibro-inflammatory progenitors, a specialized subpopulation of perivascular cells activated during metabolic inflammation, modulate macrophage homeostasis [18].

Ghrelin acts directly on adipocytes to stimulate adipogenesis through preadipocyte differentiation and antagonism of isoproterenol-induced lipolysis. The expression of ghrelin receptors in adipocytes is upregulated during preadipocyte differentiation [19]. Ghrelin stimulates angiogenesis in the adipose tissue by inhibiting bone morphogenic protein-4 (BMP-4), which regulates adipogenic cell precursors differentiation, bone morphogenic protein-7 (BMP-7), involved in the formation of brown adipose tissue, and VEGF [20]. Ghrelin inhibits sympathetic efferents to brown adipose tissue and impairs the intracellular breakdown of triglycerides into free fatty acids [21], leading to weight gain. Although ghrelin acts as a neurotransmitter that modulates sympathetic activity to white and brown adipose tissue, its role on lipid synthesis and mobilization and adipokine release in PVAT requires further investigation.

Lipid storage promotes vascular inflammation. However, high ghrelin levels improve outcomes in early atherosclerosis [22,23]. This anti-atherosclerotic effect is attributed to a balance between macrophage cholesterol uptake and efflux regulated by ghrelin and its GHS-R1a receptor. Ghrelin stimulates the expression of the adipogenic transcription factor peroxisome proliferator-activated receptor gamma (PPARγ) from adipocytes, which is associated with enhanced cholesterol efflux by macrophages and lower risk of atherosclerotic lesions [24].

Ghrelin protects against atherosclerosis by inhibiting the GRP78/CHOP/caspase-12 signaling pathway which involves endoplasmic reticulum stress-related proteins [25,26]. Gut microbiome products, such as trimethylamine-N-oxide are involved in atherogenesis. Ghrelin shows inverse correlations with trimethylamine N-oxide [27]. The atherosclerotic process may be accelerated by endothelial cell apoptosis which causes deposition of lipids and fibrous elements on the arterial wall [28]. The inhibition of hyperglycemia-induced apoptosis in endothelial cells and vascular smooth muscle cells (VSMC) is mediated by GHS-R1a receptors. Ghrelin directly inhibits VSMC apoptosis and proliferation by activation of the cAMP/PKA pathway [29]. The stimulation of intracellular signaling pathways that inhibit apoptosis is achieved by phosphorylation and activation of ERK1/2 and PI3K/Akt [30–33]. The inhibition of plaque angiogenesis caused by oxidized low-density lipoprotein is also mediated by GHS-R1a receptors. FGF-2, a modulator of angiogenesis that mediates atherosclerotic neovascularization, is inhibited by ghrelin in vitro and in vivo. Ghrelin inhibits hypoxia-induced changes in myocardial and pulmonary angiogenesis by decreasing protein HIF-1a and VEGF, a pro-angiogenic and antiapoptotic growth factor, in the cardiac and lung tissues [34,35]. Ghrelin helps improve endothelial function and inhibits endothelial injury by increasing NO bioactivity through the activation of endothelial nitric oxide synthase (eNOS) [9].

Obesity causes the dispersal of a visceral adipose tissue affected by systemic insulin resistance, dyslipidemia, with increased levels of proinflammatory cytokines and modified secretome. PVAT seems to share its origin with vascular smooth muscle cells and not with visceral or subcutaneous adipose tissue. PVAT consists of adipocytes whose appearance differs between healthy and diseased blood vessels, the latter being enlarged [9].

4. The Role of Ghrelin in Inhibiting Proinflammatory Adipokine Secretion

Ghrelin, the appetite-inducing hormone counteracts the effects of leptin, an adipokine regulating satiety. Ghrelin and leptin receptors are co-expressed in more than 90% of the neurons modulating their activity [36]. Ghrelin levels decrease under prolonged exposure to leptin, as is the case in obese individuals, except for obesity in Prader–Willi syndrome, with

high ghrelin levels. Leptin induces ghrelin resistance. Ghrelin gene expression is reduced when leptin and IL-1β are administered [37]. Leptin suppresses ghrelin secretion by gastric cells and the expression of ghrelin receptors in the neuropeptide Y system (NPY) involved in the sympathetic nervous system-induced adipose tissue growth and vasoconstriction [38]. However, ghrelin inhibits the leptin-induced release of pro-inflammatory cytokines by increasing prostacyclin production from endothelial cells [39].

Pro-inflammatory cytokines IL-1β, IL-6, and TNF-α were shown to suppress appetite, especially in anxiety and stress [40], which may suggest an inhibiting effect on ghrelin. The anti-inflammatory effect of ghrelin on adipose tissue is achieved by inhibiting the TNF-α induced activation of caspases and apoptosis. Ghrelin limits the expression of autophagy-related genes [41]. An anti-inflammatory role of ghrelin in atherosclerosis is suggested by an increase in lipid infiltration, the expression of $CD4^+$ T cells, MAC-3 macrophage antigens, and VCAM-1 and ICAM-1 adhesion molecules in aortic arches of ghrelin receptor knockout mice [42]. The effects of ghrelin are summarized in Table 1.

Table 1. Actions of ghrelin related to adipose tissues, endothelium, and atherosclerosis.

Determining Factors	Action	References
Adipose tissue	Increases the production of adiponectin, decreases the production of leptin and resistin. Stimulates adipogenesis by reducing fat oxidation, increases food intake, and stimulates preadipocyte differentiation	Choi et al., 2003 [19] Yasuda et al., 2003 [21] Lelis et al., 2019 [20]
Adipose tissue inflammatory cells	Inhibits leptin-induced cytokine expression.	Dixit et al., 2004 [37] Perpetuo et al., 2021 [38]
Endothelium	Promotes endothelial cell proliferation, inhibits endothelial cell apoptosis and increases the expression of eNOS in arterial endothelial cells.	Tesauro et al., 2005 [9] Mengozzi et al., 2020 [8]
Atherosclerosis	Inhibits overproduction of inflammatory cytokines (IL-1, IL-6, IL-8, and TNF-α), suppresses MCP-1 and the NF-κB pathway and decreases the expression of Cox-2 in endothelial cells.	Bedendi et al., 2003 [39] Shu et al., 2013 [43] Ai et al., 2017 [25] Yang et al., 2020 [26] Virdis et al., 2016 [44]

5. Leukocyte–Endothelial Cell–Platelet Interaction

In the leukocyte-platelet aggregates which characterize atherosclerosis, platelets recruit and activate leukocytes. For their part, leukocytes act on the hemostatic system by activating platelets through immuno-thrombosis, contributing to either pro-inflammatory (cytokine and chemokine release, reactive oxygen production, and lymphocyte development) or anti-inflammatory effects (inhibited monocyte recruitment and cytokine or chemokine production via platelet receptor glycoprotein Ibα and sCD40L). Platelets are involved in plaque rupture and atherothrombosis in an attempt to preserve blood vessel integrity. By recruiting immune cells, platelets accelerate the atherosclerotic process [45,46]. Moreover, the interactions with the vascular wall are also suspected to impair leukocyte recruitment by platelets, as platelets may interact directly with endothelial cells in atherosclerosis, under the influence of cytokines [47]. In healthy non-obese individuals, ghrelin was shown to exert no effects on either platelets or endothelial cells [48]. Later studies have shown that ghrelin can inhibit platelet aggregation. Its antithrombotic effects were shown by the protective effects of ghrelin pre-treatment on liver coagulation disturbances in rats and by ghrelin involvement in the inhibition of MCP-1 expression, with indirect decreasing effects on platelet aggregation and adhesion [43,49].

In excessive adipose tissue, chronic inflammation leads to increased platelet volume. Platelets become highly activated and aggregated. In obese adipose tissues of mice, the

interactions between leukocytes and endothelial cells are higher than in lean mice and the platelets are hyperactivated [50].

6. Inflammation and Oxidative Stress in PVAT. The Role of Ghrelin in Vasoreactivity

PVAT influences vasodilation and vasocontraction and regulates vascular tone and diameter. PVAT-derived ROS can directly inhibit smooth muscle cell contractions by activating the receptor of NO, soluble guanylyl cyclase. Hydrogen peroxide release is another mechanism of PVAT-induced anticontractile vascular effects [51]. Healthy perivascular adipocytes inhibit vasoconstriction by activating the potassium channels in smooth muscle cells through the adipocyte-derived relaxing factor (ADRF). However, the vasodilatory effect of PVAT is mostly present in an association of intact endothelium with intact PVAT [14]. In non-obese type 2 diabetes animal models, no relaxing properties of PVAT from rat aortas were found [52].

Ghrelin, a modulator of gastric motility, has kinetic properties which also impact the vascular tone. PVAT modifies the local production of angiotensinogen, which regulates blood pressure [53]. Ghrelin inhibits angiotensin II-induced proliferation and contraction of human aortic smooth muscle cells [54]. Ghrelin inhibits the vasoconstrictor angiotensin-II by increasing the intracellular concentration of cAMP and increasing the bioavailability of NO, which has vasodilatory properties. The decrease in blood pressure may be also mediated by the brain, where ghrelin suppresses sympathetic activity [38]. The vasodilatory effects of ghrelin [55] are confirmed by the finding that low ghrelin levels are associated with increased blood pressure [56]. Ghrelin was found to suppress oxidative stress in hypertensive rats [57]. High levels of ghrelin were associated with hypertension only in obese women [38]. Ghrelin inhibits a major source of intravascular ROS formation, the isoform cyclooxygenase-2 (COX-2) found in hypertensive patients [30].

Ghrelin secretion declines with age [58] and aging is a major risk factor for atherosclerosis. The decreased levels of ghrelin are aggravated by MS, as obese and diabetic individuals are known to have low levels of ghrelin [59,60]. The increase in adipose tissue mass has major implications on the characteristics of PVAT, with detrimental effects on vascular health. Due to its cardiovascular protective effects, ghrelin could compensate for these vascular dysfunctions. However, various ghrelin polymorphisms, such as Leu72Met, indicate an increased risk of coronary artery disease [33]. Moreover, despite its orexigenic effect, circulating ghrelin levels decline in obesity, diabetes, and MS, but this decrease applies to des-acyl ghrelin concentrations, the most abundant form of ghrelin, whereas acylated ghrelin remains unchanged or increases [41].

7. Conclusions

The present study collated the protective and detrimental effects of PVAT and ghrelin in inflammation and atherosclerosis and showed that ghrelin could also have an important role in vascular fat accumulation and pathophysiology. Extensive research has been conducted on the role of ghrelin in vascular and adipose tissues. The effect of ghrelin on PVAT remains poorly understood and should be further investigated. The two isoforms of circulating ghrelin, acylated and des-acylated ghrelin should be analyzed independently, due to their distinct role in atherosclerosis protection and adipose tissue remodeling.

Author Contributions: Conceptualization, S.N.P. and V.M.; Conducted the systematic literature search, S.N.P., F.A., I.S.C.-S., writing—original draft preparation, S.N.P., B.M.M., A.V. and T.O.; writing—review and editing, R.F.P., L.V., B.T., D.T. and V.M. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by a project funded by the RO-MD Cross-Border Program, Priority 4.1—"Support to the development of health services and access to health", project code: 1HARD/4.1/93.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Balakumar, P.; Alqahtani, A.; Khan, N.A.; Alqahtani, T.; Jagadeesh, G. The physiologic and physiopathologic roles of perivascular adipose tissue and its interactions with blood vessels and the renin-angiotensin system. *Pharmacol. Res.* **2021**, *173*, 105890. [CrossRef] [PubMed]
2. Queiroz, M.; Sena, C.M. Perivascular adipose tissue in age-related vascular disease. *Ageing Res. Rev.* **2020**, *59*, 101040. [CrossRef] [PubMed]
3. Weigle, D.S.; Cummings, D.E.; Newby, P.D.; Breen, P.A.; Frayo, R.S.; Matthys, C.C.; Callahan, H.S.; Purnell, J.Q. Roles of leptin and ghrelin in the loss of body weight caused by a low fat, high carbohydrate diet. *J. Clin. Endocrinol. Metab.* **2003**, *88*, 1577–1586. [CrossRef]
4. Davies, J.S.; Kotokorpi, P.; Eccles, S.R.; Barnes, S.K.; Tokarczuk, P.F.; Allen, S.K.; Whitworth, H.S.; Guschina, I.A.; Evans, B.A.; Mode, A.; et al. Ghrelin induces abdominal obesity via GHS-R-dependent lipid retention. *Mol. Endocrinol.* **2009**, *23*, 914–924. [CrossRef] [PubMed]
5. Papotti, M.; Ghe, C.; Cassoni, P.; Catapano, F.; Deghenghi, R.; Ghigo, E.; Muccioli, G. Growth hormone secretagogue binding sites in peripheral human tissues. *J. Clin. Endocrinol. Metab.* **2000**, *85*, 3803–3807. [CrossRef]
6. Kleinz, M.J.; Maguire, J.J.; Skepper, J.N.; Davenport, A.P. Functional and immunocytochemical evidence for a role of ghrelin and des-octanoyl ghrelin in the regulation of vascular tone in man. *Cardiovasc. Res.* **2006**, *69*, 227–235. [CrossRef]
7. Tesauro, M.; Schinzari, F.; Rovella, V.; Di Daniele, N.; Lauro, D.; Mores, N.; Veneziani, A.; Cardillo, C. Ghrelin restores the endothelin 1/nitric oxide balance in patients with obesity-related metabolic syndrome. *Hypertension* **2009**, *54*, 995–1000. [CrossRef]
8. Mengozzi, A.; Masi, S.; Virdis, A. Obesity-Related Endothelial Dysfunction: Moving from classical to emerging mechanisms. *Endocr. Metab. Sci.* **2020**, *1*, 100063.
9. Tesauro, M.; Schinzari, F.; Iantorno, M.; Rizza, S.; Melina, D.; Lauro, D.; Cardillo, C. Ghrelin improves endothelial function in patients with metabolic syndrome. *Circulation* **2005**, *112*, 2986–2992. [CrossRef]
10. Cardillo, C.; Kilcoyne, C.M.; Cannon, R.O., 3rd; Panza, J.A. Interactions between nitric oxide and endothelin in the regulation of vascular tone of human resistance vessels in vivo. *Hypertension* **2000**, *35*, 1237–1241. [CrossRef]
11. Antonopoulos, A.S.; Papanikolaou, P.; Tousoulis, D. The role of perivascular adipose tissue in microvascular function and coronary atherosclerosis. In *Microcirculation: From Bench to Bedside*; Dorobantu, M., Badimon, L., Eds.; Springer International Publishing: Cham, Switzerland, 2020; pp. 77–94. [CrossRef]
12. Acosta, J.R.; Tavira, B.; Douagi, I.; Kulyte, A.; Arner, P.; Ryden, M.; Laurencikiene, J. Human-Specific Function of IL-10 in Adipose Tissue Linked to Insulin Resistance. *J. Clin. Endocrinol. Metab.* **2019**, *104*, 4552–4562. [CrossRef] [PubMed]
13. Contreras, G.A.; Yang, Y.; Flood, E.D.; Garver, H.; Bhattacharya, S.; Fink, G.D.; Watts, S.W. Blood pressure changes PVAT function and transcriptome: Use of the mid-thoracic aorta coarcted rat. *Am. J. Physiol. Heart Circ. Physiol.* **2020**, *319*, H1313–H1324. [CrossRef] [PubMed]
14. Rajsheker, S.; Manka, D.; Blomkalns, A.L.; Chatterjee, T.K.; Stoll, L.L.; Weintraub, N.L. Crosstalk between perivascular adipose tissue and blood vessels. *Curr. Opin. Pharmacol.* **2010**, *10*, 191–196. [CrossRef] [PubMed]
15. Malka, K.T.; Clum, P.; Tero, B.; Huang, C.; Vary, C.; Liaw, L. Perivascular Adipose Tissue Surrounding Healthy and Diseased Human Aorta Represent Two Distinct Populations of Adipocytes. *J. Vasc. Surg.* **2021**, *74*, e325–e326.
16. Verhagen, S.N.; Vink, A.; van der Graaf, Y.; Visseren, F.L. Coronary perivascular adipose tissue characteristics are related to atherosclerotic plaque size and composition. A post-mortem study. *Atherosclerosis* **2012**, *225*, 99–104. [CrossRef]
17. Verhagen, S.N.; Buijsrogge, M.P.; Vink, A.; van Herwerden, L.A.; van der Graaf, Y.; Visseren, F.L. Secretion of adipocytokines by perivascular adipose tissue near stenotic and non-stenotic coronary artery segments in patients undergoing CABG. *Atherosclerosis* **2014**, *233*, 242–247. [CrossRef]
18. Shan, B.; Shao, M.; Zhang, Q.; Hepler, C.; Paschoal, V.A.; Barnes, S.D.; Vishvanath, L.; An, Y.A.; Jia, L.; Malladi, V.S.; et al. Perivascular mesenchymal cells control adipose-tissue macrophage accrual in obesity. *Nat. Metab.* **2020**, *2*, 1332–1349. [CrossRef]
19. Choi, K.; Roh, S.G.; Hong, Y.H.; Shrestha, Y.B.; Hishikawa, D.; Chen, C.; Kojima, M.; Kangawa, K.; Sasaki, S. The role of ghrelin and growth hormone secretagogues receptor on rat adipogenesis. *Endocrinology* **2003**, *144*, 754–759. [CrossRef]
20. Lelis, D.F.; Freitas, D.F.; Machado, A.S.; Crespo, T.S.; Santos, S.H.S. Angiotensin-(1–7), Adipokines and Inflammation. *Metabolism* **2019**, *95*, 36–45. [CrossRef]
21. Yasuda, T.; Masaki, T.; Kakuma, T.; Yoshimatsu, H. Centrally administered ghrelin suppresses sympathetic nerve activity in brown adipose tissue of rats. *Neurosci. Lett.* **2003**, *349*, 75–78. [CrossRef]
22. Ukkola, O. Ghrelin and atherosclerosis. *Curr. Opin. Lipidol.* **2015**, *26*, 288–291. [CrossRef] [PubMed]
23. Achike, F.I.; To, N.H.; Wang, H.; Kwan, C.Y. Obesity, metabolic syndrome, adipocytes and vascular function: A holistic viewpoint. *Clin. Exp. Pharmacol. Physiol.* **2011**, *38*, 1–10. [CrossRef] [PubMed]
24. Avallone, R.; Demers, A.; Rodrigue-Way, A.; Bujold, K.; Harb, D.; Anghel, S.; Wahli, W.; Marleau, S.; Ong, H.; Tremblay, A. A growth hormone-releasing peptide that binds scavenger receptor CD36 and ghrelin receptor up-regulates sterol transporters and cholesterol efflux in macrophages through a peroxisome proliferator-activated receptor gamma-dependent pathway. *Mol. Endocrinol.* **2006**, *20*, 3165–3178. [CrossRef] [PubMed]
25. Ai, W.; Wu, M.; Chen, L.; Jiang, B.; Mu, M.; Liu, L.; Yuan, Z. Ghrelin ameliorates atherosclerosis by inhibiting endoplasmic reticulum stress. *Fundam. Clin. Pharmacol.* **2017**, *31*, 147–154. [CrossRef] [PubMed]

26. Yang, Y.; Zhou, Q.; Gao, A.; Chen, L.; Li, L. Endoplasmic reticulum stress and focused drug discovery in cardiovascular disease. *Clin. Chim. Acta* **2020**, *504*, 125–137. [CrossRef] [PubMed]
27. Ringel, C.; Dittrich, J.; Gaudl, A.; Schellong, P.; Beuchel, C.F.; Baber, R.; Beutner, F.; Teren, A.; Engel, C.; Wirkner, K.; et al. Association of plasma trimethylamine N-oxide levels with atherosclerotic cardiovascular disease and factors of the metabolic syndrome. *Atherosclerosis* **2021**, *335*, 62–67. [CrossRef]
28. Lin, X.; Ouyang, S.; Zhi, C.; Li, P.; Tan, X.; Ma, W.; Yu, J.; Peng, T.; Chen, X.; Li, L.; et al. Focus on ferroptosis, pyroptosis, apoptosis and autophagy of vascular endothelial cells to the strategic targets for the treatment of atherosclerosis. *Arch. Biochem. Biophys.* **2022**, *715*, 109098. [CrossRef]
29. Carbone, F.; Mach, F.; Montecucco, F. The role of adipocytokines in atherogenesis and atheroprogression. *Curr. Drug Targets* **2015**, *16*, 295–320. [CrossRef]
30. Virdis, A.; Lerman, L.O.; Regoli, F.; Ghiadoni, L.; Lerman, A.; Taddei, S. Human Ghrelin: A Gastric Hormone with Cardiovascular Properties. *Curr. Pharm. Des.* **2016**, *22*, 52–58. [CrossRef]
31. Zhang, M.; Wang, S.; Pan, Z.; Ou, T.; Ma, J.; Liu, H.; Li, R.; Yang, P.; Han, W.; Guan, S.; et al. AMPK/NF-kappaB signaling pathway regulated by ghrelin participates in the regulation of HUVEC and THP1 Inflammation. *Mol. Cell. Biochem.* **2018**, *437*, 45–53. [CrossRef]
32. Yuan, M.J.; Li, W.; Zhong, P. Research progress of ghrelin on cardiovascular disease. *Biosci. Rep.* **2021**, *41*, BSR20203387. [CrossRef] [PubMed]
33. Lilleness, B.M.; Frishman, W.H. Ghrelin and the Cardiovascular System. *Cardiol. Rev.* **2016**, *24*, 288–297. [CrossRef] [PubMed]
34. Conconi, M.T.; Nico, B.; Guidolin, D.; Baiguera, S.; Spinazzi, R.; Rebuffat, P.; Malendowicz, L.K.; Vacca, A.; Carraro, G.; Parnigotto, P.P.; et al. Ghrelin inhibits FGF-2-mediated angiogenesis in vitro and in vivo. *Peptides* **2004**, *25*, 2179–2185. [CrossRef] [PubMed]
35. Mirzaei Bavil, F.; Karimi-Sales, E.; Alihemmati, A.; Alipour, M.R. Effect of ghrelin on hypoxia-related cardiac angiogenesis: Involvement of miR-210 signalling pathway. *Arch. Physiol. Biochem.* **2022**, *128*, 270–275. [CrossRef] [PubMed]
36. Cui, H.; Lopez, M.; Rahmouni, K. The cellular and molecular bases of leptin and ghrelin resistance in obesity. *Nat. Rev. Endocrinol.* **2017**, *13*, 338–351. [CrossRef]
37. Dixit, V.D.; Schaffer, E.M.; Pyle, R.S.; Collins, G.D.; Sakthivel, S.K.; Palaniappan, R.; Lillard, J.W., Jr.; Taub, D.D. Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. *J. Clin. Investig.* **2004**, *114*, 57–66. [CrossRef]
38. Perpetuo, L.; Voisin, P.M.; Amado, F.; Hirtz, C.; Vitorino, R. Ghrelin and adipokines: An overview of their physiological role, antimicrobial activity and impact on cardiovascular conditions. *Vitam. Horm.* **2021**, *115*, 477–509.
39. Bedendi, I.; Alloatti, G.; Marcantoni, A.; Malan, D.; Catapano, F.; Ghe, C.; Deghenghi, R.; Ghigo, E.; Muccioli, G. Cardiac effects of ghrelin and its endogenous derivatives des-octanoyl ghrelin and des-Gln14-ghrelin. *Eur. J. Pharmacol.* **2003**, *476*, 87–95. [CrossRef]
40. Yu, Y.; Fernandez, I.D.; Meng, Y.; Zhao, W.; Groth, S.W. Gut hormones, adipokines, and pro- and anti-inflammatory cytokines/markers in loss of control eating: A scoping review. *Appetite* **2021**, *166*, 105442. [CrossRef]
41. Rodriguez, A. Novel molecular aspects of ghrelin and leptin in the control of adipobiology and the cardiovascular system. *Obes. Facts* **2014**, *7*, 82–95. [CrossRef]
42. Zhang, M.; Qu, X.; Yuan, F.; Yang, Y.; Xu, L.; Dai, J.; Wang, W.; Fei, J.; Hou, X.; Fang, W. Ghrelin receptor deficiency aggravates atherosclerotic plaque instability. *Front. Biosci.* **2015**, *20*, 604–613. [CrossRef]
43. Shu, Z.W.; Yu, M.; Chen, X.J.; Tan, X.R. Ghrelin could be a candidate for the prevention of in-stent restenosis. *Cardiovasc. Drugs Ther.* **2013**, *27*, 309–314. [PubMed]
44. Virdis, A.; Taddei, S. Endothelial Dysfunction in Resistance Arteries of Hypertensive Humans: Old and New Conspirators. *J. Cardiovasc. Pharmacol.* **2016**, *67*, 451–457. [CrossRef] [PubMed]
45. Schrottmaier, W.C.; Mussbacher, M.; Salzmann, M.; Assinger, A. Platelet-leukocyte interplay during vascular disease. *Atherosclerosis* **2020**, *307*, 109–120. [CrossRef] [PubMed]
46. Wang, L.; Tang, C. Targeting Platelet in Atherosclerosis Plaque Formation: Current Knowledge and Future Perspectives. *Int. J. Mol. Sci.* **2020**, *21*, 9760. [CrossRef]
47. Ed Rainger, G.; Chimen, M.; Harrison, M.J.; Yates, C.M.; Harrison, P.; Watson, S.P.; Lordkipanidze, M.; Nash, G.B. The role of platelets in the recruitment of leukocytes during vascular disease. *Platelets* **2015**, *26*, 507–520. [CrossRef]
48. Elbatarny, H.S.; Netherton, S.J.; Ovens, J.D.; Ferguson, A.V.; Maurice, D.H. Adiponectin, ghrelin, and leptin differentially influence human platelet and human vascular endothelial cell functions: Implication in obesity-associated cardiovascular diseases. *Eur. J. Pharmacol.* **2007**, *558*, 7–13. [CrossRef]
49. Arici, O.F.; Cetin, N. Protective role of ghrelin against carbon tetrachloride (CCl(4))-induced coagulation disturbances in rats. *Regul. Pept.* **2011**, *166*, 139–142. [CrossRef]
50. Nishimura, S.; Manabe, I.; Nagasaki, M.; Seo, K.; Yamashita, H.; Hosoya, Y.; Ohsugi, M.; Tobe, K.; Kadowaki, T.; Nagai, R.; et al. In vivo imaging in mice reveals local cell dynamics and inflammation in obese adipose tissue. *J. Clin. Investig.* **2008**, *118*, 710–721. [CrossRef]
51. Costa, R.M.; Filgueira, F.P.; Tostes, R.C.; Carvalho, M.H.; Akamine, E.H.; Lobato, N.S. H2O2 generated from mitochondrial electron transport chain in thoracic perivascular adipose tissue is crucial for modulation of vascular smooth muscle contraction. *Vasc. Pharmacol.* **2016**, *84*, 28–37. [CrossRef]

52. Azul, L.; Leandro, A.; Boroumand, P.; Klip, A.; Seica, R.; Sena, C.M. Increased inflammation, oxidative stress and a reduction in antioxidant defense enzymes in perivascular adipose tissue contribute to vascular dysfunction in type 2 diabetes. *Free Radic. Biol. Med.* **2020**, *146*, 264–274. [CrossRef] [PubMed]
53. Landecho, M.F.; Tuero, C.; Valenti, V.; Bilbao, I.; de la Higuera, M.; Fruhbeck, G. Relevance of Leptin and Other Adipokines in Obesity-Associated Cardiovascular Risk. *Nutrients* **2019**, *11*, 2664. [CrossRef]
54. Rossi, F.; Castelli, A.; Bianco, M.J.; Bertone, C.; Brama, M.; Santiemma, V. Ghrelin inhibits contraction and proliferation of human aortic smooth muscle cells by cAMP/PKA pathway activation. *Atherosclerosis* **2009**, *203*, 97–104. [CrossRef] [PubMed]
55. Okumura, H.; Nagaya, N.; Enomoto, M.; Nakagawa, E.; Oya, H.; Kangawa, K. Vasodilatory effect of ghrelin, an endogenous peptide from the stomach. *J. Cardiovasc. Pharmacol.* **2002**, *39*, 779–783. [CrossRef]
56. Mao, Y.; Tokudome, T.; Kishimoto, I. Ghrelin and Blood Pressure Regulation. *Curr. Hypertens. Rep.* **2016**, *18*, 15. [CrossRef]
57. Kawczynska-Drozdz, A.; Olszanecki, R.; Jawien, J.; Brzozowski, T.; Pawlik, W.W.; Korbut, R.; Guzik, T.J. Ghrelin inhibits vascular superoxide production in spontaneously hypertensive rats. *Am. J. Hypertens.* **2006**, *19*, 764–767. [CrossRef]
58. Carraro, G.; Albertin, G.; Aragona, F.; Forneris, M.; Casale, V.; Spinazzi, R.; Nussdorfer, G.G. Age-dependent decrease in the ghrelin gene expression in the human adrenal cortex: A real-time PCR study. *Int. J. Mol. Med.* **2006**, *17*, 319–321.
59. Cappellari, G.G.; Semolic, A.; Cremasco, G.; Vinci, P.; Zanetti, M.; Barazzoni, R. Unacylated ghrelin plasma levels are lower and predict 5-year low muscle mass in elderly obese subjects. *Nutrition* **2021**, *87*, 111316.
60. Lindqvist, A.; Shcherbina, L.; Prasad, R.B.; Miskelly, M.G.; Abels, M.; Martinez-Lopez, J.A.; Fred, R.G.; Nergard, B.J.; Hedenbro, J.; Groop, L.; et al. Ghrelin suppresses insulin secretion in human islets and type 2 diabetes patients have diminished islet ghrelin cell number and lower plasma ghrelin levels. *Mol. Cell. Endocrinol.* **2020**, *511*, 110835. [CrossRef]