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sciendo

284 ENDOCRINE REGULATIONS, Vol. 56, No. 4, 284–294, 2022

doi:10.2478/enr-2022-0031

Pathophysiological and clinical aspects of the circadian rhythm of arterial stiffness in diabetes mellitus: A minireview

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Several cross-sectional trials have revealed increased arterial stiffness connected with the cardiac autonomic neuropathy in types 2 and 1 diabetic patients. The pathophysiological relationship between arterial stiffness and autonomic dysfunction in diabetes mellitus is still underinvestigated and the question whether the presence of cardiac autonomic neuropathy leads to arterial stiffening or increased arterial stiffness induced autonomic nervous system impairment is still open. Both arterial stiffness and dysfunction of the autonomic nervous system have common pathogenetic pathways, counting state of the chronic hyperinsulinemia and hyperglycemia, increased formation of advanced glycation end products, activation of protein kinase C, development of endothelial dysfunction, and chronic low-grade inflammation. Baroreceptor dysfunction is thought to be one of the possible reasons for the arterial wall stiffening development and progression. On the contrary, violated autonomic nervous system function can affect the vascular tone and by this way alter the large arteries walls elastic properties. Another possible mechanism of attachment and/or development of arterial stiffness is the increased heart rate and autonomic dysfunction corresponding progression. This minireview analyzes the current state of the relationship between the diabetes mellitus and the arterial stiffness. Particular attention is paid to the analysis, interpretation, and application of the results obtained in patients with type 2 diabetes mellitus and diabetic cardiac autonomic neuropathy.

Key words: diabetic cardiac autonomic neuropathy, diabetes mellitus, arterial stiffness, 24-h monitoring

The dysfunction in the heart rate variability (HRV) and abnormalities in the blood pressure may increase the risk of cardiovascular disease (CVD) over the next six years from 4% to 100% (Mehlum et al. 2018; Warburton et al. 2019). It has been reported that the probability of stroke or cardiac death can immediately be reduced by chronobiologically assessing blood pressure and heart rate variability and optimizing the treatment efficacy timing (Maciorowska et al. 2020; Rana et al. 2020). Physiological cardiovascular activities are controlled by the cardiac autonomic nervous system. The autonomic nervous system disturbances result in vascular dynamics and heart rate control violations, particularly in the cardiac autonomic neuropathy (Merz et al. 2015; Vinik et al. 2018). The autonomic imbalance between the two, parasympathetic and sympathetic parts of the autonomic nervous system regulation of the cardiovascular function leads to metabolic abnormalities and increased morbidity and mortality in patients with diabetes mellitus (Bissinger 2017; Valensi 2021). Circadian rhythms disorders have been demonstrated in diabetes mellitus persons due to alterations in glucose metabolism, circadian clock oscillations, autonomic function, and neuroendocrine sleep architecture.

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Its close relationship with diurnal profiles of blood pressure and heart rate has also be found (Onaolapo and Onaolapo 2018).

The metabolic syndrome (MetS), hypertension, myocardial infarction, and diabetes mellitus are characterized by an increased sympathetic and decreased parasympathetic activity (Gorky and Schwaber 2019). It should be noted that sympathetic activation has already been observed in the offspring of type 2 diabetic patients associated with hyperinsulinemia (Frontoni et al. 2000). However, type 2 diabetes mellitus (T2D) patients had decreased both parasympathetic and sympathetic activities (Straznicky et al. 2016). The latter can be explained by T2D, a metabolic disease responsible for a cardiac autonomic neuropathy that affects both sympathetic and parasympathetic fibers (Chamarthi et al. 2019; Valensi 2021; Ziegler et al. 2021).

Patients with T2D have been noted to have a relationship between changes in heart rate, "nondipping" during 24-h ambulatory blood pressure monitoring and increased mortality. This may represent various pathophysiologic processes: preferential parasympathetic denervation in the cardiac autonomic neuropathy of long-standing diabetes mellitus, heart failure, obstructive sleep apnea, increased sympathetic activity in chronic kidney disease, etc. (Grossman 2013; Serhiyenko and Serhiyenko 2018; Serhiyenko et al. 2018).

The autonomic nervous system dysfunction is a risk factor for CVD. Nevertheless, the exact mechanism linking CVD with autonomic dysfunction is unknown (Pop-Busui 2010). The cardiac autonomic nervous system disturbances represent a common risk factor for the cardiovascular morbidity (Hajar 2017). Low baroreflex sensitivity and decreased HRV belongs to the early signs of the cardiac autonomic dysfunction (Pop-Busui 2010; Spallone et al. 2011; Ziegler et al. 2014; Pop-Busui et al. 2017).

According to the Toronto Consensus Panel on Diabetic Neuropathy, cardiac autonomic neuropathy is an "impairment of autonomic control of the cardiovascular system in the setting of diabetes after excluding other causes" (Spallone et al. 2011). Cardiac autonomic neuropathy is a well-known factor for cardiovascular morbidity, namely stroke, congestive heart failure, heart attack, and sudden death syndrome (Yun et al. 2018). These endpoints are associated with cardiac structure remodeling followed by changes in hypertension, such as fibrosis and hypertrophy. This remodeling accompanies changes in distribution, expression, and cell membrane ion channels function, Ca^{2+}-cycling proteins, intercellular gap junction connexin-43 channels, and extracellular matrix composition (Pop-Busui et al. 2017; Serhiyenko et al. 2022).

Recently, the evaluation of a new CVDs risk factor, namely, "syndrome of vascular aging," has been actively discussed. The arteries rigidity increase due to a decrease of elastin, an increase of collagen content, and a violation of endothelial-mediated vasodilation are common in physiological aging. However, the arteries' rigidity can also be increased due to several other factors (Agnoletti et al. 2013; Bagherzadeh et al. 2013; Mansour et al. 2013; Xu et al. 2016).

Some features of epidemiology and pathophysiological mechanisms

Diabetic cardiac autonomic neuropathy has been reported in at least 20% of unselected patients and up to 65% in patients with increasing age and disease duration (Spallone et al. 2011). The prevalence of cardiac autonomic neuropathy in patients with T2D is about 7% and increases with disease duration by 4.6–6% per year (Spallone et al. 2011; Spallone 2019).

As the damping function of the aorta depends on its stiffness, pulse wave velocity, aortic pulse pressure, and aortic augmentation index may be recommended for assessment. Central systolic blood pressure is a stronger predictor of CVD than the central diastolic blood pressure. It reflects more blood flow in the cerebral and coronary vessels (Liu et al. 2020; Jeon et al. 2021). Consequently, measurements of aortic augmentation index and aortic pulse pressure parameters may be more important for evaluating the cardiovascular system state than just the evaluation of pulse wave velocity (Bagherzadeh et al. 2013; Xu et al. 2016).

Many epidemiological trials have reported that increased arterial stiffness predicts morbidity and mortality, independently of other CVD risk factors. Evaluation of carotid-femoral pulse wave velocity is a standard gold method for arterial stiffness measurement and its increase is associated with subclinical CVDs (Kim and Kim 2019; Podolec et al. 2019). Furthermore, arterial stiffness increases with physiological aging or several pathological processes associated with chronic renal disease, metabolic syndrome, hypertension, and diabetes mellitus. Development of diabetes mellitus may intensify the arterial stiffness through the development of pathological changes in arteries, especially in type or structure of elastin and/or collagen throughout the arterial wall that are connected with the increased sympathetic tone, oxidative stress, chronic low-grade inflammation, and reduced nitric oxide bioavailability (Gaszner et al. 2012; de Oliveira Alvim et al. 2013; Okamoto et al. 2016).

According to Pop-Busui (2010) diabetes-related cardiac autonomic neuropathy results from complex

interactions between glycemic control, duration of disease, systolic and diastolic blood pressure, and aging-related neuronal death (Pop-Busui 2010). It is considered that the main culprit is hyperglycemia, glucose variability that stimulates a cascade of multiple complex mechanisms and pathways that cause oxidative stress and toxic glycosylation products ultimately leading to neuronal dysfunction and death (Agashe and Petak 2018; Spallone 2018). There are several pathophysiological mechanisms common to autonomic cardiac dysfunction and arterial stiffness. First, arterial stiffness may be involved in the progression of insulin resistance, one of the important triggers for the development of autonomic nervous system disorders in diabetes mellitus including diabetic cardiac autonomic neuropathy. Second, endothelial dysfunction in diabetic cardiac autonomic neuropathy can lead to diastolic capillary dysfunction, wrinkling or sparse distribution, which, in turn, contributes to the development of arterial wall rigidity. Conversely, the connection and progression of arterial stiffness is an aggressive factor in capillary damage. Third, diastolic capillary dysfunction in the development of arterial rigidity can lead to decreased tissue perfusion, which contributes to the progression of insulin resistance in diabetic cardiac autonomic neuropathy. Fourth, increased oxidative stress and chronic low-grade inflammation are known to be common pathophysiological chains of arterial stiffness and diabetic cardiac autonomic neuropathy. Fifth, the arterial stiffness and the diabetic cardiac autonomic neuropathy may have the same genetic background (Xu et al. 2016; Agashe and Petak 2018; Spallone 2018; Chirinos et al. 2019; Zheng et al. 2020).

Chronic hyperglycemia in terms of diabetes mellitus leads to vascular dysfunction, which is associated with the activation of pro-inflammatory transcription factors and increased arterial stiffness, leading to vasculopathy (Petrie et al. 2018). Increased accumulation of advanced glycation end-products is closely related to the alteration of the important matrix of molecules in the vascular wall (Kopytek et al. 2020). Moreover, some studies have indicated development of vascular smooth muscle cells dysfunction among persons with diabetes compared to healthy persons demonstrating that T2D may reduce the endothelial nitric oxide bioavailability and attenuate the vascular smooth muscle cells sensitivity to nitric oxide. These pathways are involved in developing the arterial stiffness increase associated with hyperglycemia. Comparing the arterial stiffness in patients with primary autonomic failure and healthy age- and sex-matched persons demonstrated an increase in the arterial stiffness parameters in the first group of patients. These results imply a pathophysiological link between the cardiac autonomic dysfunction and the arterial stiffness and also indicate that the arterial wall elastic properties strongly depend on the autonomic nervous system integrity (de Oliveira Alvim et al. 2013; Chawla et al. 2014; Zhao et al. 2015; Chorepsima et al. 2017; Bakkar et al. 2020; Cseh et al. 2020).

Currently, the link between the arterial stiffness and the autonomic dysfunction is under investigation and the question whether cardiac autonomic dysfunction may cause arterial stiffness or increased arterial stiffness may induce autonomic dysfunction, is still open. State of low-grade inflammation, chronic hyperglycemia, hyperinsulinemia, activation of protein kinase C, formation of advanced glycation end-products, and the development of endothelial dysfunction are known to be involved in the pathogenesis of the arterial stiffness and the cardiac autonomic dysfunction (Madamanchi et al. 2005; Jia et al. 2016; Chorepsima et al. 2017; Guan et al. 2017).

Hyperglycemia

Activation of protein kinase C and polyol pathways, nonenzymatic glycosylation, and oxidative stress are the common pathways leading to vascular and neuronal damages by the state of chronic hyperglycemia. The hyperglycemia triggered mechanisms result in arterial stiffness and endothelial dysfunction, which are responsible for the development and progressing of chronic diabetic complications (Frontoni et al. 2013; Ciftel et al. 2014; Seko 2020). Hyperglycemia triggers endothelial dysfunction through free radicals levels increase, decreased nitric oxide synthesis, and failure of antioxidant defense mechanisms. Chronic glycemia increases the proliferation of vascular smooth muscle cells and state of low-grade chronic inflammation increases the advanced glycation end-products generation, augments cross-linking of collagen in the arterial wall, decreases the expression of matrix metalloproteinase-2 and -9 (enzymes degrading elastin), enhances the angiotensin-2 generation in vascular tissue, and increases the endothelial permeability (Zhao et al. 2015; Fakhruddin et al. 2017; Oguntibeju 2019). The development of endothelial dysfunction is a key event in the atherosclerotic process initiation. Hyperglycemia leads to "functional" stiffening of arteries, as a continuous nitric oxide release by endothelium contributes to the functional regulation of arterial elasticity, aimed to adapt peripheral conduit artery mechanics to changes in blood flow (Kozakova and Palombo 2016).

Insulin resistance

Results of prospective trials have demonstrated the contribution of insulin resistance to CVD development in patients with diabetes mellitus and non-diabetic persons (Di Pino and DeFronzo 2019). The increase of the risk of CVDs events has been proven across quintiles of the Homeostasis model assessment of insulin resistance (HOMA-insulin resistance) (Spallone et al. 2018; Moshkovits et al. 2021). Development of insulin resistance leads to an enhanced generation of reactive oxygen species, excessive free fatty acids release from adipose tissue, and decreased synthesis/release of nitric oxide. Increased circulating free fatty acids lead to the activation of nuclear factor kappa-light-chain-enhancer of activated B cells, which induces the expression of various proinflammatory genes and endothelial function impairment (Kozakova and Palombo 2016; Guan et al. 2017; Galicia-Garcia et al. 2020). Hyperinsulinemia increases cholesterol synthesis/transport in cultured arterial smooth muscle cells, the synthesis of hepatic very low-density lipoproteins, augments collagen synthesis, stimulates the arterial smooth muscle cells proliferation, and turns on multiple genes involved in the inflammation process (Kozakova and Palombo 2016). In the subjects with T2D, insulin resistance and alcohol use have been related to increased arterial stiffness, proving that increased arterial stiffness can mediate the association between T2D and increased risk of atherosclerosis (van Dijk et al. 2003; Elias et al. 2018).

Results of trials have demonstrated negative association between insulin sensitivity and mean carotid intima-media thickness, partly explained by the presence of established CVD risk factors (Lu et al. 2021). In persons without diabetes, the association between carotid intima-media thickness and HOMA-insulin resistance index has been explained by traditional CVD risk factors, first of all by hypertension (Guan et al. 2017). The association between carotid atherosclerosis and HOMA- insulin resistance index depended mainly on the clustered expression of the MetS components. The relation between lower insulin sensitivity was mediated by circulating adipocytokines and free fatty acids (Fahed et al. 2022). These results suggest that insulin resistance *per se* has no strong effect on the atherosclerotic process and that its effect on the carotid wall is mediated by other hemodynamic and cellular changes related to the diabetes mellitus and insulin resistance, like hypertension, dyslipidemia, free fatty acids, adipocytokines, and chronic inflammation (Kozakova and Palombo 2016).

Moreover, a novel relationship between arterial stiffness, hyperinsulinemia, and cardiac autonomic neuropathy has been shown in a T2D population suggesting their impact on the progression of CVD development in this cohort of patients (Bagherzadeh et al. 2013; Pop-Busui et al. 2017). The mechanisms linking atherosclerosis and autonomic imbalance are still incompletely clarified. Recent studies have indicated a connection between low-grade inflammation and autonomic dysfunction among persons with CVDs, namely an inverse association between levels of inflammatory molecules and activity of autonomic nervous system. Namely, decreased HRV parameters have been found (Ulleryd et al. 2017). The imbalance of inflammatory mediators drives the atherosclerosis progression and plays a major role in all phases of the disease.

Inflammation

The first increase in blood glucose levels in persons with diabetes mellitus is accompanied by a microcirculatory dysfunction and an endothelial inflammation (Song et al. 2014; Cakar et al. 2017; Ulleryd et al. 2017). Expression of E-selectin can be induced in response to inflammatory stimuli including an increase of tumor necrosis factor-alpha and interleukin-1. The E-selectin (CD62) is an adhesion molecule associated with the development of MetS and its components: IR, obesity, and CVDs (Adamska et al. 2014). In patients with prediabetes, the levels of E-selectin correlate with glucose levels and the highest levels of E-selectin characterize the development of diabetes mellitus. These findings are consistent with the state that the increase of endothelial inflammation continues with diabetes mellitus progression (Cakar et al. 2015, 2017).

Results of recent trials suggest a link between autonomic dysfunction and inflammation and between inflammation and atherosclerosis. These data have suggested that the atherogenic impact of autonomic nervous system dysfunction is mediated by inflammation (Rupprecht et al. 2020). There are some investigations that were aimed to study the whole pathogenetic way (autonomic nervous system dysfunction – chronic low-grade inflammation – development of atherosclerosis) in the same patient cohort or the development of carotid atherosclerosis as the primary end-point (Alfaddagh et al. 2020). Recently, a marker of preclinical atherosclerosis, i.e. intima-media thickness, was connected with a reducing heart rate variability and an increasing C-reactive protein in patients suffering from depression (Ulleryd et al. 2017). Ulleryd et al. (2017) have hypothesized that inflammation can mediate the pathogenetic link between the autonomic dysfunction

and atherosclerosis. An inverse association has been found between the chronic low-grade inflammation and function of the cardiac autonomic system, which can result in the atherosclerosis progression leading to CVDs.

Increased carotid intima-media thickness is considered to be an early atherosclerosis marker and the presence of atherosclerotic plaques suggests a more advanced stage of the disease (Tschiderer et al. 2020). The carotid intima-media thickness increase, higher prevalence of carotid atherosclerotic plaques, and increased carotid plaque volume are often seen in T2D persons and they are associated with preprandial glycemia levels, glucose variability, and glycated hemoglobin A1c levels in the patients with and without diabetes mellitus (Kozakova and Palombo 2016).

Endothelial dysfunction

Impaired endothelial function and atherosclerosis are the main pathogenetic factors of the end-organ impairment. Vascular endothelial cells have many unique functions including homeostasis, blood vessel tone, fluid filtration, hormone trafficking, neutrophil recruitment, and angiogenesis. Endothelial dysfunction is known as the precursor of atherosclerosis (Mancia et al. 2013; Botts et al. 2021). Development and increase of inflammation and endothelial dysfunction correlate with increased glucose levels through the development of T2D. Endothelial dysfunction is the most recognized pathological process of the chronic diabetes complications development. Endothelial dysfunction may upgrade insulin resistance and dysregulation of glucose with the further development of diabetes mellitus, but the exact role of endothelial dysfunction in prediabetes and diabetes is still under investigation (Cakar et al. 2015).

Endothelial dysfunction and increased arterial wall thickness are the key factors leading to the development of micro- and macro-vascular complications of diabetes mellitus. Chronic hyperglycemia leads to an arterial stiffening, causing functional and structural changes in large vessels. Consequently, endothelial dysfunction managing and arterial elasticity maintenance are significant through optimal glycemic control and glycemic goals achievement (Climie et al. 2019). Additionally, the prevention of diabetic complications is promising through the management of the endothelial dysfunction and the arterial stiffness. The normalization of arterial stiffness and a decrease in the endothelial dysfunction are likely to decrease the risk of CVDs development, accordingly decreasing the morbidity and mortality levels in diabetic patients (Ciftel et al. 2014).

The increased arterial stiffness is a standard indicator for the atherosclerotic process. Its development and progression are connected with the following risk factors: aging, dyslipidemia, diabetes mellitus, hypertension, and smoking. Increased arterial stiffness is tightly connected to chronic heart diseases, cerebrovascular disease, and peripheral arterial disease (Christen et al. 2010; Cakar et al. 2015). The pulse wave velocity is the gold-standard method for the evaluation of arterial stiffness and is an independent predictor of morbidity and mortality due to CVDs (Loehr et al. 2016). Multiple studies have reported the increase of arterial stiffness parameters in diabetes mellitus patients and confirmed that increased pulse wave velocity predicts a higher mortality level in these patients (Chorepsima et al. 2017). An interesting finding has been reported indicating that IAxao parameters were similar among T2D patients and non-diabetic controls; however, after multiple adjustments of several risk factors in the regression model, the relation of aortic augmentation index to diabetes status was found (Chen et al. 2015). At first glance, there was no difference found between the IAxao parameters in non-diabetic controls and T2D patients, but the IAxao increase was found in diabetic patients after adjustment of heart rate (Yeboah et al. 2016). Yeboah et al. (2016) have hypothesized that non-obese and non-hypertensive persons with T2D have increased the arterial wall stiffness parameters compared to the age- and gender-matched controls without T2D.

Cardiac autonomic dysfunction and blood pressure

Increased pulse wave velocity among T2D patients is associated with the blood pressure levels increase and cardiac autonomic dysfunction, while the link between impaired cardiac autonomic function and arterial stiffness is not mediated by increased heart rate or low baroreflex sensitivity. The prognostic role of nondipping and reverse dipping is well documented in diabetes mellitus. Diabetes is a favorable scenario for the altered blood pressure variability, which might mediate the harmful effects of cardiac autonomic neuropathy (Spallone 2019). Chorepsima et al. (2017) have shown that the development of cardiac autonomic neuropathy increases the arterial stiffness and it should be evaluated and reported in trials aimed to investigate factors affecting the pulse wave velocity. Diabetes mellitus state corresponded with a lower peripheral arterial stiffness reversed from the associations seen for brachial-ankle and carotid-femoral pulse wave velocity (Loehr et al. 2016).

The gradual fragmentation of elastin fibers in persons aged over the course of a 60-year of life is accompanied by collagen overproduction and Ca^{2+} deposition in the extracellular matrix. These degenerative changes lead to an increased stiffness in the elastic type of vessels and pulse pressure (Christen et al. 2010; Laurent and Boutouyrie 2020). The exact impact of hypertension and aging on the vascular wall ductility and the relationship of these effects is highly complicated. These conditions' pathophysiological changes are unidirectional (as the increase in collagen content), while others have multidirectional effects complicating the patients' examination results (Angoff et al. 2021).

Moreover, numerous traditional risk factors increase the vascular wall rigidity, including hyperglycemia, smoking, dyslipidemia, etc. (Christen et al. 2010). Loehr et al. (2016) have hypothesized that the remodeling of the arterial wall by the state of diabetes mellitus may differ pathophysiologically in muscular versus large elastic arteries and that elasticity loss and recoil do not necessarily need to be translated into the muscular arteries stiffening. Tsuchikura et al. (2010) have found opposing effect directions for the association of the coronary artery disease and the peripheral and central stiffness parameters, including a subset of persons with T2D. In addition, the results from the ARIC study have shown that the brachial-ankle pulse wave velocity and carotid-femoral pulse wave velocity were positively associated with glycated hemoglobin A1c and age, whereas these results were not confirmed for femoral-ankle pulse wave velocity. These trials have demonstrated that the associations of peripheral stiffness with coronary artery disease or its risk factors differ from associations with central arterial stiffness (Loehr et al. 2016; Meyer et al. 2016).

Conclusion

Recent evidence suggests that cardiac autonomic dysfunction leads to an increased arterial wall stiffness and thickness (Chirinos et al. 2019). One of the explanations could be that the calcification of the tunica media of the arterial wall is common in patients with cardiovascular disease. The severity of diabetic cardiovascular disease is the primary determinant of the arterial calcification extent and the arterial calcification is the major determinant of the arterial stiffness (Chorepsima et al. 2017). These data confirm that arterial wall calcification may be a pathophysiological pathway explaining the link between arterial stiffness and impaired cardiac autonomic function. The increased tone of the sympathetic nervous system is associated with arterial stiffness as in hypertensive persons with and without T2D as well as healthy controls. Increased heart rate *per se* may lead to the arterial stiffness independently of the autonomic nervous system activity changes (Chorepsima et al. 2017; Valensi 2021).

Another hypothesis is that arterial stiffness may lead to a cardiovascular disease development *via* impaired baroreceptor function induced by arterial wall stiffening. The results of several studies have suggested a significant association between an increased arterial stiffness and low baroreflex sensitivity in older patients with congestive heart rate. Nevertheless, no significant difference in central baroreflex sensitivity have been found among persons with normal and increased pulse wave velocity. These data confirm that diabetes mellitus has a strong effect on the baroreflex sensitivity and exceeds other factors' effects. (Chorepsima et al. 2017; Valensi 2021; Serhiyenko et al. 2022).

Some data have indicated that the development of prediabetes is associated with increased large arterial stiffness. A recent publication from the ADDITION-Leicester cohort study has reported an increased carotid-femoral pulse wave velocity in subjects with impaired glucose tolerance and fasting glucose compared to persons with physiological glucose values. The increase was similar to persons with newly diagnosed T2D (Gomez-Sanchez et al. 2017; Gagliardino et al. 2021).

The carotid stiffness parameters increase is positively correlated with the increase of fasting glucose, insulin, glycated hemoglobin A1c, HOMA-insulin resistance index, waist circumference, triglycerides, and decrease of high-density lipoprotein cholesterol (Gomez-Sanchez et al. 2021). A recent study in adult persons without CVD has demonstrated direct association of carotid-femoral pulse wave velocity with HOMA-insulin resistance index and an inverse relationship with telomere length. It has been concluded that a combination of insulin resistance and chronic inflammation could decrease telomere length (a marker of biological age and cellular senescence) and accelerate vascular aging (Kozakova and Palombo 2016).

There are several potential pharmacological and non-pharmacological interventions aiming to reduce the arterial stiffness. In particular, sodium glucose cotransporter-2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) significantly reduced the risk of cardiovascular and all-cause mortality in patients with T2D with established CVD and/or with cardiovascular risk factors. For diabetologists (who are accustomed to dealing with the burden of cardiac autonomic neuropathy) the relationship between sodium glucose cotransporter-2 inhibitors and the autonomic nervous system represents one of the most

intriguing aspects of the multiple effects of this family of drugs, especially given the poor availability of disease-modifying treatments for such complication. Improved endothelial function and arterial rigidity probably represents one of the mechanisms by which these drugs may exert their beneficial effects (Lamacchia and Sorrentino 2021; Spallone and Valensi 2021). However, evidence on their effect on arterial stiffness in patients with T2D and cardiac autonomic neuropathy remains limited and controversial. Large randomized controlled trials are required to shed further light in this potential association (Patoulias et al. 2020; Ang et al. 2021).

Future studies targeted on the impact of arterial stiffness on the cardiac autonomic dysfunction may shed a light on the arterial stiffness usefulness potential as diagnostic and treatment targets to improve the diabetes mellitus clinical outcomes.

Acknowledgements

This minireview was conducted according to the Declaration of Helsinki (2004) and the Ethics Committee of the Danylo Halitsky Lviv National Medical University and approved before its initiation (protocol №1 from 01 Jan 2016). The work was performed within the frame of the State task of the Danylo Halitsky National Medical University, Lviv, Ukraine.

Conflict of interest: *The authors declare no conflict of interest.*

References

Adamska A, Karczewska-Kupczewska M, Nikolajuk A, Otziomek E, Gorska M, Kowalska I, Straczkowski M. Relationships of serum soluble E-selectin concentration with insulin sensitivity and metabolic flexibility in lean and obese women. Endocrine 45, 422–429, 2014.

Agashe S, Petak S. Cardiac autonomic neuropathy in diabetes mellitus. Methodist Debakey Cardiovasc J 14, 251–256, 2018.

Agnoletti D, Zhang Y, Borghi C, Blacher J, Safar ME. Effects of antihypertensive drugs on central blood pressure in humans: a preliminary observation. Am J Hypertens 26, 1045–1052, 2013.

Alfaddagh A, Martin SS, Leucker TM, Michos ED, Blaha MJ, Lowenstein CJ, Jones SR, Toth PP. Inflammation and cardiovascular disease: from mechanisms to therapeutics. Am J Prev Cardiol 4,100130, 2020.

Ang L, Kidwell KM, Dillon B, Reiss J, Fang F, Leone V, Mizokami-Stout K, Pop-Busui R. Dapagliflozin and measures of cardiovascular autonomic function in patients with type 2 diabetes (T2D). J Diabetes Complications 35, 107949, 2021.

Angoff R, Mosarla RC, Tsao CW. Aortic stiffness: epidemiology, risk factors, and relevant biomarkers. Front Cardiovasc Med 8, 709396, 2021.

Bagherzadeh A, Nejati-Afkham A, Tajallizade-Khoob Y, Shafiee A, Sharifi F, Esfahani MA, Badamchizade Z, Alatab S, Fakhrzadeh H. Association of cardiac autonomic neuropathy with arterial stiffness in type 2 diabetes mellitus patients. J Diabetes Metab Disord 12, 55, 2013.

Bakkar NZ, Dwaib HS, Fares S, Eid AH, Al-Dhaheri Y, El-Yazbi AF. Cardiac autonomic neuropathy: A progressive consequence of chronic low-grade inflammation in type 2 diabetes and related metabolic disorders. Int J Mol Sci 21, 9005, 2020.

Bissinger A. Cardiac autonomic neuropathy: why should cardiologists care about that? J Diabetes Res 2017, 5374176, 2017.

Botts SR, Fish JE, Howe KL. Dysfunctional vascular endothelium as a driver of atherosclerosis: emerging insights into pathogenesis and treatment. Front Pharmacol 12, 787541, 2021.

Cakar M, Balta S, Sarlak H, Akhan M, Demirkol S, Karaman M, Ay SA, Kurt O, Cayci T, Inal S, Demirbas S. Arterial stiffness and endothelial inflammation in prediabetes and newly diagnosed diabetes patients. Arch Endocrinol Metab 59, 407–413, 2015.

Cakar M, Akhan M, Dogan T, Taskin G, Ozturk K, Cinar M, Arslan E, Yilmaz S. Investigation of the arterial stiffness and associated factors in patients with familial Mediterranean fever. Anatol J Cardiol 17, 132–138, 2017.

Chamarthi B, Vinik A, Ezrokhi M, Cincotta AH. Circadian-timed quick-release bromocriptine lowers elevated resting heart rate in patients with type 2 diabetes mellitus. Endocrinol Diabetes Metab 3, e00101, 2019.

Chawla D, Bansal S, Banerjee BD, Madhu SV, Kalra OP, Tripathi AK. Role of advanced glycation end product (AGE)-induced receptor (RAGE) expression in diabetic vascular complications. Microvasc Res 95, 1–6, 2014.

Chen Q, Chiheb S, Fysekidis M, Jaber Y, Brahimi M, Nguyen MT, Millasseau S, Cosson E, Valensi P. Arterial stiffness is elevated in normotensive type 2 diabetic patients with peripheral neuropathy. Nutr Metab Cardiovasc Dis 73, 1138–1149, 2015.

Chirinos JA, Segers P, Hughes T, Townsend R. Large-artery stiffness in health and disease: JACC State-of-the-Art review. J Am Coll Cardiol 74, 1237–1263, 2019.

Chorepsima S, Eleftheriadou I, Tentolouris A, Moyssakis I, Protogerou A, Kokkinos A, Sfikakis PP, Tentolouris N. Pulse wave velocity and cardiac autonomic function in type 2 diabetes mellitus. BMC Endocr Disord 17, 27, 2017.

Christen AI, Armentano RL, Miranda A, Graf S, Santana DB, Zocalo Y, Baglivo HP, Sanchez RA. Arterial wall structure and dynamics in type 2 diabetes mellitus methodological aspects and pathophysiological findings. Curr Diabetes Rev 6, 367–377, 2010.

Ciftel M, Ertug H, Parlak M, Akcurin G, Kardelen F. Investigation of endothelial dysfunction and arterial stiffness in children with type 1 diabetes mellitus and the association with diastolic dysfunction. Diab Vasc Dis Res 11, 19–25, 2014.

Climie RE, van Sloten TT, Bruno RM, Taddei S, Empana JP, Stehouwer CDA, Sharman JE, Boutouyrie P, Laurent S. Macrovasculature and microvasculature at the crossroads between type 2 diabetes mellitus and hypertension. Hypertension 73, 1138–1149, 2019.

Cseh D, Climie RE, Offredo L, Guibout C, Thomas F, Zanoli L, Danchin N, Sharman JE, Laurent S, Jouven X, Boutouyrie P, Empana JP. Type 2 diabetes mellitus is independently associated with decreased neural baroreflex sensitivity: The Paris Prospective Study III. Arterioscler Thromb Vasc Biol 40, 1420–1428, 2020.

de Oliveira Alvim R, Santos PCJL, Musso MM, de Sa Cunha R, Krieger JE, Mill JG, Pereira AC. Impact of diabetes mellitus on arterial stiffness in a representative sample of an urban Brazilian population. Diabetol Metab Syndr 5, 45, 2013.

Di Pino A, DeFronzo RA. Insulin resistance and atherosclerosis: implications for insulin-sensitizing agents. Endocr Rev 40, 1447–1467, 2019.

Elias MF, Crichton GE, Dearborn PJ, Robbins MA, Abhayaratna WP. Associations between type 2 diabetes mellitus and arterial stiffness: A prospective analysis based on the Maine-Syracuse Study. Pulse 5, 88–98, 2018.

Fahed G, Aoun L, Bou Zerdan M, Allam S, Bou Zerdan M, Bouferraa Y, Assi HI. Metabolic syndrome: updates on pathophysiology and management in 2021. Int J Mol Sci 23, 786, 2022.

Fakhruddin S, Alanazi W, Jackson KE. Diabetes-induced reactive oxygen species: mechanism of their generation and role in renal injury. J Diabetes Res 2017, 8379327, 2017.

Frontoni S, Di Bartolo P, Avogaro A, Bosi E, Paolisso G, Ceriello A. Glucose variability: An emerging target for the treatment of diabetes mellitus. Diabetes Res Clin Pract, 102, 86–95, 2013.

Frontoni S, Pellegrinotti M, Bracaglia D, Farrace S, Caselli A, Baroni A, De Angelis C, Menzinger G, Gambardella S. Hyperinsulinaemia in offspring of type 2 diabetic patients: impaired response of carbohydrate metabolism, but preserved cardiovascular response. Diabet Med 17, 606–611, 2000.

Gagliardino JJ, Salazar MR, Espeche WG, Tolosa Chapasian PE, Gomez Garizoain D, Olano RD, Stavile RN, Balbin E, Martinez C, Leiva Sisnieguez BC, Leiva Sisnieguez CE, Carbajal HA. Arterial stiffness: its relation with prediabetes and metabolic syndrome and possible pathogenesis. J Clin Med 10, 3251, 2021.

Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martin C. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci 21, 6275, 2020.

Gaszner B, Lenkey Z, Illyes M, Sarszegi Z, Horvath IG, Magyari B, Molnar F, Konyi A, Cziraki A. Comparison of aortic and carotid arterial stiffness parameters in patients with verified coronary artery disease. Clin Cardiol 35, 26–31, 2012.

Gomez-Sanchez L, Garcia-Ortiz L, Patino-Alonso MC, Recio-Rodriguez JI, Feuerbach N, Marti R, Agudo-Conde C, Rodriguez-Sanchez E, Maderuelo-Fernandez JA, Ramos R, Gomez-Marcos MA; MARK Group. Glycemic markers and relation with arterial stiffness in Caucasian subjects of the MARK study. PLoS One 12, e0175982, 2017.

Gomez-Sanchez L, Gomez-Sanchez M, Lugones-Sanchez C, Tamayo-Morales O, Gonzalez-Sanchez S, Rodriguez-Sanchez E, Garcia-Ortiz L, Gomez-Marcos MA, On Behalf Of The Eva Investigators. Association of insulin resistance with vascular ageing in a general caucasian population: An EVA Study. J Clin Med 10, 5748, 2021.

Gorky J, Schwaber J. Conceptualization of a parasympathetic endocrine system. Front Neurosci 13, 1008, 2019.

Grossman E. Ambulatory blood pressure monitoring in the diagnosis and management of hypertension. Diabetes Care Suppl 2, 307–311, 2013.

Guan Y, Yu C, Shi M, Ni J, Wu Y, Gu H, Bai L, Liu J, Tu J, Wang J, Ning X. The association between elevated fasting plasma glucose levels and carotid intima-media thickness in non-diabetic adults: A population-based cross-sectional study. Oncotarget 8, 111053–111063, 2017.

Hajar R. Risk factors for coronary artery disease: historical perspectives. Heart Views 18, 109–114, 2017.

Jeon KH, Kim HL, Lim WH, Seo JB, Kim SH, Zo JH, Kim MA. Associations between measurements of central blood pressure and target organ damage in high-risk patients. Clin Hypertens 1, 23, 2021.
Jia G, DeMarco VG, Sowers JR. Insulin resistance and hyperinsulinaemia in diabetic cardiomyopathy. Nat Rev Endocrinol, 12, 144–153, 2016.
Kim HL, Kim SH. Pulse wave velocity in atherosclerosis. Front Cardiovasc Med 6, 41, 2019.
Kopytek M, Zabczyk M, Mazur P, Undas A, Natorska J. Accumulation of advanced glycation end products (AGEs) is associated with the severity of aortic stenosis in patients with concomitant type 2 diabetes. Cardiovasc Diabetol 19, 92, 2020.
Kozakova M, Palombo C. Diabetes mellitus, arterial wall, and cardiovascular risk assessment. Int J Environ Res Public Health 13, 201, 2016.
Lamacchia O, Sorrentino MR. Diabetes mellitus, arterial stiffness and cardiovascular disease: clinical implications and the influence of SGLT2i. Curr Vasc Pharmacol 19, 233–240, 2021.
Laurent S, Boutouyrie P. Arterial stiffness and hypertension in the elderly. Front Cardiovasc Med 7, 544302, 2020.
Liu JJ, Liu S, Lee J, Gurung RL, Yiamunaa M, Ang K, Shao YM, Choo RWM, Tavintharan S, Tang WE, Sum CF, Lim SC. Aortic pulse wave velocity, central pulse pressure, augmentation index and chronic kidney disease progression in individuals with type 2 diabetes: a 3- year prospective study. BMC Nephrol 21, 359, 2020.
Loehr LR, Meyer ML, Poon AK, Selvin E, Palta P, Tanaka H, Pankow JS, Wright JD, Griswold ME, Wagenknecht LE, Heiss G. Prediabetes and diabetes are associated with arterial stiffness in older adults: The ARIC Study. Am J Hypertens 29, 1038–1045, 2016.
Lu YW, Chang CC, Chou RH, Tsai YL, Liu LK, Chen LK, Huang PH, Lin SJ. Gender difference in the association between TyG index and subclinical atherosclerosis: results from the I-Lan Longitudinal Aging Study. Cardiovasc Diabetol 20, 206, 2021.
Maciorowska M, Krzesinski P, Wierzbowski R, Gielerak G. Heart rate variability in patients with hypertension: the effect of metabolic syndrome and antihypertensive treatment. Cardiovasc Ther 2020, 8563135, 2020.
Madamanchi NR, Vendrov A, Runge MS. Oxidative stress and vascular disease. Arterioscler Thromb Vasc Biol 25, 29–38, 2005.
Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 31, 1281–1357, 2013.
Mansour AS, Yannoutsos A, Majahalme N, Agnoletti D, Safar ME, Ouerdane S, Blacher J. Aortic stiffness and cardiovascular risk in type 2 diabetes. J Hypertens 31, 1584–1592, 2013.
Mehlum MH, Liestol K, Kjeldsen SE, Julius S, Hua TA, Rothwell PM, Mancia G, Parati G, Weber MA, Berge E. Blood pressure variability and risk of cardiovascular events and death in patients with hypertension and different baseline risks. Eur Heart J 39, 2243–2251, 2018.
Merz CNB, Elboudwarej O, Mehta P. The autonomic nervous system and cardiovascular health and disease: a complex balancing act. JACC Heart Fail 3, 383–385, 2015.
Meyer ML, Tanaka H, Palta P, Cheng S, Gouskova N, Aguilar D, Heiss G. Correlates of segmental pulse wave velocity in older adults: The Atherosclerosis Risk in Communities (ARIC) Study. Am J Hypertens 29, 114–122, 2016.
Moshkovits Y, Rott D, Chetrit A, Dankner R. The association between insulin sensitivity indices, ECG findings and mortality: A 40-year cohort study. Cardiovasc Diabetol 20, 97, 2021.
Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. Int J Physiol Pathophysiol Pharmacol 10, 3251, 2019.
Okamoto M, Nakamura F, Musha T, Kobayashi Y. Association between novel arterial stiffness indices and risk factors of cardiovascular disease. BMC Cardiovasc Disord 16, 211, 2016.
Onaolapo AY, Onaolapo OJ. Circadian dysrhythmia-linked diabetes mellitus: examining melatonin's roles in prophylaxis and management. World J Diabetes 9, 99–114, 2018.
Patoulias D, Papadopoulos C, Stavropoulos K, Zografou I, Doumas M, Karagiannis A. Prognostic value of arterial stiffness measurements in cardiovascular disease, diabetes, and its complications: The potential role of sodium-glucose co-transporter-2 inhibitors. J Clin Hypertens 22, 562–571, 2020.
Petrie JR, Guzik TJ, Touyz RM. Diabetes, hypertension, and cardiovascular disease: clinical insights and vascular mechanisms. Can J Cardiol 34, 575–584, 2018.
Podolec M, Siniarski A, Pajak A, Rostoff P, Gajos G, Nessler J, Olszowska M, Nowakowski M, Szafraniec K, Kopec G. Association between carotid-femoral pulse wave velocity and overall cardiovascular risk score assessed by the SCORE system in urban Polish population. Kardiol Pol 77, 363–370, 2019.

Pop-Busui R. Cardiac autonomic neuropathy in diabetes: A clinical perspective. Diabetes Care 33, 434–441, 2010.
Pop-Busui R, Boulton AJ, Feldman EL, Bril V, Freeman R, Malik RA, Sosenko JM, Ziegler D. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care 40, 136–154, 2017.
Rana S, Prabhu SD, Young ME. Chronobiological influence over cardiovascular function: The good, the bad, and the ugly. Circ Res 126, 258–279, 2020.
Rupprecht S, Finn S, Hoyer D, Guenther A, Witte OW, Schultze T, Schwab M. Association between systemic inflammation, carotid arteriosclerosis, and autonomic dysfunction. Transl Stroke Res 11, 50–59, 2020.
Seko Y. A novel and dominant factor that mediates oxidative stress-induced apoptotic signaling - autocrine/paracrine mechanism of the secreted form of eukaryotic translation initiation factor 5A. Vessel Plus 4, 22, 2020.
Serhiyenko VA, Serhiyenko AA. Cardiac autonomic neuropathy: Risk factors, diagnosis and treatment. World J Diabetes 9, 1–24, 2018.
Serhiyenko VA, Serhiyenko LM, Serhiyenko AA. Diabetic cardiac autonomic neuropathy and arterial stiffness-which comes first? Diabetes Updates 1, 1–5, 2018.
Serhiyenko VA, Serhiyenko LM, Serhiyenko AA. Features of circadian rhythms of heart rate variability, arterial stiffness and outpatient monitoring of blood pressure in diabetes mellitus: Data, mechanisms and consequences. In Circadian Rhythms and Their Importance, Nova Science Publishers, New York (ed. Sinha RP), 279-341, 2022.
Song MK, Davies NM, Roufogalis BD, Huang TH. Management of cardiorenal metabolic syndrome in diabetes mellitus: A phytotherapeutic perspective. J Diabetes Res 2014, 313718, 2014.
Spallone V. Blood pressure variability and autonomic dysfunction. Curr Diab Rep 18, 137, 2018.
Spallone V. Update on the impact, diagnosis and management of cardiovascular autonomic neuropathy in diabetes: what is defined, what is new, and what is unmet. Diabetes Metab J 43, 3–30, 2019.
Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R, Stevens M, Kempler P, Hilsted J, Tesfaye S, Low P, Valensi P; Toronto Consensus Panel on Diabetic Neuropathy. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev 27, 639–653, 2011.
Spallone V, Kempler P, Czupryniak L, Gurieva I, Mankovsky BN, Fritzen K, Patzer KH, Schnell, Stirban A, Tesfaye S, Veresiu IA, Ziegler D. The interplay between dysglycaemia and autonomic function. Diabetes, Stoff Herz 27, 135–144, 2018.
Spallone V, Valensi P. SGLT2 inhibitors and the autonomic nervous system in diabetes: A promising challenge to better understand multiple target improvement. Diabetes Metab 47, 101224, 2021.
Straznicky NE, Grima MT, Sari CI, Lambert EA, Phillips SE, Eikelis N, Mariani JA, Kobayashi D, Hering D, Dixon JB, Lambert GW. Comparable attenuation of sympathetic nervous system activity in obese subjects with normal glucose tolerance, impaired glucose tolerance, and treatment naïve type 2 diabetes following equivalent weight loss. Front Physiol 7, 516, 2016.
Tschiderer L, Klingenschmid G, Seekircher L, Willeit P. Carotid intima-media thickness predicts carotid plaque development: meta-analysis of seven studies involving 9341 participants. Eur J Clin Invest 50, e13217, 2020.
Tsuchikura S, Shoji T, Kimoto E, Shinohara K, Hatsuda S, Koyama H, Emoto M, Nishizawa Y. Central versus peripheral arterial stiffness in association with coronary, cerebral and peripheral arterial disease. Atherosclerosis 211, 480–485, 2010.
Ulleryd MA, Prahl U, Borsbo J, Schmidt C, Nilsson S, Bergstrom G, Johansson ME. The association between autonomic dysfunction, inflammation and atherosclerosis in men under investigation for carotid plaques. PLoS One 12, e0174974, 2017.
Valensi P. Autonomic nervous system activity changes in patients with hypertension and overweight: role and therapeutic implications. Cardiovasc Diabetol 20, 170, 2021.
van Dijk RA, Bakker SJ, Scheffer PG, Heine RJ, Stehouwer CD. Associations of metabolic variables with arterial stiffness in type 2 diabetes mellitus: focus on insulin sensitivity and postprandial triglyceridaemia. Eur J Clin Invest 33, 307–315, 2003.
Vinik AI, Casellini C, Parson HK, Colberg SR, Nevoret ML. Cardiac autonomic neuropathy in diabetes: A predictor of cardiometabolic events. Front Neurosci 12, 591, 2018.
Warburton DER, Bredin SSD, Shellington EM, Cole C, de Faye A, Harris J, Kim DD, Abelsohn A. A systematic review of the short-term health effects of air pollution in persons living with coronary heart disease. J Clin Med 8, 274, 2019.
Xu M, Huang Y, Xie L, Peng K, Ding L, Lin L, Wang P, Hao M, Chen Y, Sun Y, Qi L, Wang W, Ning G, Bi Y. Diabetes and risk of arterial stiffness: A Mendelian randomization analysis. Diabetes 65, 1731–1740, 2016.

Yeboah K, Antwi DA, Gyan B. Arterial stiffness in nonhypertensive type 2 diabetes patients in Ghana. Int J Endocrinol 2016, 6107572, 2016.
Yun JS, Park YM, Cha SA, Ahn YB, Ko SH. Progression of cardiovascular autonomic neuropathy and cardiovascular disease in type 2 diabetes. Cardiovasc Diabetol 17, 109, 2018.
Zhao XY, Wang XF, Li L, Zhang L, Shen DL, Li DH, Jin QS, Zhang JY. Effects of high glucose on human umbilical vein endothelial cell permeability and myosin light chain phosphorylation. Diabetol Metab Syndr 7, 98, 2015.
Zheng M, Zhang X, Chen S, Song Y, Zhao Q, Gao X, Wu S. Arterial stiffness preceding diabetes: A longitudinal study. Circ Res 127, 1491–1498, 2020.
Ziegler D, Keller J, Maier C, Pannek J, German Diabetes Association. Diabetic neuropathy. Exp Clin Endocrinol Diabetes 122, 406–415, 2014.
Ziegler D, Holz A, Gurieva I, Horvath V, Mankovsky BN, Radulian G, Schnell O, Spallone V, Stirban A, Tesfaye S, Kempler P. Current perspectives in prediabetic neuropathy. Diabetes Stoffw Herz 30, 36–48, 2021.