metabolites

MDPI

Review

Metabolomics of Arterial Stiffness

Kaido Paapstel [1,2,3,*] and Jaak Kals [1,4,5,6]

[1] Endothelial Research Centre, University of Tartu, 8 Puusepa Street, 51014 Tartu, Estonia; jaak.kals@kliinikum.ee
[2] Department of Cardiology, Institute of Clinical Medicine, University of Tartu, 8 Puusepa Street, 51014 Tartu, Estonia
[3] Heart Clinic, Tartu University Hospital, 8 Puusepa Street, 51014 Tartu, Estonia
[4] Department of Surgery, Institute of Clinical Medicine, University of Tartu, 8 Puusepa Street, 51014 Tartu, Estonia
[5] Surgery Clinic, Tartu University Hospital, 8 Puusepa Street, 51014 Tartu, Estonia
[6] Department of Biochemistry, Institute of Biomedicine and Translational Medicine, Centre of Excellence for Genomics and Translational Medicine, University of Tartu, 19 Ravila Street, 50411 Tartu, Estonia
* Correspondence: kaido.paapstel@kliinikum.ee

Abstract: Arterial stiffness (AS) is one of the earliest detectable signs of structural and functional alterations of the vessel wall and an independent predictor of cardiovascular events and death. The emerging field of metabolomics can be utilized to detect a wide spectrum of intermediates and products of metabolism in body fluids that can be involved in the pathogenesis of AS. Research over the past decade has reinforced this idea by linking AS to circulating acylcarnitines, glycerophospholipids, sphingolipids, and amino acids, among other metabolite species. Some of these metabolites influence AS through traditional cardiovascular risk factors (e.g., high blood pressure, high blood cholesterol, diabetes, smoking), while others seem to act independently through both known and unknown pathophysiological mechanisms. We propose the term 'arteriometabolomics' to indicate the research that applies metabolomics methods to study AS. The 'arteriometabolomics' approach has the potential to allow more personalized cardiovascular risk stratification, disease monitoring, and treatment selection. One of its major goals is to uncover the causal metabolic pathways of AS. Such pathways could represent valuable treatment targets in vascular ageing.

Keywords: arterial stiffness; vascular ageing; pulse wave analysis; pulse wave velocity; metabolomics; metabolism; cardiovascular risk

Citation: Paapstel, K.; Kals, J. Metabolomics of Arterial Stiffness. *Metabolites* **2022**, *12*, 370. https://doi.org/10.3390/metabo12050370

Academic Editors: Manfredi Rizzo, Zlatko Fras, Borut Jug and Peter E. Penson

Received: 23 March 2022
Accepted: 18 April 2022
Published: 20 April 2022

1. Introduction

Blood pressure (BP), traditional blood lipid biomarkers (i.e., total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), and glucose are widely used in everyday clinical practice for cardiovascular (CV) risk assessment. Unfortunately, the classical biomarkers can only partially explain the distribution of CV risk in the general population. Many metabolic, inflammatory, and hemodynamic drivers of the residual CV risk are thus missed, and a more tailored approach to CV risk stratification is clearly needed. Currently, doctors may be misled by normal cholesterol and glucose blood levels when assessing CV risk in patients whose CV health can also be affected by quite different metabolite species. Prehypertensive patients with increased arterial stiffness (AS) may be unfairly withheld from antihypertensive treatment, and those with excellent vascular function may be overtreated. To overcome these clinical uncertainties, more randomized controlled trials (RCTs) looking beyond traditional CV risk factors are needed.

Recent large-scale RCTs have partially addressed residual inflammatory CV risk by targeting tubuline polymerization [1,2] and neutralizing interleukin-1β [3] and interleukin-6 [4]. Novel NOD-like receptor protein 3 inflammasome inhibitors are being developed with the

aim of further limiting the detrimental effects of inflammation [5]. Similar developments are needed to reduce residual metabolic CV risk (risk despite optimal blood glucose and cholesterol control) and residual hemodynamic CV risk (risk despite optimal peripheral BP control). First steps have been taken with the recent SPARTE study, which demonstrated that the AS-driven hypertension treatment strategy can better prevent vascular ageing compared with guideline-based BP control alone [6]. Unfortunately, as the trial lacked sufficient statistical power to demonstrate greater reduction in CV events, it should be replicated with a larger number of patients.

To date, residual metabolic CV risk has been addressed mainly in observational and laboratory research. These studies have often implemented metabolomics, which is an emerging analytical profiling technique [7–9]. An increasing number of metabolomics studies link AS to different low-molecular weight metabolite (LMWM) species. The current narrative review aims to provide an overview of existing literature on the relationship between LMWMs and AS. We discuss the current state and future perspectives of this research field. Both targeted and untargeted studies were included. We also propose the novel term 'arteriometabolomics' to indicate the research that applies metabolomics methods for studying AS.

2. Arterial Stiffness and Its Prognostic Value

AS describes the rigidity of the arterial wall, i.e., the capability of an artery to expand and contract in response to pressure changes. The pressure load of each heartbeat in large conduit vessels is borne mainly by two extracellular matrix proteins: elastin and collagen. An increase in the collagen/elastin ratio during the ageing process is a classical determinant of AS [10]. Other mechanisms that promote AS include low-grade inflammation [11,12], oxidative stress (OxS) [13], endothelial dysfunction (ED) [11], vascular smooth muscle proliferation and stiffness [14], collagen and elastin cross-linking [15], calcification [16], metabolic alterations [17], genetic mutations, and epigenetic abnormalities [18,19]. Thus, both ageing [20,21] and a number of chronic diseases that are associated with the above mechanisms (e.g., hypertension [22], diabetes [23], chronic kidney disease [24]) are closely linked to AS [25].

AS is an important determinant of target organ damage and an independent CV risk factor. There is strong evidence that aortic stiffness, measured as carotid–femoral pulse wave velocity (cf-PWV), independently predicts CV risk [26,27] and all-cause mortality [28]. Since the waves propagate faster in stiffer vessels than in elastic ones, PWV expresses the time required for an arterial pressure wave to travel between two points in the arterial tree and is one of the simplest and reliable reflectors of AS [29] (Figure 1). Current European guidelines for the management of arterial hypertension state that cf-PWV assessment can help determine asymptomatic organ damage [30].

Another reflector of arterial function is the arterial pressure waveform [31] (Figure 1). It is a composite of the forward pressure wave, created by ventricular contraction, and a reflected wave from vascular branch points or sites of impedance mismatch. In elastic arteries, the reflected wave returns to the central aorta in diastole enhancing coronary perfusion pressure [32]. In stiff arteries, however, the reflected wave returns late in the systole, increases central aortic pressure, and impairs coronary artery perfusion [32]. Reduced buffering capacity of the large arteries also leads to excess pulsatility and organ damage in low-resistance vascular beds [33]. From the aortic waveform, various hemodynamic and arterial function parameters can be calculated. Left ventricular late systolic loading, for example, can be quantified using the augmentation index (AIx), which is defined as the difference between the second and first systolic peaks of the central arterial waveform, expressed as the percentage of central pulse pressure. Although cf-PWV is the 'gold standard' for measuring AS [29], AIx has also shown independent associations with CV events and all-cause mortality [34].

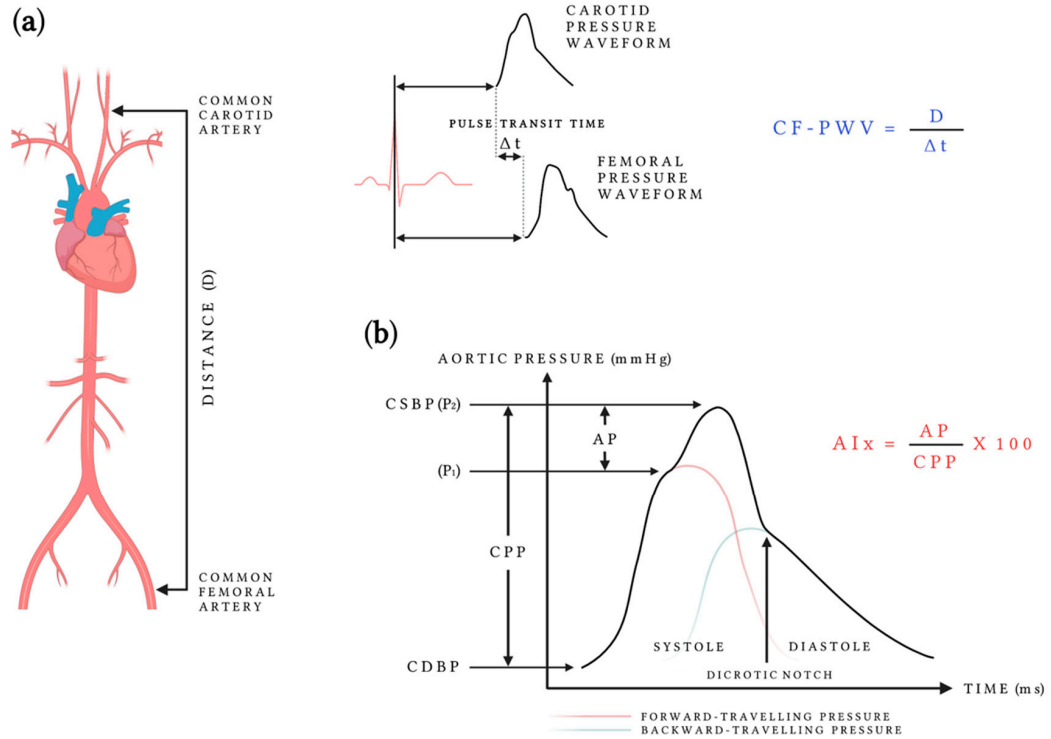

Figure 1. (**a**) Aortic pulse wave velocity measurement with applanation tonometry [28]: pulse transit time is measured from the foot of the carotid pressure waveform to that of the femoral pressure waveform using sequential recordings referenced to the electrocardiogram; the distance between the two recording sites is measured on the body surface and is calculated as the ratio of this distance to the pulse transit time; (**b**) the central aortic waveform is a composite of forward-traveling pressure created by ventricular contraction and backward-traveling pressure reflecting from vascular branch points or sites of impedance mismatch. The phenomenon of left ventricular late-systolic loading can be quantified using Aix—defined as the difference between the second (P2) and first (P1) systolic peaks of the central arterial waveform, expressed as the percentage of CPP [28]. Abbreviations: AIx, augmentation index; AP, augmentation pressure; CDBP, central diastolic blood pressure; cf-PWV, carotid–femoral pulse wave velocity; CPP, central pulse pressure; CSBP, central systolic blood pressure.

The methodologies used to determine AS fall under five categories: (1) devices that use a probe or tonometer to record the pulse wave with a transducer, (2) devices using cuffs placed around the limbs or the neck, which record the arrival of the pulse wave oscillometrically, (3) ultrasonography approaches, (4) magnetic-resonance-imaging-based approaches, and (5) invasive measurements with pressure catheters. These methods differ in their applicability, strengths, and limitations, which have been addressed in detail in previous reviews [35,36].

To date, AS assessment has primarily been used for research purposes. Although the independent prognostic value of cf-PWV is now overwhelming, it still remains to be proven whether its measurement truly facilitates clinical decisions. More large-scale trials comparing clinical approaches with and without cf-PWV monitoring are needed. Development of pharmacological agents that directly target AS would also help to pave its way into clinical practice. Current therapeutic options that ameliorate AS include antihypertensives (renin–angiotensin–aldosterone system (RAAS) inhibitors [37], calcium channel blockers [38]), statins [39], and antidiabetic agents [40,41] along with non-pharmacological interventions such as weight loss [42], exercise [42], low salt diet [43], and smoking cessation [44].

3. Brief Overview of Metabolomics

Metabolomics is a field of science that combines high-throughput analytical techniques with bioinformatics and focuses on chemical processes involving LMWMs (<1500 Da), including amino acids (AAs), peptides, lipids, carbohydrates, and nucleic and fatty acids (FAs). It reflects changes in the genome, transcriptome, and proteome and thus represents the endpoint of the 'omics' cascade [45,46]. The complete collection of LMWMs found in a given organelle, cell, organ, biofluid, or organism is defined as the metabolome. LMWMs in the metabolome are either of endogenous (genetics) or exogenous (nutrition, medication, environment) origin. The endogenous metabolome is highly conserved and represents similar LMWMs, although at different concentrations, across species. The exogenous metabolome, however, is highly variable, reflecting dietary and environmental factors, as well as microbiome composition. Both types of LMWMs can serve as indicators of normal and pathological processes in the organism [45].

Two distinct approaches, targeted and untargeted metabolomics, can be followed to analyze a set of LMWMs in biofluids or tissues. The aim of the targeted approach is to quantify only a preselected set of known LMWMs based on internal or external standards [47]. This approach ensures quantitative accuracy and confidence in LMWM identifications but has a limited reach [47,48]. Untargeted metabolomics, on the other hand, refers to the analysis of all measurable LMWMs in a biological sample but is less accurate in both metabolite identification and quantification [48,49]. There are advantages and disadvantages to both strategies [48], and the choice of approach usually depends on the objectives of the experiment.

To carry out a high-quality metabolomics study, the following steps are usually followed: experimental design, sample collection and extraction, data acquisition, and data analysis and interpretation. Accordingly, (1) a targeted or nontargeted animal or human study is designed; (2) samples of blood, urine, tissue extract, or some other type of biological specimen are collected; (3) mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, or infrared spectroscopy are employed; and (4) uni-, bi-, or multivariate statistical methods, or a combination of these are used. The two most common analytical platforms for data acquisition and processing in metabolomics are MS and NMR spectroscopy [50]. The NMR approach [51] offers fast LMWM quantification with little sample preparation and very high analytic reproducibility but detects a smaller number of metabolites and requires larger samples compared to MS due to lower sensitivity. The MS approach [52] is often coupled with chromatographic techniques (liquid chromatography, gas chromatography) or with capillary electrophoresis and requires ionization of the analyte before it can be detected. These methods are more time consuming than NRM spectroscopy but are also more sensitive and can identify a wider range of metabolites. Eventually, both types of techniques can provide large-scale and complex datasets on which multivariate statistical analysis (e.g., principal component analysis (PCA), partial least squares regression) and metabolomic pathway analysis are performed to discover hidden patterns and to extract biologically relevant information (e.g., disease-associated metabolic pathways) [53–55].

Because of the inherent sensitivity to even subtle changes in the actual phenotype, metabolomics is steadily gaining popularity in different areas of medical research. Altered lipid metabolism in CV disease (CVD), in particular, has been the focus of a number of recent studies [8,56]. Metabolomic profiling seems to improve both the risk stratification and early identification of CVD. It also holds promise for an enhanced understanding of pathophysiological processes (e.g., arterial stiffening) that lead to disorders of the heart and blood vessels.

4. 'Arteriometabolomics' Approach

'Arteriometabolomics' involves identification and quantification of thousands of LMWMs, metabolic pathways, and their interactions with arterial structural and functional parameters. Current CV risk assessment relies on traditional risk markers (including

peripheral BP, blood lipoproteins), but analytical metabolomics methods and AS assessment offer an opportunity to further interrogate the human metabolome and vascular system (Figure 2). The linkage between the arteries and metabolomics can be studied at different levels of the organism—from vascular smooth muscle cell stiffness and metabolism to systemic AS and circulating metabolites. Discoveries made at one level can inspire searches at another. A detailed insight into the roles of individual LMWM species in AS could elucidate the pathophysiology of vascular ageing and lead to novel CV risk markers and potential treatment targets. To date, AS has been associated with numerous LMWMs among which lipids, with an extraordinary diversity in their structure, emerge the most.

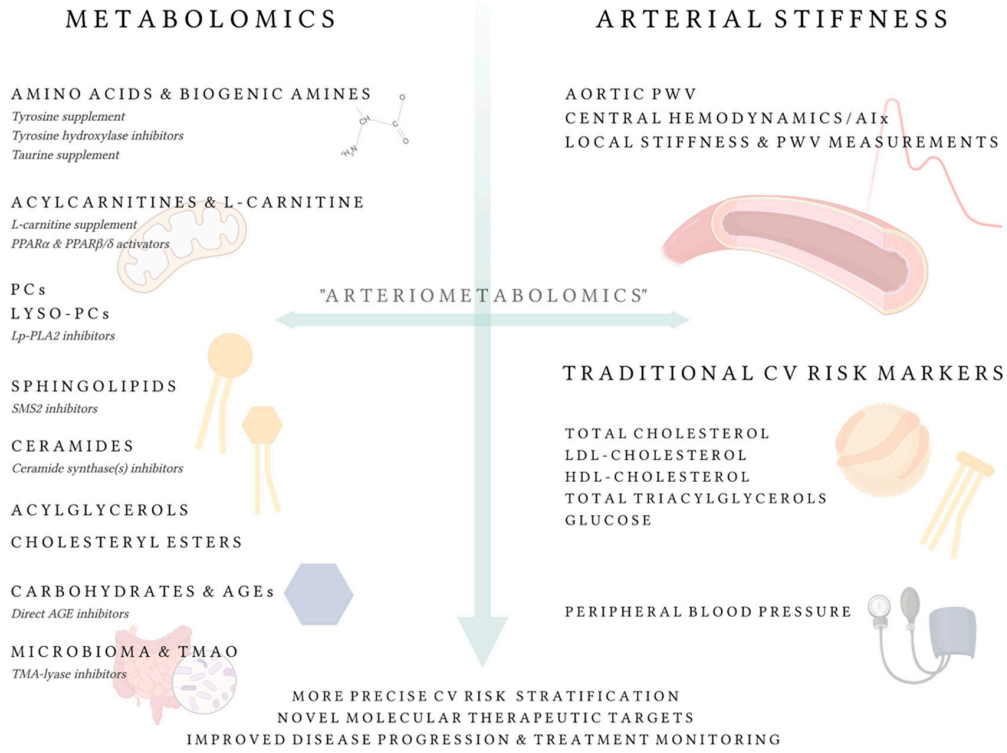

Figure 2. 'Arteriometabolomics'—the crossroad of metabolomics and arterial stiffness research. Metabolites or groups of metabolites that have been associated with arterial stiffness are listed on the left. Metabolism-related compounds that deserve further preclinical/clinical study as potential therapeutics against vascular ageing are displayed in italics. Abbreviations: AGE, advanced glycation end-product; CV, cardiovascular; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp-PLA2, lipoprotein-associated phospholipase A2; lyso-PC, lysophosphatidylcholine; PC, phosphatidylcholine; PPAR, peroxisome proliferator-activated receptor; PWV, pulse wave velocity; SMS2, sphingomyelin synthase 2; TMA, trimethylamine; TMAO, trimethylamine N-oxide.

4.1. Linkage between Low-Molecular Weight Metabolites and Vascular Research: Current State

4.1.1. L-Carnitine, Trimethylamine N-Oxide, and Acylcarnitines

L-carnitine is an endogenous vitamin-like molecule involved in lipid metabolism, synthesized in vivo (from essential AAs lysine and methionine (Met)) and supplemented by diet (e.g., red meat, poultry, dairy) [57]. When carnitine conjugates with long-chain fatty acyl-coenzyme-As (CoAs) on the outer mitochondrial membrane, acylcarnitines (ACs) are formed. Such formation is required in order to transport activated long-chain FAs (>C10) across the inner mitochondrial membrane. Once inside the mitochondrial matrix, AC reconjugates with a CoA molecule after which reformed acyl-CoA undergoes β-oxidation to produce energy. In the case of carnitine deficiency, FA oxidation is impaired [58]. Primary carnitine deficiency is a potentially lethal genetic disorder that causes muscle weakness, myopathy, hypoglycemia, and liver dysfunction [59]. Secondary carnitine deficiency, on

the other hand, can result from a decrease in carnitine intake or from an increase in renal excretion and is clinically less pronounced [59].

Subclinical vascular effects of carnitine deficiency and supplementation have been previously studied. Carnitine attenuates free FA-induced ED and modulates platelet activation by limiting the production of endogenous reactive oxygen species (ROS) [60]. Studies in chronic kidney disease patients associate lower circulating levels of carnitine with AS [61,62]. Whether the relationship between carnitine and AS is causal (e.g., through increasing long-chain FA β-oxidation and reducing insulin resistance [63]) is not clear. An ongoing RCT (ClinicalTrials.gov ID: NCT04128969) in adolescents aims to answer this question by measuring the effects of oral carnitine supplementation on cf-PWV, as well as by using the Mendelian randomization technique [64].

Interestingly, L-carnitine supplementation may increase the blood levels of a gut microbe-dependent metabolite trimethylamine N-oxide (TMAO) [65]. Dietary L-carnitine, choline, and betaine have been previously shown to be metabolized by gut microbes to trimethylamine (TMA), which is then carried via the portal circulation to the liver and converted into TMAO [65–67]. Several studies indicate that TMAO independently predicts future CVD [68,69] and may promote atherogenesis by affecting cholesterol homeostasis [70] and promoting vascular inflammation [71]. In a recent experimental study by Brunt et al. in mice and humans, TMAO was reported to promote aortic stiffening and age-related ED via superoxide-driven OxS [72]. The authors suggested that TMAO-targeted treatment strategies (e.g., TMA lyase inhibitor 3,3-dimethyl-1-butanol) could have the potential to be effective for vascular ageing [72,73]. In an earlier study in mice by Brunt et al., gut microbiota suppression with antibiotics reversed ED and AS and attenuated vascular OxS and inflammation [74]. Although these findings are intriguing and may potentially shed light on the hidden impact of the gut microbiota on vascular ageing, a considerable number of studies have called causation between TMAO and CVD into question [75–78]. The microbiome involved in the metabolism of TMAO may play an independent role in disease progression, making TMAO a marker and not an inducer of disease [75]. Further, the amounts of TMA/TMAO or their precursors, which have been frequently used in animal models, exceed the levels present either in a normal diet or in therapeutic supplements [75,79]. The causal role of TMAO in CVD and AS is thus a matter of debate. Besides TMAO, other gut microbiota-derived metabolites (incl. indoxyl sulfate [80,81], *P*-cresyl sulfate [82], phenylacetylglutamine [83], and equol [84]), as well as the composition of the gut microbiota [85–87] have been associated with AS.

Some recent metabolomics studies link AS to higher circulating levels of ACs. Accumulation of ACs has been associated with cellular stress [88], inflammation [89], and IR [90] in various study populations. ACs accumulate when the oxidative metabolism of FAs in mitochondria or peroxisomes is impaired (e.g., oxygen deficiency, mitochondrial inborn errors), or when FA release by adipose tissue triglycerides exceeds the capacity of β-oxidation. Short- and odd-chained ACs usually derive from disrupted branched-chain amino acid (BCAA) catabolism. Higher circulating levels of ACs have been associated with increased AS in patients with type 2 diabetes [91], coronary artery disease (CAD) [92], and osteoarthritis (OA) [93], as well as in elderly adults without CVD [94]. PCA-derived factors, primarily composed of medium- and long-chain ACs, were independent determinants of PWV for CAD patients in a targeted metabolomics study by our group [92], as well as for the elderly in a study by Koh et al. [94]. We also found a positive relationship between activity of carnitine–palmitoyltransferase 1 (CPT-1) and cf-PWV for the patients with CAD [92]. The CPT-1 is the key rate-limiting enzyme for β-oxidation of long-chain FAs, and changes in its activity can promote mitochondrial dysfunction and AC accumulation. In a study by Toral et al., up-regulation of CPT-1 (by peroxisome proliferator-activated receptor β/δ (PPAR-β/δ)) prevented free FA-induced ED in isolated vessels and cultured endothelial cells, as well as in mice fed a high fat diet [95]. In a study by Chang et al., however, aortic stiffening was not attenuated by a CPT-1 inhibitor oxfenicine in streptozotocin-induced diabetic rats [96].

4.1.2. Phospholipids

Phospholipids are amphiphilic molecules that serve mainly as structural components in cellular membranes, lipoproteins, and natural surfactants, among others [97]. They consist of FAs and a phosphate-containing headgroup (e.g., choline, ethanolamine, serine (Ser), inositol) attached to an alcohol residue (e.g., glycerol). Plasma FA composition of plasma lipids has been previously associated with AS. Kim et al. showed correlation between FA composition in serum phospholipids and PWV [98]. Among FA composition, linoleic acid (C18:2) was found to be a major independent determinant of AS. In a study by Anderson et al., a PCA-derived component with higher proportions of arachidonic (C20:4), eicosapentaenoic (EPA, C20:5), and docosahexaenoic (DHA, C22:6) and lower proportions of oleic (C18:1), palmitic (C16:0), and linoleic acid (C18:2) levels was linked to lower PWV and systolic BP [99]. The authors concluded that these effects were likely to be mediated either via endothelial metabolism or altered membrane structural properties across the vascular wall. Likewise, lower proportions of serum phospholipid DHA and red blood cell phospholipid EPA were associated with increased AS in studies by Lee et al. [100] and Nishizawa et al. [101], respectively. In a study by Hall et al., an EPA-enriched high-fat meal improved postprandial vascular function, irrespective of changes in OxS [102].

The most abundant phospholipids in cellular membranes and lipoproteins are phosphatidylcholines (PCs) [103]. If a PC molecule becomes partially hydrolyzed by phospholipase A2 or phospholipase A1, one of the two fatty acids bound to the glycerol backbone is removed, and lysophosphatidylcholine (lysoPC) is generated. The production of lysoPC can also result from lecithin-cholesterol acyltransferase (LCAT) activity [104] or hepatic secretion [105]. While some PC and lysoPC species seem to possess pro-atherogenic properties, others may have anti-atherogenic qualities. They also serve as reservoirs and transporters of phosphate, glycerol, and choline. Moreover, both lipid classes participate in cell signaling [106,107] and seem to be associated with vascular ageing.

To date, PCs and lysoPCs are probably the most thoroughly studied phospholipids in regard to AS. In an observational study of patients with symptomatic atherosclerosis, we found that lower serum levels of PC-acyl-acyl C32:2 and several lysoPCs (C16:0, C17:0, C18:0, and C20:4) were related to increased AS, increased resting heart rate, or ED [108]. Kurotani et al. examined the FA composition of serum PC and compared it between Sri Lankan and Japanese patients with diabetes, dyslipidemia, or hypertension. Odd-chain saturated FAs were found to be inversely associated with AS only among the Sri Lankans, possibly due to higher consumption of dairy products and fish in this population [109]. In a study by Petersen et al., however, increases in serum lipid species associated with dairy were positively related to BP and carotid intima-media thickness and unrelated to PWV and AIx [110].

Polonis et al. identified four down-regulated lysoPCs (C16:0, C18:0, C18:1, and C18:2) that were independently associated with high PWV values in patients with hypertension [111]. Positive associations between lysoPCs (C14:0, C16:0, C16:1) and AS, however, have also been reported [91,98,112,113]. The inverse relationship between long-chain lysoPCs and AS is counterintuitive, since the production of lysoPCs depends largely on pro-atherogenic lipoprotein-associated phospholipase A2 (Lp-PLA2). Further, a considerable amount of evidence from ex vivo studies links lysoPCs to ED [114–116]. The ability of lysoPCs, present in oxidized low-density lipoprotein (oxLDL) particles, to impair endothelium-dependent relaxation seems to be a function of the chain length of the acyl group [117]. It has been proposed that lower circulating lysoPC levels could reflect increased catabolism and more efficient removal of lysoPCs from blood into tissues [118,119], either in the form of oxLDL or directly from albumin [120]. Moreover, lower activity of LCAT may also partially explain reduced circulating lysoPC levels in atherosclerotic patients [121,122]. The pro- or antiatherogenicity of lysoPC molecule most probably depends on the physical properties of its fatty acid residue (e.g., C16:0, C18:1, C20:4).

4.1.3. Sphingolipids and Ceramides

Sphingolipids and their metabolites are involved in various biological functions and are particularly abundant in tissues of the central nervous system [123]. Like glycerophospholipids, they serve as major plasma membrane structural components (e.g., sphingomyelin (SM)) and as critical signaling molecules (e.g., sphingosine 1-phosphate (S1P), ceramide). De novo sphingolipid synthesis from palmitoyl-CoA and Ser (or alanine, glycine, myristate, stearate) is initiated by Ser palmitoyltransferase. Sequential reactions lead to the generation of ceramides, which are the simplest sphingolipids containing a fatty acid attached to a sphingosine backbone [123,124]. More complex sphingolipids are formed by addition of polar head groups (e.g., phosphocholine, sugar) to ceramide.

Previous studies suggest that sphingolipids may be important mediators of vascular ageing. The sphingolipid precursor Ser was associated with PWV in a large-scale study of female twins by Menni et al. [83]. Ceramides, glycosphingolipids, and S1P have been repeatedly shown to participate in the atherogenic processes [125]. Interestingly, sphingosine-1-phosphate (S1P) and ceramide regulate vascular tone with opposing effects [126]. The cellular balance of these two sphingolipids is called the ceramide/S1P rheostat. A study by Li et al. in rats showed that the imbalance of the aortic ceramide/S1P rheostat may mediate the increase in aortic tone [127]. Ceramides contribute to the NO-mediated arterial dysfunction and elevate ROS production by disrupting the mitochondrial function [128]. A study in mice by Bhat et al. demonstrated that ceramide plays a critical role in phenotype transition and mineral deposition in arterial smooth muscle cells leading to arterial medial calcification and increased PWV [129]. Further, attempts to alleviate vascular dysfunction and atherosclerosis via ceramide synthesis inhibition in animal models have been encouragingly successful [130–132].

Glycosphingolipids are formed when sugars (e.g., glucose, galactose) are sequentially added via specific glycosyltransferases (glucosylceramide synthase (GCS), lactosylceramide synthase (LCS)) to ceramide. Like ceramides, this group of lipids can also be causally involved in AS. In a study by Chatterjee et al., inhibition of GCS and LCS drastically and dose-dependently ameliorated atherosclerosis in ApoE$^{-/-}$ mice, and this was accompanied by complete reversal of aortic intima-media thickening and PWV [133]. Subsequently, in a 3-year follow-up study in middle-aged overweight humans, increases in the circulating levels of lactosylceramide, one of the most abundant glycosphingolipids, were independently associated with increases in AS [134]. Circulating lactosylceramide was also an independent predictor of increased AS in subjects with impaired fasting glucose in a study by Jung et al. [135].

SM production from ceramide and PC is catalyzed by SM synthase (SMS). SM concentration is increased in the human atheromatous aorta and coronary vessels [136,137]. In a study by Jiang et al., human plasma SM levels were positively and independently related to CAD, and higher levels were proposed to be a potential marker for atherogenic remnant lipoprotein accumulation [138]. In the Bogalusa Heart Study, a metabolite module related to SM metabolism was associated with PWV in a biracial cohort of 1202 participants [139]. Another large study with 6814 middle-aged asymptomatic adults associated plasma SM levels with quantitative measures of subclinical atherosclerosis, although these associations were lost after adjustment for classical CV risk markers [140]. The authors suggested that plasma SM may partially mediate the associations between traditional risk factors and subclinical atherosclerosis by participating in the intermediate pathways. So far, SMS2 seems to be the most promising SM metabolism-associated therapeutic target with fewer adverse effects than SMS1 isoform in animal models [141]. However, since some SM species (e.g., C23:0, C24:0) have also been associated with a protective effect on CV mortality [142], the true role of SMs in AS still remains to be determined.

4.1.4. Acylglycerols and Cholesteryl Esters

Acylglycerols are esters formed by esterification of glycerol and one to three fatty acids, yielding monoacylglycerol (MAG), diacylglycerol (DAG), or triacylglycerol (TAG). TAGs are

the major source of circulating FAs and energy [143]. A positive energy balance (i.e., energy intake exceeding expenditure) leads to an excess of available FAs and TAGs, which may cause IR if accumulating in muscle or liver cells [144]. DAGs are second messengers and intermediates in TAG metabolism and have also been associated with IR [145]. Their role in the development of IR might depend both on the degree of saturation of FA residues in DAG moieties and on the location of the compounds in myocytes [146]. Similarly, a large lipidomics study by Stegemann et al. suggested that associations with higher CV risk are most pronounced for TAGs and cholesteryl esters (CEs) of lower carbon number and double-bond content (i.e., saturated and monounsaturated FAs) [119]. Research addressing associations of molecular composition of acylglycerols with AS, however, is scarce, and more studies applying metabolomics techniques are needed. In the Bogalusa Heart Study, a module composed of MAGs and DAGs, among other glycerolipids, was associated with both AIx and PWV [139]. Almost all of the DAGs in this module consisted of the following acyl groups in different combinations: 16:0, 18:1, 18:2, 20:4. Kulkarni et al. demonstrated that disturbances in the DAG axis independently influence the risk of incident hypertension [147]. The authors suggested that DAG 16:0/22:5 and DAG 16:0/22:6 may be modifiable factors or even targets for treating hypertension. AS, however, was not assessed in that study.

CEs are formed when cholesterol is esterified with long-chain FAs, a reaction catalyzed by acyl-CoA cholesterol acyltransferase (ACAT-1 and ACAT-2) in the cell [148] and LCAT in the blood [149]. CEs serve as the inactive storage or transportation form of cholesterol and are major constituents of blood lipoproteins. Moreover, they accumulate in the atherosclerotic plaques [150], and their circulating levels correlate with development of CAD [151]. Molecular composition of CE species is thus of high interest for CV research. CEs can play a significant role in the pathogenesis of AS, since atherosclerosis is closely linked to arterial stiffening [152]. However, to date, studies investigating associations of individual CE species with AS are lacking.

4.1.5. Amino Acids and Biogenic Amines

AAs are organic compounds that contain a basic amino group, a carboxylic acid functional group, and a side chain that determines the characteristics specific to each AA [153]. They are needed for building proteins and for biosynthesis of compounds such as neurotransmitters and hormones and can also be used as a source of energy. Biogenic amines are formed mainly by decarboxylation of AAs. Prior studies suggest that some AAs and biogenic amines participate in the pathophysiology of AS, and some may even have therapeutic applications.

A metabolomics study in symptomatic peripheral arterial disease patients conducted by our group showed associations between PWV and aromatic AAs (phenylalanine (Phe), tyrosine (Tyr)) [154]. This finding was confirmed in a subsequent larger-scale cohort study of 461 individuals where aromatic AAs, BCAAs (leucine, isoleucine, valine), and histidine (His) were independently associated with PWV [155]. Further, BCAAs and His were also associated with PWV in the large-scale Bogalusa Heart Study [139] as well as in a smaller study by Koh et al. [94]. BCAAs were also correlated with AS in a middle-aged Chinese population [156]. Findings from these studies suggest that the metabolic pathways of BCAAs and aromatic AAs could be involved in AS. Mechanisms underlying the role of BCAAs in AS may involve promotion of inflammation and OxS in endothelial cells [157], insulin signaling disruption, and chronic mTOR (mammalian target of rapamycin) activation that can lead to diabetes [158–160], which is a powerful determinant of vascular ageing [23]. Similarly, alterations in glucose metabolism could also at least partially explain the relationship between Tyr and PWV. Tyr is derived from dietary sources as well as from Phe and is a precursor for catecholamines. Circulating Tyr is associated with insulin resistance [161] and can affect BCAA levels, since they compete for the same AA transporter for cellular uptake [162]. Recently, inhibition of Tyr hydroxylase, a rate-limiting enzyme of catecholamine biosynthesis, preserved elastin integrity, attenuated

vascular OxS, and reduced the inflammatory infiltrate in mice [163]. Thus, this enzyme could serve as a potential therapeutic target for AS.

Some derivatives of the aromatic AA tryptophan (Trp) and His have also been shown to correlate with AS. Higher circulating levels of indoxyl sulfate, an uremic toxin that is produced by the metabolism of dietary Trp, showed positive associations with aortic stiffness in patients with CAD [164] and type 2 diabetes [165]. Sumatriptan supplementation acutely increased AS in healthy subjects in a small RCT by Vanmolkot and de Hoon, and kynurenic acid was independently associated with AS in patients with atrial fibrillation [166]. His derivatives, however, have shown inverse relationships with vascular function. Urinary 1-methylhistidine, together with β-alanine and L-proline, were independent adverse contributors to AS in young black boys [167], and lower serum levels of 3-methylhistidine were associated with increased aortic stiffness in maintenance hemodialysis patients [168]. Interestingly, a recent study on the influence of tart cherries (Prunus Cerasus) on vascular function found changes in urinary metabolites related to Trp and His metabolism, but there occurred no correlation with AS [169].

Another potential target to attenuate vascular ageing is the arginine (Arg) metabolic pathway. Being the substrate for nitric oxide synthase (NOS), Arg has important nitric oxide (NO) dependent vasodilatory and antithrombotic effects but also several NO independent effects that help to maintain and improve vascular health [170]. For these reasons, it has become a popular dietary supplement, although the CV benefits from long-term supplementation remain questionable. When L-Arg was added to standard postinfarction therapies, it did not improve AS measurements or the ejection fraction and was found to be potentially associated with higher mortality in patients following a first ST-segment elevation myocardial infarction [171]. Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of NOS isoforms [172] and is released following the proteolysis of Arg-methylated proteins [173]. Higher ADMA levels predispose to ED and are associated with AS [174,175] and carotid intima-media thickness increase [153]. Its isoform, symmetric dimethylarginine (an inhibitor of cellular L-Arg uptake), Arg-to-ADMA ratio, and citrulline-to-Arg ratio also seem to correlate with AS indicators [176–179].

Homocysteine (Hcy) is an intermediate product in the biosynthesis of the AAs Met and cysteine and a key determinant of the methylation cycle. Higher circulating Hcy levels are associated with AS [180,181], although the independence of this relationship has also been questioned [182]. Hcy may increase AS via direct effects (smooth muscle proliferation, ED, collagen synthesis, and elastolysis) on the arterial wall [183–185]. The results from interventional studies with Met loading [186–188] and folic acid supplementation [189,190], however, have been ambiguous. Moreover, the effects of folic acid on AS seem to be independent of Hcy levels.

Taurine (Tau) is a biogenic amine with antioxidant and vasodilatory effects [191]. Supplementation of this biogenic amine reduced vascular wall tone, slowed PWV, and led to a decline in AIx and central BP in healthy students [192]. In a study by Ra et al., Tau attenuated delayed post-exercise increase in PWV in young healthy men probably via its antioxidant effects and reversed AIx and ED in another small study in young male diabetics [193]. More recently, the effects of Tau supplementation on BP and on the vascular function were studied in prehypertensive individuals in a placebo-controlled RCT [194]. Tau supplementation significantly decreased BP and improved endothelium-dependent and endothelium-independent vasodilation in these subjects. The hypotensive effect involved the hydrogen sulfide-mediated inhibition of calcium influx.

4.1.6. Carbohydrates and Advanced Glycation End-Products

Glucose (Glc) is a monosaccharide that is vital for fueling both aerobic and anaerobic cellular respiration. Dietary Glc comes in different forms such as mono- (e.g., galactose, fructose, lactose, sucrose), di- (e.g., sucrose, lactose), or polysaccharides (e.g., starch). Excess Glc in the organism is stored as glycogen or converted to fat. These sources help to meet

the energy needs during exercise, between meals, and while sleeping. In starvation, Glc can also be derived from the process of gluconeogenesis.

A rapid elevation in blood Glc levels after a meal is an independent risk factor for CVD and a greater risk factor than fasting glucose [195]. Previous studies suggest that AS is increased during both acute and chronic hyperglycemia. The postprandial increase in AS seems to be at least partially dependent on the type (high vs. low glycemic index foods) [196] and amount [197] of consumed carbohydrate. The well-established association between chronic hyperglycemia and increased AS is significantly mediated by the formation of advanced glycation end-products (AGEs) [15]. Glycation is a spontaneous non-enzymatic reaction of reducing sugars with proteins, DNA, and lipids, which forms so-called Amadori products. The Amadori products undergo a variety of irreversible dehydration and rearrangement reactions that lead to the formation of AGEs [15], many of which can be identified and quantified using analytical metabolomics methods. In the arterial wall, glycation contributes to collagen and elastin cross-linking, inflammation [198], and ED [199], which leads to extracellular matrix remodeling. AGEs that have been associated with AS include glucosepane [200], carboxymethyl-lysine [201], pentosidine [202], and methylglyoxal [203]. Some traditional medications such as RAAS inhibitors [204] and statins [205] are known to reduce AGE formation as a by-product of their action [206]. Development of destiffening medicines, which could directly prevent AGE cross-linking or break existing cross-links in the arterial wall, is an area of active research and has a great clinical potential. Currently investigated direct AGE inhibitors include pyridoxamine and epalrestat [207].

4.1.7. Other Metabolites

Uric acid (UA) is a purine derivative and a well established CVD risk marker [208,209]. However, it is not clear whether UA is merely a marker or mediator of CVD and vascular dysfunction [209,210]. Serum UA was recently longitudinally associated with AS in men but not in women [211]. The results from cross-sectional studies have also been equivocal [212–216]. It has been speculated that the association between UA and AS may appear only at high UA levels and may be mediated by xanthine oxidase-induced OxS [211,217].

Polyphenols are naturally occurring compounds found largely in fruits, vegetables, cereals, and beverages [218]. Numerous polyphenols including resveratrol, isoflavones, anthocyanins, and flavan-3-ols, have been shown to be associated with AS [219,220]. Polyphenols can also impact the composition of the gut microbiota and may be metabolized by gut bacteria into bioactive compounds that produce effects on vascular function [221].

Urinary caffeine, paraxanthine, and theophylline excretions were associated with decreased PWV in a study by Ponte et al., suggesting a protective effect of caffeine intake beyond its BP-lowering effect [222]. The acute and long-term effects of caffeine intake on AS and BP, however, are still to be fully elucidated [223].

Urine isocitrate (a citric acid cycle intermediate), hydroxymethylglutarate (a precursor to cholesterol and coenzyme Q10 synthesis), and formiminoglutamate (an intermediate in the catabolism of L-His to L-glutamic acid) were independently associated with AS in Korean adults [224]. The results from coenzyme Q10 supplementation trials have been controversial [225–227].

4.2. Future Outlook

It is clear from the literature review given above that 'arteriometabolomics' is a powerful research tool that allows simultaneous exploration of metabolic and hemodynamic alterations. Combining the increasingly growing knowledge from metabolome analysis with the constantly evolving understanding of AS could lead to the development and validation of novel biomarker panels with a predictive power beyond conventional circulating CVD markers and peripheral BP measurement. In clinical practice, a more detailed overview of subclinical metabolic and hemodynamic (e.g., increased cf-PWV) derangements could be most helpful for low to medium CV risk patients in whom traditional

biomarkers/parameters give borderline or equivocal results. It could also help monitor disease (e.g., hypertension, diabetes) progression and treatment efficacy.

Metabolic pathways that prove to be causally associated with AS could emerge as novel therapeutic targets for vascular ageing. Destiffening medicines capable of ameliorating the intrinsic elastic properties of the arterial wall, regardless of BP and cardiac output, would further help protect against CV complications (i.e., reduce residual hemodynamic risk). Recently, the concept of supernormal vascular ageing (SUPERNOVA) was proposed [228]. According to this concept, SUPERNOVA can be diagnosed in individuals who present an exceptionally low AS for their age and sex. The arteries of such subjects are of great scientific interest because determining the unique molecular characteristics of their walls could lead to novel molecular targets. While some progress has already been made in determining therapeutic targets for AS, metabolomics research could further contribute to this endeavor. As reviewed above, the current more intriguing candidate metabolic modulators to improve AS include L-carnitine [64] and Tau [195] supplements, TMA-lyase inhibitors [72], PPARβ/δ activators [95], Tyr hydroxylase inhibitors [163], ceramide synthase inhibitors [141], SMS2 inhibitors [141], and direct AGE inhibitors [207].

A thorough understanding of pathophysiology is a prerequisite for the development of novel therapies for any disease. Metabolomics studies in humans have so far largely focused on systemic shifts in metabolism. Significantly less is known about the local features of metabolism in different organs (e.g., heart, kidneys) and regions of the body (e.g., lower extremity). The research approach based on arteriovenous gradients (AVGs) assessment isolates local changes in the levels of LMWMs of interest from changes in the systemic circulation and is therefore a more direct reflection of the (patho)physiology of the study region. In such an approach, for any given LMWM, venous/arterial ratio <1 is consistent with net uptake by the organ or region of the body, whereas the ratio >1 suggests net release. AVG assessment has been previously used to study local metabolism in the kidneys of patients with chronic kidney disease [229,230] and in the hearts of patients who underwent diagnostic coronary angiography [231]. A study by Lavi et al. associated coronary AVGs of total lysoPC with the coronary endothelial function, setting an example for future local/regional 'arteriometabolomics' research [232]. In addition to the heart and kidneys, the metabolism and arterial function (e.g., arterial distensibility, pulse wave imaging, elastography [36]) of other organs and body regions could be similarly studied (e.g., ischemic limb in lower extremity arterial disease patients).

5. Conclusions

There is already a significant amount of scientific evidence to support the link between AS and metabolism. Some LMWMs seem to influence the arterial wall through traditional CV risk factors, while others may act independently through both known and unknown pathophysiological mechanisms. The integration of metabolomics methods into arterial wall research broadens our understanding of the pathophysiology of AS and may lead to the discovery of more accurate CV biomarkers and novel destiffening therapies.

Author Contributions: Conceptualization, K.P. and J.K.; writing—original draft preparation, K.P.; writing—review and editing, J.K.; visualization, K.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by personal research grants from the Estonian Research Council (PRG no. 1054, PRG no. 1437, and PRG no. 435).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data sharing not applicable. No new data were created or analyzed in this study.

Acknowledgments: Figures 1 and 2 were created using BioRender (https://biorender.com). We thank Ester Jaigma for the linguistic revision.

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

References

1. Nidorf, S.M.; Fiolet, A.T.L.; Mosterd, A.; Eikelboom, J.W.; Schut, A.; Opstal, T.S.J.; The, S.H.K.; Xu, X.-F.; Ireland, M.A.; Lenderink, T.; et al. Colchicine in patients with chronic coronary disease. *N. Engl. J. Med.* **2020**, *383*, 1838–1847. [CrossRef] [PubMed]
2. Tardif, J.-C.; Kouz, S.; Waters, D.D.; Bertrand, O.F.; Diaz, R.; Maggioni, A.P.; Pinto, F.J.; Ibrahim, R.; Gamra, H.; Kiwan, G.S.; et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N. Engl. J. Med.* **2019**, *381*, 2497–2505. [CrossRef] [PubMed]
3. Ridker, P.M.; Everett, B.M.; Thuren, T.; MacFadyen, J.G.; Chang, W.H.; Ballantyne, C.; Fonseca, F.; Nicolau, J.; Koenig, W.; Anker, S.D.; et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N. Engl. J. Med.* **2017**, *377*, 1119–1131. [CrossRef] [PubMed]
4. Broch, K.; Anstensrud, A.K.; Woxholt, S.; Sharma, K.; Tøllefsen, I.M.; Bendz, B.; Aakhus, S.; Ueland, T.; Amundsen, B.H.; Damås, J.K.; et al. Randomized trial of interleukin-6 receptor inhibition in patients with acute ST-segment elevation myocardial infarction. *J. Am. Coll. Cardiol.* **2021**, *77*, 1845–1855. [CrossRef] [PubMed]
5. Olsen, M.B.; Gregersen, I.; Sandanger, Ø.; Yang, K.; Sokolova, M.; Halvorsen, B.E.; Gullestad, L.; Broch, K.; Aukrust, P.; Louwe, M.C. Targeting the inflammasome in cardiovascular disease. *JACC Basic Transl. Sci.* **2022**, *7*, 84–98. [CrossRef]
6. Laurent, S.; Chatellier, G.; Azizi, M.; Calvet, D.; Choukroun, G.; Danchin, N.; Delsart, P.; Girerd, X.; Gosse, P.; Khettab, H.; et al. SPARTE study: Normalization of arterial stiffness and cardiovascular events in patients with hypertension at medium to very high risk. *Hypertension* **2021**, *78*, 983–995. [CrossRef]
7. Patti, G.J.; Yanes, O.; Siuzdak, G. Innovation: Metabolomics: The apogee of the omics trilogy. *Nat. Rev. Mol. Cell Biol.* **2012**, *13*, 263–269. [CrossRef]
8. Griffin, J.L.; Atherton, H.J.; Shockcor, J.P.; Atzori, L. Metabolomics as a tool for cardiac research. *Nat. Rev. Cardiol.* **2011**, *8*, 630–643. [CrossRef]
9. McGarrah, R.W.; Crown, S.B.; Zhang, G.-F.; Shah, S.H.; Newgard, C.B. Cardiovascular metabolomics. *Circ. Res.* **2018**, *122*, 1238–1258. [CrossRef]
10. Åstrand, H.; Stålhand, J.; Karlsson, J.; Karlsson, M.; Sonesson, B.; Länne, T. In vivo estimation of the contribution of elastin and collagen to the mechanical properties in the human abdominal aorta: Effect of age and sex. *J. Appl. Physiol.* **2011**, *110*, 176–187. [CrossRef]
11. Van Bussel, B.C.; Schouten, F.; Henry, R.M.; Schalkwijk, C.G.; De Boer, M.R.; Ferreira, I.; Smulders, Y.M.; Twisk, J.W.; Stehouwer, C.D. Endothelial dysfunction and low-grade inflammation are associated with greater arterial stiffness over a 6-year period. *Hypertension* **2011**, *58*, 588–595. [CrossRef] [PubMed]
12. Mäki-Petäjä, K.M.; Elkhawad, M.; Cheriyan, J.; Joshi, F.R.; Östör, A.J.K.; Hall, F.C.; Rudd, J.H.F.; Wilkinson, I.B. Anti-tumor necrosis factor-α therapy reduces aortic inflammation and stiffness in patients with rheumatoid arthritis. *Circulation* **2012**, *126*, 2473–2480. [CrossRef] [PubMed]
13. Zhou, R.H.; Vendrov, A.E.; Tchivilev, I.; Niu, X.L.; Molnar, K.C.; Rojas, M.; Carter, J.D.; Tong, H.; Stouffer, G.A.; Madamanchi, N.R.; et al. Mitochondrial oxidative stress in aortic stiffening with age the role of smooth muscle cell function. *Arter.-Scler. Thromb. Vasc. Biol.* **2012**, *32*, 745–755. [CrossRef] [PubMed]
14. Lacolley, P.; Regnault, V.; Segers, P.; Laurent, S. Vascular smooth muscle cells and arterial stiffening: Relevance in development, aging, and disease. *Physiol. Rev.* **2017**, *97*, 1555–1617. [CrossRef]
15. Sell, D.R.; Monnier, V.M. Molecular basis of arterial stiffening: Role of glycation—A mini-review. *Gerontology* **2012**, *58*, 227–237. [CrossRef]
16. Haydar, A.A.; Covic, A.; Colhoun, H.; Rubens, M.; Goldsmith, D.J. Coronary artery calcification and aortic pulse wave velocity in chronic kidney disease patients. *Kidney Int.* **2004**, *65*, 1790–1794. [CrossRef]
17. Ghiadoni, L.; Penno, G.; Giannarelli, C.; Plantinga, Y.; Bernardini, M.; Pucci, L.; Miccoli, R.; Taddei, S.; Salvetti, A.; Del Prato, S. Metabolic syndrome and vascular alterations in normotensive subjects at risk of diabetes mellitus. *Hypertension* **2008**, *51*, 440–445. [CrossRef]
18. Murray, R.; Kitaba, N.; Antoun, E.; Titcombe, P.; Barton, S.; Cooper, C.; Inskip, H.M.; Burdge, G.C.; Mahon, P.A.; Deanfield, J.; et al. Influence of maternal lifestyle and diet on perinatal DNA methylation signatures associated with childhood arterial stiffness at 8 to 9 years. *Hypertension* **2021**, *78*, 787–800. [CrossRef]
19. Lacolley, P.; Regnault, V.; Laurent, S. Mechanisms of arterial stiffening: From mechanotransduction to epigenetics. *Arter.-Scler. Thromb. Vasc. Biol.* **2020**, *40*, 1055–1062. [CrossRef]
20. Wu, S.; Jin, C.; Li, S.; Zheng, X.; Zhang, X.; Cui, L.; Gao, X. Aging, arterial stiffness, and blood pressure association in Chinese adults. *Hypertension* **2019**, *73*, 893–899. [CrossRef]
21. Sun, Z. Aging, arterial stiffness, and hypertension. *Hypertension* **2015**, *65*, 252–256. [CrossRef] [PubMed]
22. Safar, M.E.; Asmar, R.; Benetos, A.; Blacher, J.; Boutouyrie, P.; Lacolley, P.; Laurent, S.; London, G.; Pannier, B.; Protogerou, A.; et al. Interaction between hypertension and arterial stiffness an expert reappraisal. *Hypertension* **2018**, *72*, 796–805. [CrossRef] [PubMed]
23. Prenner, S.B.; Chirinos, J.A. Arterial stiffness in diabetes mellitus. *Atherosclerosis* **2015**, *238*, 370–379. [CrossRef] [PubMed]
24. Townsend, R.R. Arterial stiffness in CKD: A review. *Am. J. Kidney Dis.* **2019**, *73*, 240–247. [CrossRef] [PubMed]
25. Hsu, B.-G.; Tsai, J.-P. Arterial stiffness: A brief review. *Tzu-Chi Med. J.* **2021**, *33*, 115–121. [CrossRef]

26. Vlachopoulos, C.; Terentes-Printzios, D.; Laurent, S.; Nilsson, P.M.; Protogerou, A.D.; Aznaouridis, K.; Xaplanteris, P.; Koutagiar, I.; Tomiyama, H.; Yamashina, A.; et al. Association of estimated pulse wave velocity with survival: A secondary analysis of SPRINT. *JAMA Netw. Open* **2019**, *2*, e1912831. [CrossRef]
27. Hametner, B.; Wassertheurer, S.; Mayer, C.C.; Danninger, K.; Binder, R.K.; Weber, T. Aortic pulse wave velocity predicts cardiovascular events and mortality in patients undergoing coronary angiography: A comparison of invasive measurements and noninvasive estimates. *Hypertension* **2021**, *77*, 571–581. [CrossRef]
28. Vlachopoulos, C.; Aznaouridis, K.; Stefanadis, C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: A systematic review and meta-analysis. *J. Am. Coll. Cardiol.* **2010**, *55*, 1318–1327. [CrossRef]
29. Laurent, S.; Cockcroft, J.; Van Bortel, L.; Boutouyrie, P.; Giannattasio, C.; Hayoz, D.; Pannier, B.; Vlachopoulos, C.; Wilkinson, I.; Struijker-Boudier, H. Expert consensus document on arterial stiffness: Methodological issues and clinical applications. *Eur. Heart J.* **2006**, *27*, 2588–2605. [CrossRef]
30. Williams, B.; Mancia, G.; Spiering, W.; Rosei, E.A.; Azizi, M.; Burnier, M.; Clement, D.L.; Coca, A.; de Simone, G.; Dominiczak, A.; et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. *Eur. Heart J.* **2018**, *39*, 3021–3104. [CrossRef]
31. Nichols, W.W. Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. *Am. J. Hypertens.* **2005**, *18*, 3S–10S. [CrossRef] [PubMed]
32. Nichols, W.W.; Edwards, D.G. Arterial elastance and wave reflection augmentation of systolic blood pressure: Deleterious effects and implications for therapy. *J. Cardiovasc. Pharmacol. Ther.* **2001**, *6*, 5–21. [CrossRef] [PubMed]
33. Mitchell, G.F. Aortic stiffness, pressure and flow pulsatility, and target organ damage. *J. Appl. Physiol.* **2018**, *125*, 1871–1880. [CrossRef]
34. Vlachopoulos, C.; Aznaouridis, K.; O'Rourke, M.F.; Safar, M.E.; Baou, K.; Stefanadis, C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: A systematic review and meta-analysis. *Eur. Heart J.* **2010**, *31*, 1865–1871. [CrossRef]
35. Townsend, R.R.; Wilkinson, I.B.; Schiffrin, E.L.; Avolio, A.P.; Chirinos, J.A.; Cockcroft, J.R.; Heffernan, K.S.; Lakatta, E.G.; McEniery, C.M.; Mitchell, G.F.; et al. Recommendations for improving and standardizing vascular research on arterial stiffness: A scientific statement from the American Heart Association. *Hypertension* **2015**, *66*, 698–722. [CrossRef] [PubMed]
36. Segers, P.; Rietzschel, E.R.; Chirinos, J.A. How to measure arterial stiffness in humans. *Arter. Thromb. Vasc. Biol.* **2020**, *40*, 1034–1043. [CrossRef]
37. Mahmud, A.; Feely, J. Review: Arterial stiffness and the renin-angiotensin-aldosterone system. *J. Renin-Angiotensin-Aldosterone Syst.* **2004**, *5*, 102–108. [CrossRef]
38. London, G.M.; Pannier, B.; Guerin, A.P.; Marchais, S.J.; Safar, M.E.; Cuche, J.L. Cardiac hypertrophy, aortic compliance, peripheral resistance, and wave reflection in end-stage renal disease: Comparative effects of ACE inhibition and calcium channel blockade. *Circulation* **1994**, *90*, 2786–2796. [CrossRef]
39. Ichihara, A.; Hayashi, M.; Koura, Y.; Tada, Y.; Kaneshiro, Y.; Saruta, T. Long-term effects of statins on arterial pressure and stiffness of hypertensives. *J. Hum. Hypertens.* **2005**, *19*, 103–109. [CrossRef]
40. Striepe, K.; Jumar, A.; Ott, C.; Karg, M.V.; Schneider, M.P.; Kannenkeril, D.; Schmieder, R.E. Effects of the selective sodium-glucose cotransporter 2 inhibitor empagliflozin on vascular function and central hemodynamics in patients with type 2 diabetes mellitus. *Circulation* **2017**, *136*, 1167–1169. [CrossRef]
41. Cherney, D.Z.I.; Perkins, B.A.; Soleymanlou, N.; Har, R.; Fagan, N.; Johansen, O.E.; Woerle, H.J.; von Eynatten, M.; Broedl, U.C. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. *Cardiovasc. Diabetol.* **2014**, *13*, 28. [CrossRef] [PubMed]
42. Cooper, J.N.; Buchanich, J.M.; Youk, A.; Brooks, M.M.; Barinas-Mitchell, E.; Conroy, M.B.; Sutton-Tyrrell, K. Reductions in arterial stiffness with weight loss in overweight and obese young adults: Potential mechanisms. *Atherosclerosis* **2012**, *223*, 485–490. [CrossRef]
43. D'Elia, L.; Galletti, F.; La Fata, E.; Sabino, P.; Strazzullo, P. Effect of dietary sodium restriction on arterial stiffness: Systematic review and meta-analysis of the randomized controlled trials. *J. Hypertens.* **2018**, *36*, 734–743. [CrossRef] [PubMed]
44. Jatoi, N.A.; Jerrard-Dunne, P.; Feely, J.; Mahmud, A. Impact of smoking and smoking cessation on arterial stiffness and aortic wave reflection in hypertension. *Hypertension* **2007**, *49*, 981–985. [CrossRef] [PubMed]
45. Wishart, D.S. Metabolomics for investigating physiological and pathophysiological processes. *Physiol. Rev.* **2019**, *99*, 1819–1875. [CrossRef] [PubMed]
46. Aderemi, A.V.; Ayeleso, A.O.; Oyedapo, O.O.; Mukwevho, E. Metabolomics: A scoping review of its role as a tool for disease biomarker discovery in selected non-communicable diseases. *Metabolites* **2021**, *11*, 418. [CrossRef]
47. Reyon, D.; Khayter, C.; Regan, M.R.; Joung, J.K.; Sander, J.D. Engineering designer transcription activator-like effector nucleases (TALENs) by REAL or REAL-fast assembly. *Curr. Protoc. Mol. Biol.* **2012**, *100*, 12–15. [CrossRef]
48. Ribbenstedt, A.; Ziarrusta, H.; Benskin, J.P. Development, characterization and comparisons of targeted and non-targeted metabolomics methods. *PLoS ONE* **2018**, *13*, e0207082. [CrossRef]
49. Schrimpe-Rutledge, A.C.; Codreanu, S.G.; Sherrod, S.D.; McLean, J.A. Untargeted metabolomics strategies—Challenges and emerging directions. *J. Am. Soc. Mass Spectrom.* **2016**, *27*, 1897–1905. [CrossRef]
50. Emwas, A.H.M. The strengths and weaknesses of NMR spectroscopy and mass spectrometry with particular focus on metabolomics research. *Methods Mol. Biol.* **2015**, *1277*, 161–193.

51. Emwas, A.H.M.; Roy, R.; McKay, R.T.; Tenori, L.; Saccenti, E.; Nagana Gowda, G.A.; Raftery, D.; AlAhmari, F.; Jaremko, L.; Jaremko, M.; et al. NMR spectroscopy for metabolomics research. *Metabolites* **2019**, *9*, 123. [CrossRef] [PubMed]
52. Alseekh, S.; Aharoni, A.; Brotman, Y.; Contrepois, K.; D'Auria, J.; Ewald, J.; Ewald, J.C.; Fraser, P.D.; Giavalisco, P.; Hall, R.D.; et al. Mass spectrometry-based metabolomics: A guide for annotation, quantification and best reporting practices. *Nat. Methods* **2021**, *18*, 747–756. [CrossRef] [PubMed]
53. Lamichhane, S.; Sen, P.; Dickens, A.M.; Hyötyläinen, T.; Orešič, M. An overview of metabolomics data analysis: Current tools and future perspectives. *Compr. Anal. Chem.* **2018**, *82*, 387–413.
54. Xia, J.; Wishart, D.S.; Valencia, A. MetPA: A web-based metabolomics tool for pathway analysis and visualization. *Bioinformatics* **2011**, *26*, 2342–2344. [CrossRef] [PubMed]
55. Karnovsky, A.; Li, S. Pathway analysis for targeted and untargeted metabolomics. *Methods Mol. Biol.* **2020**, *2104*, 387–400. [CrossRef]
56. McGranaghan, P.; Kirwan, J.A.; Garcia-Rivera, M.A.; Pieske, B.; Edelmann, F.; Blaschke, F.; Appunni, S.; Saxena, A.; Rubens, M.; Veledar, E.; et al. Lipid metabolite biomarkers in cardiovascular disease: Discovery and biomechanism translation from human studies. *Metabolites* **2021**, *11*, 621. [CrossRef]
57. Flanagan, J.L.; Simmons, P.A.; Vehige, J.; Willcox, M.D.; Garrett, Q. Role of carnitine in disease. *Nutr. Metab.* **2010**, *7*, 30. [CrossRef]
58. Marcovina, S.M.; Sirtori, C.; Peracino, A.; Gheorghiade, M.; Borum, P.; Remuzzi, G.; Ardehali, H. Translating the basic knowledge of mitochondrial functions to metabolic therapy: Role of L-carnitine. *Transl. Res.* **2013**, *161*, 73–84. [CrossRef]
59. Pons, R.; De Vivo, D.C. Primary and secondary carnitine deficiency syndromes. *J. Child Neurol.* **1995**, *10*, S8–S24. [CrossRef]
60. Mohammadi, M.; Hajhossein Talasaz, A.; Alidoosti, M. Preventive effect of L-carnitine and its derivatives on endothelial dysfunction and platelet aggregation. *Clin. Nutr. ESPEN* **2016**, *15*, 1–10. [CrossRef]
61. Lai, Y.-H.; Lee, M.-C.; Ho, G.-J.; Liu, C.-H.; Hsu, B.-G. Association of low serum L-carnitine levels with peripheral arterial stiffness in patients who undergo kidney transplantation. *Nutrients* **2019**, *11*, 2000. [CrossRef] [PubMed]
62. Hsieh, Y.J.; Hsu, B.G.; Lai, Y.H.; Wang, C.H.; Lin, Y.L.; Kuo, C.H.; Tsai, J.P. Association of low serum L-carnitine levels with aortic stiffness in patients with non-dialysis chronic kidney disease. *Nutrients* **2020**, *12*, 2918. [CrossRef] [PubMed]
63. Xu, Y.; Jiang, W.; Chen, G.; Zhu, W.; Ding, W.; Ge, Z.; Tan, Y.; Ma, T.; Cui, G. L-carnitine treatment of insulin resistance: A systematic review and meta-analysis. *Adv. Clin. Exp. Med.* **2017**, *26*, 333–338. [CrossRef] [PubMed]
64. National Library of Medicine (U.S.). Causal Mechanisms in Adolescent Arterial Stiffness. ClinicalTrials.gov Identifier: NCT04128969. October 2019. Available online: https://clinicaltrials.gov/ct2/show/NCT04128969 (accessed on 6 March 2022).
65. Koeth, R.A.; Wang, Z.; Levison, B.S.; Buffa, J.A.; Org, E.; Sheehy, B.T.; Britt, E.B.; Fu, X.; Wu, Y.; Li, L.; et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat. Med.* **2013**, *19*, 576–585. [CrossRef] [PubMed]
66. Koeth, R.A.; Levison, B.S.; Culley, M.K.; Buffa, J.A.; Wang, Z.; Gregory, J.C.; Org, E.; Wu, Y.; Li, L.; Smith, J.D.; et al. γ-butyrobetaine is a proatherogenic intermediate in gut microbial metabolism of L-carnitine to TMAO. *Cell Metab.* **2014**, *20*, 799–812. [CrossRef]
67. Wang, Z.; Klipfell, E.; Bennett, B.J.; Koeth, R.; Levison, B.S.; DuGar, B.; Feldstein, A.E.; Britt, E.B.; Fu, X.; Chung, Y.-M.; et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature* **2011**, *472*, 57–63. [CrossRef]
68. Schiattarella, G.G.; Sannino, A.; Toscano, E.; Giugliano, G.; Gargiulo, G.; Franzone, A.; Trimarco, B.; Esposito, G.; Perrino, C. Gut microbe-generated metabolite trimethylamine-N-oxide as cardiovascular risk biomarker: A systematic review and dose-response meta-analysis. *Eur. Heart J.* **2017**, *38*, 2948–2956. [CrossRef]
69. Lee, Y.; Nemet, I.; Wang, Z.; Lai, H.T.M.; de Oliveira Otto, M.C.; Lemaitre, R.N.; Fretts, A.M.; Sotoodehnia, N.; Budoff, M.; DiDonato, J.A.; et al. Longitudinal plasma measures of trimethylamine N-oxide and risk of atherosclerotic cardiovascular disease events in community-based older adults. *J. Am. Heart Assoc.* **2021**, *10*, e020646. [CrossRef]
70. Canyelles, M.; Tondo, M.; Cedó, L.; Farràs, M.; Escolà-Gil, J.C.; Blanco-Vaca, F. Trimethylamine N-oxide: A link among diet, gut microbiota, gene regulation of liver and intestine cholesterol homeostasis and HDL function. *Int. J. Mol. Sci.* **2018**, *19*, 3228. [CrossRef]
71. Chen, M.L.; Zhu, X.H.; Ran, L.; Lang, H.D.; Yi, L.; Mi, M.T. Trimethylamine-N-oxide induces vascular inflammation by activating the NLRP3 inflammasome through the SIRT3-SOD2-MtROS signaling pathway. *J. Am. Heart Assoc.* **2017**, *6*, e006347. [CrossRef]
72. Brunt, V.E.; Casso, A.G.; Gioscia-Ryan, R.A.; Sapinsley, Z.J.; Ziemba, B.P.; Clayton, Z.S.; Bazzoni, A.E.; VanDongen, N.S.; Richey, J.J.; Hutton, D.A.; et al. Gut microbiome-derived metabolite trimethylamine N-oxide induces aortic stiffening and increases systolic blood pressure with aging in mice and humans. *Hypertension* **2021**, *78*, 499–511. [CrossRef]
73. Pierce, G.L.; Roy, S.J.; Gimblet, C.J. The gut-arterial stiffness axis: Is TMAO a novel target to prevent age-related aortic stiffening? *Hypertension* **2021**, *78*, 512–515. [CrossRef]
74. Brunt, V.E.; Gioscia-Ryan, R.A.; Casso, A.G.; VanDongen, N.S.; Ziemba, B.P.; Sapinsley, Z.J.; Richey, J.J.; Zigler, M.C.; Neilson, A.P.; Davy, K.P.; et al. Trimethylamine-N-oxide promotes age-related vascular oxidative stress and endothelial dysfunction in mice and healthy humans. *Hypertension* **2020**, *76*, 101–112. [CrossRef] [PubMed]
75. Papandreou, C.; Moré, M.; Bellamine, A. Trimethylamine N-oxide in relation to cardiometabolic health—Cause or effect? *Nutrients* **2020**, *12*, 1330. [CrossRef] [PubMed]
76. Lindskog Jonsson, A.; Caesar, R.; Akrami, R.; Reinhardt, C.; Fak Hallenius, F.; Boren, J.; Backhed, F. Impact of gut microbiota and diet on the development of atherosclerosis in ApoE$^{-/-}$ mice. *Arter. Thromb. Vasc. Biol.* **2018**, *38*, 2318–2326. [CrossRef] [PubMed]

77. Collins, H.L.; Drazul-Schrader, D.; Sulpizio, A.C.; Koster, P.D.; Williamson, Y.; Adelman, S.J.; Owen, K.; Sanli, T.; Bellamine, A. L-carnitine intake and high trimethylamine N-oxide plasma levels correlate with low aortic lesions in ApoE$^{-/-}$ trnsgenic mice expressing CETP. *Atherosclerosis* **2016**, *244*, 29–37. [CrossRef] [PubMed]
78. Aldana-Hernández, P.; Leonard, K.A.; Zhao, Y.Y.; Curtis, J.M.; Field, C.J.; Jacobs, R.L. Dietary choline or trimethylamine N-oxide supplementation does not influence atherosclerosis development in Ldlr$^{-/-}$ and ApoE$^{-/-}$ male mice. *J. Nutr.* **2020**, *150*, 249–255. [CrossRef]
79. Fennema, D.; Phillips, I.R.; Shephard, E.A. Trimethylamine and trimethylamine N-oxide, a flavin-containing monooxygenase 3 (FMO3)-mediated host-microbiome metabolic axis implicated in health and disease. *Drug Metab. Dispos.* **2016**, *44*, 1839–1850. [CrossRef]
80. Wang, S.-C.; Lai, Y.-H.; Liu, C.-H.; Wang, C.-H.; Hsu, B.-G.; Tsai, J.-P. Association between serum indoxyl sulfate levels with carotid-femoral pulse wave velocity in patients with chronic kidney disease. *Ren. Fail.* **2021**, *43*, 796–802. [CrossRef]
81. Barreto, F.C.; Barreto, D.V.; Liabeuf, S.; Meert, N.; Glorieux, G.; Temmar, M.; Choukroun, G.; Vanholder, R.; Massy, Z.A.; European Uremic Toxin Work Group (EUTox). Serum indoxyl sulfate is associated with vascular disease and mortality in chronic kidney disease patients. *Clin. J. Am. Soc. Nephrol.* **2009**, *4*, 1551–1558. [CrossRef]
82. Lai, Y.-H.; Wang, C.-H.; Kuo, C.-H.; Lin, Y.-L.; Tsai, J.-P.; Hsu, B.-G. Serum P-cresyl sulfate is a predictor of central arterial stiffness in patients on maintenance hemodialysis. *Toxins* **2019**, *12*, 10. [CrossRef] [PubMed]
83. Menni, C.; Mangino, M.; Cecelja, M.; Psatha, M.; Brosnan, M.J.; Trimmer, J.; Mohney, R.P.; Chowienczyk, P.; Padmanabhan, S.; Spector, T.D.; et al. Metabolomic study of carotid–femoral pulse-wave velocity in women. *J. Hypertens.* **2015**, *33*, 791–796. [CrossRef] [PubMed]
84. Törmälä, R.; Appt, S.; Clarkson, T.B.; Groop, P.-H.; Rönnback, M.; Ylikorkala, O.; Mikkola, T.S. Equol production capability is associated with favorable vascular function in postmenopausal women using tibolone; no effect with soy supplementation. *Atherosclerosis* **2008**, *198*, 174–178. [CrossRef] [PubMed]
85. Kashtanova, D.; Tkacheva, O.; Popenko, A.; Egshatyan, L.; Tyakht, A.; Alexeev, D.; Kotovskaya, Y.; Plokhova, E.; Boytsov, S. Gut microbiota and vascular biomarkers in patients without clinical cardiovascular diseases. *Artery Res.* **2017**, *18*, 41–48. [CrossRef]
86. Menni, C.; Lin, C.; Cecelja, M.; Mangino, M.; Matey-Hernandez, M.L.; Keehn, L.; Mohney, R.P.; Steves, C.; Spector, T.D.; Kuo, C.-F.; et al. Gut microbial diversity is associated with lower arterial stiffness in women. *Eur. Heart J.* **2018**, *39*, 2390–2397. [CrossRef] [PubMed]
87. Dinakis, E.; Nakai, M.; Gill, P.A.; Yiallourou, S.; Sata, Y.; Muir, J.; Carrington, M.; Head, G.A.; Kaye, D.M.; Marques, F.Z. The gut microbiota and their metabolites in human arterial stiffness. *Heart Lung Circ.* **2021**, *30*, 1716–1725. [CrossRef]
88. McCoin, C.S.; Knotts, T.A.; Ono-Moore, K.D.; Oort, P.J.; Adams, S.H. Long-chain acylcarnitines activate cell stress and myokine release in C_2C_{12} myotubes: Calcium-dependent and -independent effects. *Am. J. Physiol. Metab.* **2015**, *308*, E990–E1000. [CrossRef]
89. Rutkowsky, J.M.; Knotts, T.A.; Ono-Moore, K.D.; McCoin, C.S.; Huang, S.; Schneider, D.; Singh, S.; Adams, S.H.; Hwang, D.H. Acylcarnitines activate proinflammatory signaling pathways. *Am. J. Physiol. Endocrinol. Metab.* **2014**, *306*, E1378–E1387. [CrossRef]
90. Aguer, C.; McCoin, C.S.; Knotts, T.A.; Thrush, A.B.; Ono-Moore, K.; McPherson, R.; Dent, R.; Hwang, D.H.; Adams, S.H.; Harper, M.E. Acylcarnitines: Potential implications for skeletal muscle insulin resistance. *FASEB J.* **2015**, *29*, 336–345. [CrossRef]
91. Ha, C.Y.; Kim, J.Y.; Paik, J.K.; Kim, O.Y.; Paik, Y.H.; Lee, E.J.; Lee, J.H. The association of specific metabolites of lipid metabolism with markers of oxidative stress, inflammation and arterial stiffness in men with newly diagnosed type 2 diabetes. *Clin. Endocrinol.* **2012**, *76*, 674–682. [CrossRef]
92. Paapstel, K.; Kals, J.; Eha, J.; Tootsi, K.; Ottas, A.; Piir, A.; Zilmer, M. Metabolomic profiles of lipid metabolism, arterial stiffness and hemodynamics in male coronary artery disease patients. *IJC Metab. Endocr.* **2016**, *11*, 13–18. [CrossRef]
93. Tootsi, K.; Kals, J.; Zilmer, M.; Paapstel, K.; Ottas, A.; Märtson, A. Medium- and long-chain acylcarnitines are associated with osteoarthritis severity and arterial stiffness in end-stage osteoarthritis patients: A case-control study. *Int. J. Rheum. Dis.* **2018**, *21*, 1211–1218. [CrossRef] [PubMed]
94. Koh, A.S.; Gao, F.; Liu, J.; Fridianto, K.T.; Ching, J.; Tan, R.S.; Wong, J.-I.; Chua, S.J.; Leng, S.; Zhong, L.; et al. Metabolomic profile of arterial stiffness in aged adults. *Diabetes Vasc. Dis. Res.* **2018**, *15*, 74–80. [CrossRef] [PubMed]
95. Toral, M.; Romero, M.; Jiménez, R.; Mahmoud, A.M.; Barroso, E.; Gómez-Guzmán, M.; Sánchez, M.; Cogolludo, Á.; García-Redondo, A.B.; Briones, A.M.; et al. Carnitine palmitoyltransferase-1 up-regulation by PPAR-β/δ prevents lipid-induced endothelial dysfunction. *Clin. Sci.* **2015**, *129*, 823–837. [CrossRef] [PubMed]
96. Chang, K.-C.; den Tseng, C.; Lu, S.-C.; Liang, J.-T.; Wu, M.-S.; Tsai, M.-S.; Hsu, K.-L. Effects of acetyl-L-carnitine and oxfenicine on aorta stiffness in diabetic rats. *Eur. J. Clin. Investig.* **2010**, *40*, 1002–1010. [CrossRef]
97. Li, J.; Wang, X.; Zhang, T.; Wang, C.; Huang, Z.; Luo, X.; Deng, Y. A review on phospholipids and their main applications in drug delivery systems. *Asian J. Pharm. Sci.* **2015**, *10*, 81–98. [CrossRef]
98. Kim, O.; Lim, H.; Lee, M.; Kim, J.; Lee, J. Association of fatty acid composition in serum phospholipids with metabolic syndrome and arterial stiffness. *Nutr. Metab. Cardiovasc. Dis.* **2013**, *23*, 366–374. [CrossRef]
99. Anderson, S.G.; Sanders, T.A.B.; Cruickshank, J.K. Plasma fatty acid composition as a predictor of arterial stiffness and mortality. *Hypertension* **2009**, *53*, 839–845. [CrossRef]
100. Lee, M.-H.; Kwon, N.; Yoon, S.R.; Kim, O.Y. Serum phospholipid docosahexaenoic acid is inversely associated with arterial stiffness in metabolically healthy men. *Clin. Nutr. Res.* **2016**, *5*, 190–203. [CrossRef]

101. Nishizawa, H.; Hamazaki, K.; Hamazaki, T.; Fujioka, S.; Sawazaki, S. The relationship between tissue RBC n-3 fatty acids and pulse wave velocity. *In Vivo* **2006**, *20*, 307–310.
102. Hall, W.L.; Sanders, K.A.; Sanders, T.A.B.; Chowienczyk, P.J. A high-fat meal enriched with eicosapentaenoic acid reduces postprandial arterial stiffness measured by digital volume pulse analysis in healthy men. *J. Nutr.* **2008**, *138*, 287–291. [CrossRef] [PubMed]
103. Van Der Veen, J.N.; Kennelly, J.P.; Wan, S.; Vance, J.E.; Vance, D.E.; Jacobs, R.L. The critical role of phosphatidylcholine and phosphatidylethanolamine metabolism in health and disease. *Biochim. Biophys. Acta (BBA) Biomembr.* **2017**, *1859*, 1558–1572. [CrossRef] [PubMed]
104. Subbaiah, P.V.; Albers, J.J.; Chen, C.H.; Bagdade, J.D. Low density lipoprotein-activated lysolecithin acylation by human plasma lecithin-cholesterol acyltransferase. Identity of lysolecithin acyltransferase and lecithin-cholesterol acyltransferase. *J. Biol. Chem.* **1980**, *255*, 9275–9280. [CrossRef]
105. Sekas, G.; Patton, G.M.; Lincoln, E.C.; Robins, S.J. Origin of plasma lysophosphatidylcholine: Evidence for direct hepatic secretion in the rat. *J. Lab. Clin. Med.* **1985**, *105*, 190–194.
106. Matsumoto, T.; Kobayashi, T.; Kamata, K. Mechanisms underlying lysophosphatidylcholine-induced potentiation of vascular contractions in the Otsuka Long-Evans Tokushima Fatty (OLETF) rat aorta. *Br. J. Pharmacol.* **2006**, *149*, 931–941. [CrossRef]
107. Hara, S.; Shike, T.; Takasu, N.; Mizui, T. Lysophosphatidylcholine promotes cholesterol efflux from mouse macrophage foam cells. *Arter. Thromb. Vasc. Biol.* **1997**, *17*, 1258–1266. [CrossRef]
108. Paapstel, K.; Kals, J.; Eha, J.; Tootsi, K.; Ottas, A.; Piir, A.; Jakobson, M.; Lieberg, J.; Zilmer, M. Inverse relations of serum phosphatidylcholines and lysophosphatidylcholines with vascular damage and heart rate in patients with atherosclerosis. *Nutr. Metab. Cardiovasc. Dis.* **2017**, *28*, 44–52. [CrossRef]
109. Kurotani, K.; Karunapema, P.; Jayaratne, K.; Sato, M.; Hayashi, T.; Kajio, H.; Fukuda, S.; Hara, H.; Okazaki, O.; Jayatilleke, A.U.; et al. Circulating odd-chain saturated fatty acids were associated with arteriosclerosis among patients with diabetes, dyslipidemia, or hypertension in Sri Lanka but not Japan. *Nutr. Res.* **2018**, *50*, 82–93. [CrossRef]
110. Petersen, K.S.; Keogh, J.B.; Lister, N.; Weir, J.M.; Meikle, P.J.; Clifton, P.M. Association between dairy intake, lipids and vascular structure and function in diabetes. *World J. Diabetes* **2017**, *8*, 202–212. [CrossRef]
111. Polonis, K.; Wawrzyniak, R.; Daghir-Wojtkowiak, E.; Szyndler, A.; Chrostowska, M.; Melander, O.; Hoffmann, M.; Kordalewska, M.; Raczak-Gutknecht, J.; Bartosińska, E.; et al. Metabolomic signature of Early Vascular Aging (EVA) in hypertension. *Front. Mol. Biosci.* **2020**, *7*, 12. [CrossRef]
112. Kim, J.Y.; Kim, O.Y.; Paik, J.K.; Kwon, D.Y.; Kim, H.J.; Lee, J.H. Association of age-related changes in circulating intermediary lipid metabolites, inflammatory and oxidative stress markers, and arterial stiffness in middle-aged men. *Age* **2013**, *35*, 1507–1519. [CrossRef] [PubMed]
113. Kim, M.; Jung, S.; Kim, S.Y.; Lee, S.-H.; Lee, J.H. Prehypertension-associated elevation in circulating lysophosphatidlycholines, Lp-PLA2 activity, and oxidative stress. *PLoS ONE* **2014**, *9*, e96735. [CrossRef] [PubMed]
114. Kugiyama, K.; Sugiyama, S.; Ogata, N.; Oka, H.; Doi, H.; Ota, Y.; Yasue, H. Burst production of superoxide anion in human endothelial cells by lysophosphatidylcholine. *Atherosclerosis* **1999**, *143*, 201–204. [CrossRef]
115. Murohara, T.; Scalia, R.; Lefer, A.M. Lysophosphatidylcholine promotes P-selectin expression in platelets and endothelial cells. Possible involvement of protein kinase C activation and its inhibition by nitric oxide donors. *Circ. Res.* **1996**, *78*, 780–789. [CrossRef]
116. Zhang, R.; Bai, N.; So, J.; Laher, I.; MacLeod, K.M.; Rodrigues, B. The ischemic metabolite lysophosphatidylcholine increases rat coronary arterial tone by endothelium-dependent mechanisms. *J. Mol. Cell. Cardiol.* **2009**, *47*, 112–120. [CrossRef]
117. Rao, S.P.; Riederer, M.; Lechleitner, M.; Hermansson, M.; Desoye, G.; Hallström, S.; Graier, W.F.; Frank, S. Acyl chain-dependent effect of lysophosphatidylcholine on endothelium-dependent vasorelaxation. *PLoS ONE* **2013**, *8*, e65155. [CrossRef]
118. Croset, M.; Brossard, N.; Polette, A.; Lagarde, M. Characterization of plasma unsaturated lysophosphatidylcholines in human and rat. *Biochem. J.* **2000**, *345*, 61–67. [CrossRef]
119. Stegemann, C.; Pechlaner, R.; Willeit, P.; Langley, S.R.; Mangino, M.; Mayr, U.; Menni, C.; Moayyeri, A.; Santer, P.; Rungger, G.; et al. Lipidomics profiling and risk of cardiovascular disease in the prospective population-based Bruneck study. *Circulation* **2014**, *129*, 1821–1831. [CrossRef]
120. Meikle, P.J.; Wong, G.; Tsorotes, D.; Barlow, C.K.; Weir, J.M.; Christopher, M.J.; MacIntosh, G.L.; Goudey, B.; Stern, L.; Kowalczyk, A.; et al. Plasma lipidomic analysis of stable and unstable coronary artery disease. *Arter. Thromb. Vasc. Biol.* **2011**, *31*, 2723–2732. [CrossRef]
121. Duivenvoorden, R.; Holleboom, A.G.; van den Bogaard, B.; Nederveen, A.J.; de Groot, E.; Hutten, B.A.; Schimmel, A.W.; Hovingh, G.K.; Kastelein, J.J.P.; Kuivenhoven, J.A.; et al. Cholesterol acyltransferase gene mutations have accelerated atherogenesis as assessed by carotid 3.0-T magnetic resonance imaging: Carriers of lecithin. *J. Am. Coll. Cardiol.* **2011**, *58*, 2481–2487. [CrossRef]
122. Rasmiena, A.A.; Ng, T.W.; Meikle, P.J. Metabolomics and ischaemic heart disease. *Clin. Sci.* **2013**, *124*, 289–306. [CrossRef] [PubMed]
123. Hannun, Y.A.; Obeid, L.M. Sphingolipids and their metabolism in physiology and disease. *Nat. Rev. Mol. Cell Biol.* **2018**, *19*, 175–191. [CrossRef] [PubMed]

124. Turpin-Nolan, S.M.; Brüning, J.C. The role of ceramides in metabolic disorders: When size and localization matters. *Nat. Rev. Endocrinol.* **2020**, *16*, 224–233. [CrossRef]
125. Maceyka, M.; Spiegel, S. Sphingolipid metabolites in inflammatory disease. *Nature* **2014**, *510*, 58–67. [CrossRef] [PubMed]
126. Salvia, R.; Halbac-Cotoara-zamfir, R.; Cividino, S.; Gutterman, D.D.; Quaranta, G. Manipulation of the sphingolipid rheostat influences the mediator of flow-induced dilation in the human microvasculature. *J. Am. Heart Assoc.* **2019**, *8*, e013153.
127. Li, Y.; Zhang, W.; Li, J.; Sun, Y.; Yang, Q.; Wang, S.; Luo, X.; Wang, W.; Wang, K.; Bai, W.; et al. The imbalance in the aortic ceramide/sphingosine-1-phosphate rheostat in ovariectomized rats and the preventive effect of estrogen. *Lipids Health Dis.* **2020**, *19*, 95. [CrossRef] [PubMed]
128. Cogolludo, A.; Villamor, E.; Perez-Vizcaino, F.; Moreno, L. Ceramide and regulation of vascular tone. *Int. J. Mol. Sci.* **2019**, *20*, 411. [CrossRef]
129. Bhat, O.M.; Yuan, X.; Cain, C.; Salloum, F.N.; Li, P. Medial calcification in the arterial wall of smooth muscle cell-specific Smpd1 transgenic mice: A ceramide-mediated vasculopathy. *J. Cell. Mol. Med.* **2020**, *24*, 539–553. [CrossRef]
130. Chun, L.; Junlin, Z.; Aimin, W.; Niansheng, L.; Benmei, C.; Minxiang, L. Inhibition of ceramide synthesis reverses endothelial dysfunction and atherosclerosis in streptozotocin-induced diabetic rats. *Diabetes Res. Clin. Pract.* **2011**, *93*, 77–85. [CrossRef]
131. Holland, W.L.; Brozinick, J.T.; Wang, L.-P.; Hawkins, E.D.; Sargent, K.M.; Liu, Y.; Narra, K.; Hoehn, K.L.; Knotts, T.A.; Siesky, A.; et al. Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat-, and obesity-induced insulin resistance. *Cell Metab.* **2007**, *5*, 167–179. [CrossRef]
132. Skácel, J.; Slusher, B.S.; Tsukamoto, T. Small molecule inhibitors targeting biosynthesis of ceramide, the central hub of the sphingolipid network. *J. Med. Chem.* **2021**, *64*, 279–297. [CrossRef]
133. Chatterjee, S.; Bedja, D.; Mishra, S.; Amuzie, C.; Avolio, A.; Kass, D.A.; Berkowitz, D.; Renehan, M. Inhibition of glycosphingolipid synthesis ameliorates atherosclerosis and arterial stiffness in Apolipoprotein E −/− mice and rabbits fed a high-fat and -cholesterol diet. *Circulation* **2014**, *129*, 2403–2413. [CrossRef] [PubMed]
134. Kim, M.; Jung, S.; Lee, S.H.; Lee, J.H. Association between arterial stiffness and serum L-octanoylcarnitine and lacto-sylceramide in overweight middle-aged subjects: 3-year follow-up study. *PLoS ONE* **2015**, *10*, e0119519.
135. Jung, S.; Kim, M.; Lee, Y.J.; Lee, S.H.; Lee, J.H. Associations between metabolomic-identified changes of biomarkers and arterial stiffness in subjects progressing to impaired fasting glucose. *Clin. Endocrinol.* **2015**, *83*, 196–204. [CrossRef]
136. Seth, S.K.; Newman, H.A.I. Sphingomyelin and other phospholipid metabolism in the rabbit atheromatous and normal aorta. *Circ. Res.* **1975**, *36*, 294–299. [CrossRef] [PubMed]
137. Edsfeldt, A.; Dunér, P.; Ståhlman, M.; Mollet, I.G.; Asciutto, G.; Grufman, H.; Nitulescu, M.; Persson, A.F.; Fisher, R.M.; Melander, O.; et al. Sphingolipids contribute to human atherosclerotic plaque inflammation. *Arter. Thromb. Vasc. Biol.* **2016**, *36*, 1132–1140. [CrossRef]
138. Jiang, X.-C.; Paultre, F.; Pearson, T.A.; Reed, R.G.; Francis, C.K.; Lin, M.; Berglund, L.; Tall, A.R. Plasma sphingomyelin level as a risk factor for coronary artery disease. *Arter. Thromb. Vasc. Biol.* **2000**, *20*, 2614–2618. [CrossRef]
139. Li, C.; He, J.; Li, S.; Chen, W.; Bazzano, L.; Sun, X.; Shen, L.; Liang, L.; Shen, Y.; Gu, X.; et al. Novel metabolites are associated with augmentation index and pulse wave velocity: Findings from the Bogalusa heart study. *Am. J. Hypertens.* **2019**, *32*, 547–556. [CrossRef]
140. Nelson, J.C.; Jiang, X.-C.; Tabas, I.; Tall, A.; Shea, S. Plasma sphingomyelin and subclinical atherosclerosis: Findings from the multi-ethnic study of atherosclerosis. *Am. J. Epidemiol.* **2006**, *163*, 903–912. [CrossRef]
141. Yu, Z.; Peng, Q.; Huang, Y. Potential therapeutic targets for atherosclerosis in sphingolipid metabolism. *Clin. Sci.* **2019**, *133*, 763–776. [CrossRef]
142. Sigruener, A.; Kleber, M.E.; Heimerl, S.; Liebisch, G.; Schmitz, G.; Maerz, W. Glycerophospholipid and sphingolipid species and mortality: The Ludwigshafen Risk and Cardiovascular Health (LURIC) study. *PLoS ONE* **2014**, *9*, e85724. [CrossRef] [PubMed]
143. Yen, C.L.E.; Stone, S.J.; Koliwad, S.; Harris, C.; Farese, R.V., Jr. Thematic review series: Glycerolipids DGAT enzymes and triacylglycerol biosynthesis. *J. Lipid Res.* **2008**, *49*, 2283–2301. [CrossRef] [PubMed]
144. Turner, N.; Cooney, G.J.; Kraegen, E.W.; Bruce, C.R. Fatty acid metabolism, energy expenditure and insulin resistance in muscle. *J. Endocrinol.* **2014**, *220*, T61–T79. [CrossRef] [PubMed]
145. Erion, D.M.; Shulman, G.I. Diacylglycerol-mediated insulin resistance. *Nat. Med.* **2010**, *16*, 400–402. [CrossRef]
146. Coen, P.M.; Goodpaster, B.H. Role of intramyocelluar lipids in human health. *Trends Endocrinol. Metab.* **2012**, *23*, 391–398. [CrossRef] [PubMed]
147. Kulkarni, H.; Meikle, P.J.; Mamtani, M.; Weir, J.M.; Barlow, C.K.; Jowett, J.B.; Bellis, C.; Dyer, T.D.; Johnson, M.P.; Rainwater, D.L.; et al. Plasma lipidomic profile signature of hypertension in Mexican American families: Specific role of diacylglycerols. *Hypertension* **2013**, *62*, 621–626. [CrossRef]
148. Pramfalk, C.; Eriksson, M.; Parini, P. Cholesteryl esters and ACAT. *Eur. J. Lipid Sci. Technol.* **2012**, *114*, 624–633. [CrossRef]
149. Kunnen, S.; van Eck, M. Lecithin: Cholesterol acyltransferase: Old friend or foe in atherosclerosis? *J. Lipid Res.* **2012**, *53*, 1783–1799. [CrossRef]
150. Peng, S.; Guo, W.; Morrisett, J.D.; Johnstone, M.T.; Hamilton, J.A. Quantification of cholesteryl esters in human and rabbit atherosclerotic plaques by magic-angle spinning ^{13}C-NMR. *Arter. Thromb. Vasc. Biol.* **2000**, *20*, 2682–2688. [CrossRef]

151. Miller, C.D.; Thomas, M.J.; Hiestand, B.; Samuel, M.P.; Wilson, M.D.; Sawyer, J.; Rudel, L.L. Cholesteryl esters associated with Acyl-CoA: Cholesterol acyltransferase predict coronary artery disease in patients with symptoms of acute coronary syndrome. *Acad. Emerg. Med.* **2012**, *19*, 673–682. [CrossRef]
152. van Popele, N.M.; Grobbee, D.E.; Bots, M.L.; Asmar, R.; Topouchian, J.; Reneman, R.S.; Hoeks, A.P.G.; van der Kuip, D.A.M.; Hofman, A.; Witteman, J.C.M. Association between arterial stiffness and atherosclerosis: The Rotterdam study. *Stroke* **2001**, *32*, 454–460. [CrossRef] [PubMed]
153. Wu, G. Amino acids: Metabolism, functions, and nutrition. *Amino Acids* **2009**, *37*, 41. [CrossRef] [PubMed]
154. Zagura, M.; Kals, J.; Kilk, K.; Serg, M.; Kampus, P.; Eha, J.; Soomets, U.; Zilmer, M. Metabolomic signature of arterial stiffness in male patients with peripheral arterial disease. *Hypertens. Res.* **2015**, *38*, 840–846. [CrossRef]
155. Kauko, A.; Palmu, J.; Jousilahti, P.; Havulinna, A.; Salomaa, V.; Niiranen, T. Associations between circulating metabolites and arterial stiffness. *J. Hum. Hypertens.* **2021**, *35*, 809–811. [CrossRef] [PubMed]
156. Jiang, Y.; Zhang, K.; Zhu, Z.; Cui, M.; An, Y.; Wang, Y.; Suo, C.; Fan, M.; Jin, L.; Tian, W.; et al. Associations between serum metabolites and subclinical atherosclerosis in a Chinese population: The Taizhou imaging study. *Aging* **2020**, *12*, 15302–15313. [CrossRef] [PubMed]
157. Zhenyukh, O.; González-Amor, M.; Rodrigues-Diez, R.R.; Esteban, V.; Ruiz-Ortega, M.; Salaices, M.; Mas, S.; Briones, A.M.; Egido, J. Branched-chain amino acids promote endothelial dysfunction through increased reactive oxygen species generation and inflammation. *J. Cell. Mol. Med.* **2018**, *22*, 4948–4962. [CrossRef]
158. Lee, C.C.; Watkins, S.M.; Lorenzo, C.; Wagenknecht, L.E.; Il'Yasova, D.; Chen, Y.-D.I.; Haffner, S.M.; Hanley, A.J. Branched-chain amino acids and insulin metabolism: The Insulin Resistance Atherosclerosis Study (IRAS). *Diabetes Care* **2016**, *39*, 582–588. [CrossRef]
159. Neishabouri, S.H.; Hutson, S.M.; Davoodi, J. Chronic activation of mTOR complex 1 by branched chain amino acids and organ hypertrophy. *Amino Acids* **2015**, *47*, 1167–1182. [CrossRef]
160. Tobias, D.K.; Lawler, P.R.; Harada, P.H.; Demler, O.V.; Ridker, P.M.; Manson, J.E.; Cheng, S.; Mora, S. Circulating branched-chain amino acids and incident cardiovascular disease in a prospective cohort of US women. *Circ. Genom. Precis. Med.* **2018**, *11*, e002157. [CrossRef]
161. Hellmuth, C.; Kirchberg, F.F.; Lass, N.; Harder, U.; Peissner, W.; Koletzko, B.; Reinehr, T. Tyrosine is associated with insulin resistance in longitudinal metabolomic profiling of obese children. *J. Diabetes Res.* **2016**, *2016*, 2108909. [CrossRef]
162. Monirujjaman, M.; Ferdouse, A. Metabolic and physiological roles of branched-chain amino acids. *Adv. Mol. Biol.* **2014**, *2014*, 364976. [CrossRef]
163. Cañes, L.; Alonso, J.; Ballester-Servera, C.; Varona, S.; Escudero, J.R.; Andrés, V.; Rodríguez, C.; Martínez-González, J. Targeting tyrosine hydroxylase for abdominal aortic aneurysm: Impact on inflammation, oxidative stress, and vascular remodeling. *Hypertension* **2021**, *78*, 681–692. [CrossRef] [PubMed]
164. Lin, T.-J.; Hsu, B.-G.; Wang, J.-H.; Lai, Y.-H.; Dongoran, R.A.; Liu, C.-H. Serum indoxyl sulfate as a potential biomarker of aortic arterial stiffness in coronary artery disease. *Nutr. Metab. Cardiovasc. Dis.* **2020**, *30*, 2320–2327. [CrossRef] [PubMed]
165. Katakami, N.; Omori, K.; Taya, N.; Arakawa, S.; Takahara, M.; Matsuoka, T.-A.; Tsugawa, H.; Furuno, M.; Bamba, T.; Fukusaki, E.; et al. Plasma metabolites associated with arterial stiffness in patients with type 2 diabetes. *Cardiovasc. Diabetol.* **2020**, *19*, 75. [CrossRef] [PubMed]
166. Zapolski, T.; Kamińska, A.; Kocki, T.; Wysokiński, A.; Urbanska, E.M. Aortic stiffness—Is kynurenic acid a novel marker? Cross-sectional study in patients with persistent atrial fibrillation. *PLoS ONE* **2020**, *15*, e0236413. [CrossRef]
167. Erasmus, D.; Mels, C.M.C.; Louw, R.; Lindeque, J.Z.; Kruger, R. Urinary metabolites and their link with premature arterial stiffness in black boys: The ASOS study. *Pulse* **2018**, *6*, 144–153. [CrossRef]
168. Chang, Y.C.; Wang, C.H.; Lai, Y.H.; Lin, Y.L.; Kuo, C.H.; Hsu, B.G.; Tsai, J.P. Low serum 3-methyl histidine level is associated with aortic stiffness in maintenance hemodialysis patients. *Ther. Apher. Dial.* **2021**. [CrossRef]
169. Kimble, R.; Murray, L.; Keane, K.M.; Haggerty, K.; Howatson, G.; Lodge, J.K. The influence of tart cherries (*Prunus cerasus*) on vascular function and the urinary metabolome: A randomised placebo-controlled pilot study. *J. Nutr. Sci.* **2021**, *10*, e73. [CrossRef]
170. Cziráki, A.; Lenkey, Z.; Sulyok, E.; Szokodi, I.; Koller, A. L-arginine-nitric oxide-asymmetric dimethylarginine pathway and the coronary circulation: Translation of basic science results to clinical practice. *Front. Pharmacol.* **2020**, *11*, 569914. [CrossRef]
171. Schulman, S.P.; Becker, L.C.; Kass, D.A.; Champion, H.C.; Terrin, M.L.; Forman, S.; Ernst, K.V.; Kelemen, M.D.; Townsend, S.N.; Capriotti, A.; et al. L-arginine therapy in acute myocardial infarction: The Vascular Interaction with Age in Myocardial Infarction (VINTAGE MI) randomized clinical trial. *JAMA* **2006**, *295*, 58–64. [CrossRef]
172. Kakimoto, Y.; Akazawa, S. Isolation and identification of N-G, N-G- and N-G,N'-G-dimethyl-arginine, N-epsilon-mono-, di-, and trimethyllysine, and glucosylgalactosyl- and galactosyl-delta-hydroxylysine from human urine. *J. Biol. Chem.* **1970**, *245*, 5751–5758. [CrossRef]
173. Ogawa, T.; Kimoto, M.; Sasaoka, K. Purification and properties of a new enzyme, N, N-dimethylarginine dimethylaminohydrolase, from rat kidney. *J. Biol. Chem.* **1989**, *264*, 10205–10209. [CrossRef]
174. Kals, J.; Kampus, P.; Kals, M.; Teesalu, R.; Zilmer, K.; Pulges, A.; Zilmer, M. Arterial elasticity is associated with endothelial vasodilatory function and asymmetric dimethylarginine level in healthy subjects. *Scand. J. Clin. Lab. Investig.* **2007**, *67*, 536–544. [CrossRef] [PubMed]

175. Hsu, C.-N.; Lu, P.-C.; Lo, M.-H.; Lin, I.-C.; Tain, Y.-L. The association between nitric oxide pathway, blood pressure abnormalities, and cardiovascular risk profile in pediatric chronic kidney disease. *Int. J. Mol. Sci.* **2019**, *20*, 5301. [CrossRef]
176. Chien, S.-J.; Lin, I.-C.; Hsu, C.-N.; Lo, M.-H.; Tain, Y.-L. Homocysteine and arginine-to-asymmetric dimethylarginine ratio associated with blood pressure abnormalities in children with early chronic kidney disease. *Circ. J.* **2015**, *79*, 2031–2037. [CrossRef]
177. Masaki, N.; Hakuno, D.; Toya, T.; Shiraishi, Y.; Kujiraoka, T.; Namba, T.; Yada, H.; Kimura, K.; Miyazaki, K.; Adachi, T. Association between brachial-ankle pulse wave velocity and the ratio of L-arginine to asymmetric dimethylarginine in patients undergoing coronary angiography. *J. Cardiol.* **2015**, *65*, 311–317. [CrossRef] [PubMed]
178. Klima, Ł.; Kawecka-Jaszcz, K.; Stolarz-Skrzypek, K.; Menne, J.; Fijorek, K.; Olszanecka, A.; Wojciechowska, W.; Bilo, G.; Czarnecka, D. Structure and function of large arteries in hypertension in relation to oxidative stress markers. *Kardiol. Pol.* **2013**, *71*, 917–923. [CrossRef]
179. Lin, I.-C.; Hsu, C.-N.; Lo, M.-H.; Chien, S.-J.; Tain, Y.-L. Low urinary citrulline/arginine ratio associated with blood pressure abnormalities and arterial stiffness in childhood chronic kidney disease. *J. Am. Soc. Hypertens.* **2015**, *10*, 115–123. [CrossRef]
180. Tayama, J.; Munakata, M.; Yoshinaga, K.; Toyota, T. Higher plasma homocysteine concentration is associated with more advanced systematic arterial stiffness and greater blood pressure response to stress in hypertensive patients. *Hypertens. Res.* **2006**, *29*, 403–409. [CrossRef]
181. van Dijk, S.C.; Smulders, Y.M.; Enneman, A.W.; Swart, K.M.A.; van Wijngaarden, J.P.; Ham, A.C.; van Schoor, N.M.; Dhonukshe-Rutten, R.A.M.; de Groot, L.C.P.G.M.; Lips, P.; et al. Homocysteine level is associated with aortic stiffness in elderly: Cross-sectional results from the B-PROOF study. *J. Hypertens.* **2013**, *31*, 952–959. [CrossRef]
182. Nakhai-Pour, H.R.; Grobbee, D.E.; Bots, M.L.; Muller, M.; van der Schouw, Y.T. Circulating homocysteine and large arterial stiffness and thickness in a population-based sample of middle-aged and elderly men. *J. Hum. Hypertens.* **2007**, *21*, 942–948. [CrossRef] [PubMed]
183. Welch, G.N.; Loscalzo, J. Homocysteine and atherothrombosis. *N. Engl. J. Med.* **1998**, *338*, 1042–1050. [CrossRef] [PubMed]
184. Tawakol, A.; Omland, T.; Gerhard, M.; Wu, J.T.; Creager, M.A. Hyperhomocyst (e) inemia is associated with impaired endothelium-dependent vasodilation in humans. *Circulation* **1997**, *95*, 1119–1121. [CrossRef] [PubMed]
185. Charpio, P.; Bescond, A.; Augier, T.; Chareyre, C.; Fraterno, M.; Rolland, P.-H.; Garçon, D. Hyperhomocysteinemia induces elastolysis in minipig arteries: Structural consequences, arterial site specificity and effect of captopril-hydrochlorothiazide. *Matrix Biol.* **1998**, *17*, 559–574. [CrossRef]
186. Wilkinson, I.B.; Megson, I.L.; MaCallum, H.; Rooijmans, D.F.; Johnson, S.M.; Boyd, J.L.; Cockcroft, J.R.; Webb, D.J. Acute methionine loading does not alter arterial stiffness in humans. *J. Cardiovasc. Pharmacol.* **2001**, *37*, 1–5. [CrossRef]
187. Doupis, J.; Eleftheriadou, I.; Kokkinos, A.; Perrea, D.; Pavlatos, S.; Gonis, A.; Katsilambros, N.; Tentolouris, N. Acute hyperhomocysteinemia impairs endothelium function in subjects with type 2 diabetes mellitus. *Exp. Clin. Endocrinol. Diabetes* **2010**, *118*, 453–458. [CrossRef]
188. Nestel, P.J.; Chronopoulos, A.; Cehun, M. Arterial stiffness is rapidly induced by raising the plasma homocysteine concentration with methionine. *Atherosclerosis* **2003**, *171*, 83–86. [CrossRef]
189. Durga, J.; Bots, M.L.; Schouten, E.G.; Grobbee, D.E.; Kok, F.J.; Verhoef, P. Effect of 3 y of folic acid supplementation on the progression of carotid intima-media thickness and carotid arterial stiffness in older adults. *Am. J. Clin. Nutr.* **2011**, *93*, 941–949. [CrossRef]
190. van Dijk, R.A.J.M.; Rauwerda, J.A.; Steyn, M.; Twisk, J.W.R.; Stehouwer, C.D.A. Long-term homocysteine-lowering treatment with folic acid plus pyridoxine is associated with decreased blood pressure but not with improved brachial artery endothelium-dependent vasodilation or carotid artery stiffness: A 2-year, randomized, placebo-controlled trial. *Arter.-Scler. Thromb. Vasc. Biol.* **2001**, *21*, 2072–2079.
191. Furuki, K.; Adachi, H.; Enomoto, M.; Otsuka, M.; Fukami, A.; Kumagae, S.-I.; Matsuoka, H.; Nanjo, Y.; Kakuma, T.; Imaizumi, T. Plasma Level of Asymmetric Dimethylarginine (ADMA) as a predictor of carotid intima-media thickness progression: Six-year prospective study using carotid ultrasonography. *Hypertens. Res.* **2008**, *31*, 1185–1189. [CrossRef]
192. Baliou, S.; Adamaki, M.; Ioannou, P.; Pappa, A.; Panayiotidis, M.I.; Spandidos, D.A.; Christodoulou, I.; Kyriakopoulos, A.M.; Zoumpourlis, V. Protective role of taurine against oxidative stress (Review). *Mol. Med. Rep.* **2021**, *24*, 605. [CrossRef] [PubMed]
193. Satoh, H.; Kang, J. Modulation by taurine of human arterial stiffness and wave reflection. *Adv. Exp. Med. Biol.* **2009**, *643*, 47–55. [CrossRef] [PubMed]
194. Ra, S.G.; Choi, Y.; Akazawa, N.; Ohmori, H.; Maeda, S. Taurine supplementation attenuates delayed increase in exercise-induced arterial stiffness. *Appl. Physiol. Nutr. Metab.* **2016**, *41*, 618–623. [CrossRef] [PubMed]
195. Sun, Q.; Wang, B.; Li, Y.; Sun, F.; Li, P.; Xia, W.; Zhou, X.; Li, Q.; Wang, X.; Chen, J.; et al. Taurine supplementation lowers blood pressure and improves vascular function in prehypertension: Randomized, double-blind, placebo-controlled study. *Hypertension* **2016**, *67*, 541–549. [CrossRef]
196. Tuomilehto, J.; Qiao, Q.; Borch-Johnsen, K.; Balkau, B. Glucose tolerance and mortality: Comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* **1999**, *354*, 617–621.
197. Kobayashi, R.; Sakazaki, M.; Nagai, Y.; Asaki, K.; Hashiguchi, T.; Negoro, H. Effects of different types of carbohydrates on arterial stiffness: A comparison of isomaltulose and sucrose. *Nutrients* **2021**, *13*, 4493. [CrossRef]
198. Kobayashi, R.; Sato, K.; Sakazaki, M.; Nagai, Y.; Iwanuma, S.; Ohashi, N.; Hashiguchi, T. Acute effects of difference in glucose intake on arterial stiffness in healthy subjects. *Cardiol. J.* **2021**, *28*, 446–452. [CrossRef]

199. Chavakis, T.; Bierhaus, A.; Nawroth, P.P. RAGE (Receptor for Advanced Glycation End products): A central player in the inflammatory response. *Microbes Infect.* **2004**, *6*, 1219–1225. [CrossRef] [PubMed]
200. Kemeny, S.F.; Figueroa, D.S.; Andrews, A.M.; Barbee, K.A.; Clyne, A.M. Glycated collagen alters endothelial cell actin alignment and nitric oxide release in response to fluid shear stress. *J. Biomech.* **2011**, *44*, 1927–1935. [CrossRef]
201. Sveen, K.A.; Dahl-Jørgensen, K.; Stensaeth, K.H.; Angel, K.; Seljeflot, I.; Sell, D.R.; Monnier, V.M.; Hanssen, K.F. Glucosepane and oxidative markers in skin collagen correlate with intima media thickness and arterial stiffness in long-term type 1 diabetes. *J. Diabetes Complicat.* **2015**, *29*, 407–412. [CrossRef]
202. Semba, R.D.; Sun, K.; Schwartz, A.V.; Varadhan, R.; Harris, T.B.; Satterfield, S.; Garcia, M.; Ferrucci, L.; Newman, A.B. Serum carboxymethyl-lysine, an advanced glycation end product, is associated with arterial stiffness in older adults. *J. Hypertens.* **2015**, *33*, 797–803. [CrossRef] [PubMed]
203. van Eupen, M.G.A.; Schram, M.T.; van Sloten, T.T.; Scheijen, J.; Sep, S.J.S.; van der Kallen, C.J.; Dagnelie, P.C.; Koster, A.; Schaper, N.; Henry, R.M.A.; et al. Skin autofluorescence and pentosidine are associated with aortic stiffening: The Maastricht study. *Hypertension* **2016**, *68*, 956–963. [CrossRef] [PubMed]
204. van der Bruggen, M.M.; Spronck, B.; Delhaas, T.; Reesink, K.D.; Schalkwijk, C.G. The putative role of methylglyoxal in arterial stiffening: A review. *Heart Lung Circ.* **2021**, *30*, 1681–1693. [CrossRef] [PubMed]
205. Forbes, J.M.; Thorpe, S.R.; Thallas-Bonke, V.; Pete, J.; Thomas, M.C.; Deemer, E.R.; Bassal, S.; El-Osta, A.; Long, D.M.; Panag-iotopoulos, S.; et al. Modulation of soluble receptor for advanced glycation end products by angiotensin-converting en-zyme-1 inhibition in diabetic nephropathy. *J. Am. Soc. Nephrol.* **2005**, *16*, 2363–2372. [CrossRef] [PubMed]
206. Nakamura, T.; Sato, E.; Fujiwara, N.; Kawagoe, Y.; Takeuchi, M.; Maeda, S.; Yamagishi, S.-I. Atorvastatin reduces proteinuria in non-diabetic chronic kidney disease patients partly via lowering serum levels of Advanced Glycation End products (AGEs). *Oxidative Med. Cell. Longev.* **2010**, *3*, 304–307. [CrossRef]
207. Sourris, K.C.; Watson, A.; Jandeleit-Dahm, K. Inhibitors of Advanced Glycation End product (AGE) formation and accumulation. In *Handbook of Experimental Pharmacology: Reactive Oxygen Species*; Schmidt, H.H.W., Ghezzi, P., Cuadrado, A., Eds.; Springer: Berlin/Heidelberg, Germany, 2021; Volume 264, pp. 395–423.
208. el Ridi, R.; Tallima, H. Physiological functions and pathogenic potential of uric acid: A review. *J. Adv. Res.* **2017**, *8*, 487–493. [CrossRef]
209. Saito, Y.; Tanaka, A.; Node, K.; Kobayashi, Y. Uric acid and cardiovascular disease: A clinical review. *J. Cardiol.* **2021**, *78*, 51–57. [CrossRef]
210. Alem, M.M.; Alshehri, A.; Cahusac, P.; Walters, M.R. Effect of xanthine oxidase inhibition on arterial stiffness in patients with chronic heart failure. *Clin. Med. Insights Cardiol.* **2018**, *12*, 1179546818779584. [CrossRef]
211. Canepa, M.; Viazzi, F.; Strait, J.B.; Ameri, P.; Pontremoli, R.; Brunelli, C.; Studenski, S.; Ferrucci, L.; Lakatta, E.G.; Alghatrif, M. Longitudinal association between serum uric acid and arterial stiffness: Results from the Baltimore longitudinal study of aging. *Hypertension* **2017**, *69*, 228–235. [CrossRef]
212. Chen, X.; Li, Y.; Sheng, C.-S.; Huang, Q.-F.; Zheng, Y.; Wang, J.-G. Association of serum uric acid with aortic stiffness and pressure in a Chinese workplace setting. *Am. J. Hypertens.* **2010**, *23*, 387–392. [CrossRef]
213. Liu, X.; Wu, J.; Wu, H.; Yi, C.; Huang, F.; Yu, X.; Yang, X. Association of serum uric acid with arterial stiffness in peritoneal dialysis patients. *Kidney Blood Press. Res.* **2018**, *43*, 1451–1458. [CrossRef] [PubMed]
214. Cicero, A.F.G.; Rosticci, M.; Fogacci, F.; Grandi, E.; D'Addato, S.; Borghi, C.; Brisighella Heart Study Group. High serum uric acid is associated to poorly controlled blood pressure and higher arterial stiffness in hypertensive subjects. *Eur. J. Intern. Med.* **2017**, *37*, 38–42. [CrossRef] [PubMed]
215. Cicero, A.F.G.; Salvi, P.; D'Addato, S.; Rosticci, M.; Borghi, C. Association between serum uric acid, hypertension, vascular stiffness and subclinical atherosclerosis: Data from the Brisighella heart study. *J. Hypertens.* **2014**, *32*, 57–64. [CrossRef]
216. Albu, A.; Para, I.; Porojan, M. Uric acid and arterial stiffness. *Ther. Clin. Risk Manag.* **2020**, *16*, 39–54. [CrossRef]
217. George, J.; Struthers, A.D. Role of urate, xanthine oxidase and the effects of allopurinol in vascular oxidative stress. *Vasc. Health Risk Manag.* **2009**, *5*, 265–272. [CrossRef]
218. Pandey, K.B.; Rizvi, S.I. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid. Med. Cell. Longev.* **2009**, *2*, 270–278. [CrossRef]
219. Man, A.W.C.; Li, H.; Xia, N. Resveratrol and the Interaction between gut microbiota and arterial remodelling. *Nutrients* **2020**, *12*, 119. [CrossRef] [PubMed]
220. Lilamand, M.; Kelaiditi, E.; Guyonnet, S.; Antonelli Incalzi, R.; Raynaud-Simon, A.; Vellas, B.; Cesari, M. Flavonoids and arterial stiffness: Promising perspectives. *Nutr. Metab. Cardiovasc. Dis.* **2014**, *24*, 698–704. [CrossRef]
221. de Bruyne, T.; Steenput, B.; Roth, L.; de Meyer, G.R.Y.; dos Santos, C.N.; Valentová, K.; Dambrova, M.; Hermans, N. Dietary polyphenols targeting arterial stiffness: Interplay of contributing mechanisms and gut microbiome-related metabolism. *Nutrients* **2019**, *11*, 578. [CrossRef] [PubMed]
222. Ponte, B.; Pruijm, M.; Ackermann, D.; Ehret, G.; Ansermot, N.; Staessen, J.A.; Vogt, B.; Pechère-Bertschi, A.; Burnier, M.; Martin, P.Y.; et al. Associations of urinary caffeine and caffeine metabolites with arterial stiffness in a large population-based study. *Mayo Clin. Proc.* **2018**, *93*, 586–596. [CrossRef]
223. Karatzi, K.; Papaioannou, T.G.; Psaltopoulou, T.; Tousoulis, D. Caffeine effects on arterial stiffness: To Drink or not to drink? *Mayo Clin. Proc.* **2018**, *93*, 1149–1150. [CrossRef] [PubMed]

224. Haam, J.-H.; Kim, Y.-S.; Cho, D.-Y.; Chun, H.; Choi, S.-W.; Lee, Y.K.; Lim, S.W.; Koo, H.S.; Kim, M.J. Elevated levels of urine isocitrate, hydroxymethylglutarate, and formiminoglutamate are associated with arterial stiffness in Korean adults. *Sci. Rep.* **2021**, *11*, 10180. [CrossRef] [PubMed]
225. Larijani, V.N.; Ahmadi, N.; Zeb, I.; Khan, F.; Flores, F.; Budoff, M. Beneficial effects of aged garlic extract and coenzyme Q10 on vascular elasticity and endothelial function: The FAITH randomized clinical trial. *Nutrition* **2013**, *29*, 71–75. [CrossRef] [PubMed]
226. Cicero, A.F.; Morbini, M.; Rosticci, M.; D'Addato, S.; Grandi, E.; Borghi, C. Middle-term dietary supplementation with red yeast rice plus coenzyme Q10 improves lipid pattern, endothelial reactivity and arterial stiffness in moderately hypercholesterolemic subjects. *Ann. Nutr. Metab.* **2016**, *68*, 213–219. [CrossRef]
227. Lee, Y.-J.; Cho, W.-J.; Kim, J.-K.; Lee, D.-C. Effects of coenzyme Q10 on arterial stiffness, metabolic parameters, and fatigue in obese subjects: A double-blind randomized controlled study. *J. Med. Food* **2011**, *14*, 386–390. [CrossRef]
228. Laurent, S.; Boutouyrie, P.; Cunha, P.G.; Lacolley, P.; Nilsson, P.M. Concept of extremes in vascular aging: From early vascular aging to supernormal vascular aging. *Hypertension* **2019**, *74*, 308–318. [CrossRef]
229. Rhee, E.P.; Clish, C.B.; Ghorbani, A.; Larson, M.G.; Elmariah, S.; McCabe, E.; Yang, Q.; Cheng, S.; Pierce, K.; Deik, A.; et al. A combined epidemiologic and metabolomic approach improves CKD prediction. *J. Am. Soc. Nephrol.* **2013**, *24*, 1330–1338. [CrossRef]
230. Rhee, E.P.; Clish, C.B.; Wenger, J.; Roy, J.; Elmariah, S.; Pierce, K.A.; Bullock, K.; Anderson, A.H.; Gerszten, R.E.; Feldman, H.I. Metabolomics of chronic kidney disease progression: A case-control analysis in the Chronic Renal Insufficiency Cohort study. *Am. J. Nephrol.* **2016**, *43*, 366–374. [CrossRef]
231. Lavi, S.; McConnell, J.P.; Rihal, C.S.; Prasad, A.; Mathew, V.; Lerman, L.O.; Lerman, A. Local production of lipoprotein-associated phospholipase A2 and lysophosphatidylcholine in the coronary circulation: Association with early coronary atherosclerosis and endothelial dysfunction in humans. *Circulation* **2007**, *115*, 2715–2721. [CrossRef]
232. Lavi, S.; Yang, E.H.; Prasad, A.; Mathew, V.; Barsness, G.W.; Rihal, C.S.; Lerman, L.O.; Lerman, A. The interaction between coronary endothelial dysfunction, local oxidative stress, and endogenous nitric oxide in humans. *Hypertension* **2008**, *51*, 127–133. [CrossRef]