Cardiac Autonomic Neuropathy

Subjects: Biochemistry & Molecular Biology | Pathology
Contributor: Nour-Mounira Bakkar

Cardiac autonomic neuropathy (CAN) is one of the earliest manifestations of type 2 diabetes (T2D). It constitutes the major cause of silent cardiovascular events in patients without overt cardiac disease. The high prevalence of CAN in patients newly diagnosed with T2D suggests that its pathophysiology is rooted in an earlier stage of metabolic derangement, possibly being prediabetes.

Keywords: cardiac autonomic neuropathy ; inflammation ; reactive oxygen species ; type 2 diabetes

1. Introduction

Recent knowledge about the nature of disease progression has led researchers to study the status of CAN in patients with recent-onset diabetes. Interestingly, comparisons between type 1 and type 2 diabetic individuals further confirm the fact that CAN processes in T2D start earlier than the onset of overt metabolic impairment [1]. To this end, guidelines recommend CAN screening in T2D patients as early as their first diagnosis as opposed to 5 years after onset in T1D [2]. Thus, it follows that dysglycemia is not the exclusive cause responsible for the initiation of CAN and its progression in T2D. This is clearly reflected when comparing the risk factors of CAN in both diseases. Above poor glycemic control in T1D, obesity and its associated dyslipidemia, hyperinsulinemia, and hypertension (HTN) present additional risk factors for CAN in T2D [3]. Hence, different factors in the etiology of the disease are shown to contribute differentially to CAN manifestations.

Two types of autonomic dysfunction can be associated with diabetes, either intrinsic or extrinsic [4]. The first is related to an insult caused directly to autonomic nerves, whereas the other can be secondary to cardiovascular dysfunction, such as dilated cardiomyopathy and aortic stiffness. Studies concerned with investigating the major contributors to cardiac autonomic dysfunction in T2D have indicated that it is primarily intrinsic in nature [5][6].

2. The Metabolic Syndrome: A Continuum of Low-Grade Pro-Oxidative and Proinflammatory Processes

Current understanding of the metabolic syndrome reveals the presence of an inflammatory component. Different mechanisms in the course of progression to T2D trigger the initiation of inflammatory processes that are varied in nature but are essentially linked [7]. The so-called “metabolic inflammation” (also known as meta-inflammation) distinguishes T2D from T1D. Interestingly, a population-based study comparing inflammatory profiles in normoglycemic, prediabetic, and T2D individuals offered a spectrum of differential change in inflammatory biomarkers with disease progression [8].

2.1. The Role of Altered Glucose Homeostasis in Meta-Inflammation

In the prediabetic stage, changes in glucose and insulin homeostasis have been shown to be linked to inflammation pathogenesis even before the advent of hyperglycemia [9][10]. An increase in insulin demand and production secondary to insulin resistance is accompanied by elevated pancreatic endoplasmic reticulum stress initiating pro-oxidative and proinflammatory processes [11][12]. Additionally, hyperinsulinemia-induced lipid storage was shown to promote adipose tissue-specific inflammation and a subsequent acute phase response [13][14]. This was shown to be mediated by adipose tissue expansion promoting hypoxia of poorly vascularized tissues, which constitutes the driving force for the activation of nuclear factor-κB (NF-κB), a sensor of oxidative stress [15]. On the activation of NF-κB, adipose tissues secrete proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α), which promote liver synthesis of acute phase proteins such as C reactive protein (CRP) and plasminogen activator inhibitor-1 (PAI-1) [16][17]. Consequently, adipose tissue hypertrophy leads to apoptosis attracting macrophages in crown-like structures [18][19]. Immune cells release reactive oxygen species (ROS) in response to cytokine upregulation [20]. Moreover, overnutrition overwhelms inherent mitochondrial capacity for scavenging excess ROS produced by metabolic processes promoting further upregulation of proinflammatory processes through NF-κB pathways [21]. On the onset of hyperglycemia, however,

elevated mitochondrial aerobic respiration and activity of the electron transport chain, as well as advanced glycated end products, aggravates oxidative stress, which presents another activator of inflammatory cascades mediated by NF-κB, cAMP-regulated element-binding protein, and activator protein 1 [22]. Additionally, neurohormonal stimulation by the renin–angiotensin–aldosterone system (RAAS) was shown to play a role in aggravating oxidative stress and inflammation [23].

Interestingly, metabolic inflammatory processes are evident in the cardiovascular, neuronal, and neurovascular systems, indicating their possible involvement in the etiology of cardiac autonomic dysfunction in the metabolic syndrome [24][25][26]. Hypoxia driven by vascular dysfunction activates immune cells of the central nervous system, producing cytokines such as IL-1β, which in turn triggers effectors downstream of NF-κB further producing cytokines such as IL-6. Additionally, the metabolic syndrome is a known disrupter of the integrity of the blood–brain barrier (BBB) via altering the permeability of the choroid plexus [27][28]. This was attributed to increased ROS production leading to decreased expression of tight junction proteins. Hence, it promotes infiltration of proinflammatory cytokines and immune cells from the bloodstream to the central nervous system, especially in the context of systemic inflammation characteristic of T2D. The latter contributes to compromising BBB functions by increasing the permeability of the basement membrane of the BBB, via matrix metalloproteases [29], allowing for immune cell extravasation and upregulating leukocyte adhesion molecules, such as intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), P-selectin, and E-selectin [28]. In fact, increased oxidative stress in the diabetic brain is related to decreased antioxidant defense enzymes and molecules concomitant with an increase in the polyol pathway resulting in a decrease in NADPH recycling [30]. It was also shown that hyperinsulinemia can lead to increased neuronal oxidative stress through decreased mitochondrial PI3K/Akt signaling pathway [40]. Such changes were shown to be associated with autophagic disturbances in different peripheral and central neurons [30][31][32]. Alternatively, accumulation of ROS-generating mitochondria resulting from autophagy suppression could activate, in addition to NF-κB, the NLRP3 inflammasome responsible for proinflammatory cytokine maturation [30]. Additionally, mitochondrial oxidative damage was shown to be accompanied by a decrease in ATP levels resulting from suppressed mitochondrial energization potential. Hence, the aforementioned changes could ultimately lead to neuroinflammation.

2.2. Contribution of Gut Microbiota to Meta-Inflammation

Alterations in the gut microbiome (GM) or dysbiosis has been recently linked to many morbidities, such as metabolic and immune-related disorders [33]. The GM community can affect the host health via two routes: the bacterial components or pathogen-associated molecular patterns (PAMPs), including cell-wall constituents such as lipopolysaccharides (LPS) [34], and the metabolites produced when digesting and processing food in the gut. Hence, dysbiosis outcomes depend on the bacterial Phyla alterations in the gut [35]. Moreover, GM plays a vital role in regulating the permeability of intestinal mucosa [36]. GM manipulates the host's metabolism; hence, dysbiosis was found to be linked to some compromised metabolic states and related diseases [36].

One of the major contributors to dysbiosis is dietary intake. A high-fat diet (HFD), implicated in the production of the metabolic challenge leading to metabolic syndrome and T2D, promotes an increase in serum LPS. This was proposed to occur due to increased permeability of the gut by the microbiota, which is linked to metabolic endotoxemia. LPS acts through the Toll-like receptor 4 (TLR4) signaling pathway, where TLR4 is expressed on macrophages and adipose tissue and is activated upon LPS recognition. The LPS/TLR4 complex has two main signaling pathways: the MyD88-independent pathway that gives rise to Type 1 interferons (IFNs) and the MyD88-dependent pathway that activates proinflammatory cytokines such as IL-1, IL-6 and TNF-α. Both pathways act via NF-κB [37][38][39]. Thus, upon activation, this complex stimulates white adipose tissue inflammation and proinflammatory macrophage infiltration and is also linked to an increase in monocyte chemoattractant protein-1 (MCP-1) [40].

3. Progression of CAN: From Metabolic Syndrome and Prediabetes to T2D

3.1. Determinants of CAN in Early-Onset and Advanced T2D

Comparisons with status and manifestations of CAN in T1D implicate different disease-specific characteristics in the initiation and progression of CAN in T2D. Studies conducted by Ziegler et al. assessed the status of CAN in patients with recent onset diabetes, i.e., less than or equal to 1 year after their first diagnosis [41]. Their results provide indication that the pathophysiologic trigger of CAN in recent-onset T2D is independent of hyperglycemia but rather tied to metabolic characteristics related to obesity (body mass index (BMI) >30, central obesity, and increased fat mass) and dyslipidemia, distinguishing this population from their control, and subsequently T1D, counterparts [1].

Interestingly, different studies have brought into the picture another factor in the pathogenesis of CAN in early-onset T2D; this is oxidative stress related to acute glycemic excursions, rather than chronic hyperglycemia. On progress to T2D, changes in glucose tolerance and insulin sensitivity take the form of glycemic variability. Importantly, glycemic variability was shown to have the power of predicting CAN in recent onset, where average glucose level failed [42]. Specifically, glycemic variability was higher in T2D patients with CAN, according to Ewing battery tests, than in those without CAN. A role for systemic oxidative stress in the initiation of early parasympathetic dysfunction was, thus, proposed. This particularly pertains to endothelial dysfunction [43][44] and eventually baroreceptor impairment. In fact, increased ROS production in early metabolic insults was shown to be related to decreased endothelial-dependent hyperpolarization secondary to reduced expression of potassium inward rectifier channels [45]. Such an increase is presumed to bring about elevated vascular tone through impairing eNOS activity, ultimately diminishing NO-induced vasorelaxation [46]. Moreover, a study assessing the relationship between endothelial dysfunction and CAN revealed a positive association between NO and eNOS and measures of cardiovagal control, presenting determinants of endothelial function as biomarkers for the pathogenesis of parasympathetic neuropathy in T2D patients [44].

Interestingly, a study assessed the effect of glycemic variability on BRS in T2D patients and again revealed that its elevation is independently correlated with decreased BRS [47]. Above the detrimental effects of oxidative stress on endothelial function and neuropathy, the study presumed that hyperinsulinemia caused by acute fluctuations in blood glucose could be responsible for the observed blunted BRS [47]. Additionally, results showed that BRS decreased with diabetes duration, indicating worsening status with progression of disease components. However, the study did not distinguish between the different arms of the baroreflex control and, thus, could not specify whether sympathetic or parasympathetic deterioration was responsible for this drop in sensitivity. Indeed, a study assessing the effect of glycemic control and disease duration on HRV in T2D patients revealed that worse glycemic indices and longer duration were accompanied by lower parameters of both sympathetic and parasympathetic determinants of HRV [48]. The impact of glycemic control on CAN could be partially explained by a reduction in antioxidant effectors and increase in prooxidative pathways, leading to neuronal ischemia and subsequent damage [49]. However, the contribution of hyperglycemia to inflammatory biomarkers in T2D cannot be overlooked [50]. Thus, it could be through an exaggerated inflammatory state that hyperglycemia worsens the status of CAN with disease progression[51].

3.2. Effect of Glucose Homeostasis along the Continuum of Prediabetes to Early-Onset T2D on CAN

In the same way, comparisons between prediabetic and type 2 diabetic manifestations of CAN allow us to draw conclusions about the pathophysiology of CAN development over the natural course of the disease. Hyperinsulinemia secondary to peripheral insulin resistance is the hallmark of the prediabetic stage [52]. However, the superimposition of hyperinsulinemia with sympathetic augmentation makes it unclear which causes the other. A study of a fructose-induced glucose intolerance in mice revealed that sympathetic augmentation (elevated LF of BP variability) and autonomic imbalance (increase in LF/HF) appear before hyperinsulinemia and other metabolic derangements in the course of the metabolic syndrome [53]. Major research has been channeled to the study of early sympathetic augmentation, vagal withdrawal, and altered sympatho-vagal balance; however, little remains known about the origin and etiology of sympathetic dysfunction at a later stage of the disease. While chronic hyperglycemia appears to be the eliciting factor, orthostatic hypotension was thought to be brought about by damage of efferent vasomotor neurons in splanchnic blood vessels [54]. Moreover, earlier studies reported on cardiac sympathetic denervation [55][56]. Little remains discovered, however, about the status of central control of sympathetic activity or central sympathetic neuropathy.

3.3. Influence of Obesity Indices and Dyslipidemia

When studying CAN in prediabetic and T2D patients, it is important to acknowledge the status of obesity in assessed individuals. Indeed, studies investigating the relationship between obesity and CAN revealed that various factors differentially contribute to the pathogenesis of CAN. In nondiabetic obese men, percentage body fat, waist circumference, and visceral adipose tissue volume were associated with measures of reduced HRV, with percentage body fat correlating with the greatest number of HRV parameters [57]. In fact, obesity was shown to predict development of systemic inflammation [58]. Interestingly, hyperleptinemia was shown to mediate the relationship between visceral fat accumulation and CAN in T2D patients [59]. Additionally, dyslipidemia in the presence of obesity aggravates the blunted baroreflex control in T2D and makes it more resistant to lipid-lowering treatment otherwise effective in nonobese T2D patients [60]. It is noteworthy that dyslipidemia could have detrimental effects on CAN by exacerbating systemic inflammation [50].

4. Association between Adipose, Vascular, Systemic, and Neuroinflammation and CAN

As an earlier study implicated hyperinsulinemia rather than insulin resistance in the pathogenesis of CAN, particularly impaired BRS [61], and hyperinsulinemia was shown to be the instigating cause of adipose inflammation independent of obesity [13], it can be speculated that it is through adipose inflammation that hyperinsulinemia aects cardiac autonomic control in the metabolic syndrome. Yet, autonomic, particularly sympathetic, function tends to deteriorate as diabetes progresses. Indeed, a study by Lieb et al. (2012) revealed a particularly decreased total spectral power (TSP), indicative of overall control of HRV in patients with established T2D, which was not otherwise present in newly diagnosed diabetics, who showed isolated parasympathetic blunting [62]. In fact, the strongest positive correlation was found to be present between total adiponectin-to-leptin ratio and TSP, indicating a contribution for these counteractive adipokines in dictating sympathetic tone. Additionally, increased PAI-1 was shown to be essentially increased in patients with established T2D compared to those with newly diagnosed diabetes (within 6 months of diagnosis). As such, one can conclude that, while prolonged exposure to hyperglycemia might underlie the observed CAN deterioration in T2D, this seems to occur through exacerbation of adipose tissue inflammation occurring in earlier stages of the disease. Later, Herder et al. (2017) retested the association between inflammation and CAN, especially in patients with new-onset T2D [63]. In this study, they found that the association between IL-6 and cardiac autonomic reflex tests was rather explained by confounding factors. This is in line with the results of a longitudinal study indicating that the association between baseline IL-6 levels and follow-up HRV measures was dependent on BMI [64], again potentially implicating adipose tissue expansion and inflammation. However, independent inverse associations were found between soluble adhesion molecules such as soluble ICAM and E-selectin and sympathetic and parasympathetic function, respectively, indicating a role for vascular inflammation in CAN [65]. Significantly, our previous studies examined the evolution of inflammatory changes in association with worsening of CAN as the metabolic insult progressed. We show that early prediabetic parasympathetic dysfunction is associated with perivascular adipose tissue inflammation [66]. After the development of hyperglycemia, localized adipose tissue inflammation degenerated into systemic inflammation as evident by increased serum IL-1 and signs of disseminated cardiovascular damage that were associated with increased neuronal oxidative stress, inflammation, and suppressed autophagy in the brainstem with concomitant deterioration of CAN, including both sympathetic and parasympathetic functions [51].

References

1. Kück, J.-L.; Bönhof, G.J.; Strom, A.; Zaharia, O.-P.; Müssig, K.; Szendroedi, J.; Roden, M.; Ziegler, D. Impairment in bar oreflex sensitivity in recent-onset type 2 diabetes without progression over 5 years. Diabetes 2020, 69, 1011–1019. [Go ogle Scholar] [CrossRef] [PubMed]
2. Boulton, A.J.; Vinik, A.I.; Arezzo, J.C.; Bril, V.; Feldman, E.L.; Freeman, R.; Malik, R.A.; Maser, R.E.; Sosenko, J.M.; Zie gler, D. Diabetic neuropathies: A statement by the American Diabetes Association. Diabetes Care 2005, 28, 956–962. [Google Scholar] [CrossRef] [PubMed]
3. Rolim, L.; Sá, J.; Chacra, A.R.; Dib, S.A. Diabetic cardiovascular autonomic neuropathy: Risk factors, clinical impact an d early diagnosis. Arq. Bras. Cardiol. 2008, 90, e24–e31. [Google Scholar] [CrossRef] [PubMed]
4. Goldberger, J.J.; Arora, R.; Buckley, U.; Shivkumar, K. Autonomic nervous system dysfunction: JACC focus seminar. J. Am. Coll. Cardiol. 2019, 73, 1189–1206. [Google Scholar] [CrossRef]
5. Ruiz, J.; Monbaron, D.; Parati, G.; Perret, S.; Haesler, E.; Danzeisen, C.; Hayoz, D. Diabetic neuropathy is a more impo rtant determinant of baroreflex sensitivity than carotid elasticity in type 2 diabetes. Hypertension 2005, 46, 162–167. [G oogle Scholar] [CrossRef]
6. Cseh, D.; Climie, R.E.; Offredo, L.; Guibout, C.; Thomas, F.; Zanoli, L.; Danchin, N.; Sharman, J.E.; Laurent, S.; Jouve n, X.; et al. Type 2 Diabetes Mellitus Is Independently Associated With Decreased Neural Baroreflex Sensitivity: The Pa ris Prospective Study III. Arterioscler. Thromb. Vasc. Biol. 2020, 40, 1420–1428. [Google Scholar] [CrossRef]
7. Donath, M.Y. Targeting inflammation in the treatment of type 2 diabetes: Time to start. Nat. Rev. Drug Discov. 2014, 13, 465–476. [Google Scholar] [CrossRef]
8. Grossmann, V.; Schmitt, V.H.; Zeller, T.; Panova-Noeva, M.; Schulz, A.; Laubert-Reh, D.; Juenger, C.; Schnabel, R.B.; Abt, T.G.; Laskowski, R. Profile of the immune and inflammatory response in individuals with prediabetes and type 2 di abetes. Diabetes Care 2015, 38, 1356–1364. [Google Scholar] [CrossRef]
9. Festa, A.; D'Agostino, R., Jr.; Howard, G.; Mykkanen, L.; Tracy, R.P.; Haffner, S.M. Chronic subclinical inflammation as part of the insulin resistance syndrome: The Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000, 102, 42 –47. [Google Scholar] [CrossRef]

10. Shoelson, S.E.; Goldfine, A.B. Getting away from glucose: Fanning the flames of obesity-induced inflammation. Nat. Med. 2009, 15, 373–374. [Google Scholar] [CrossRef]
11. Hotamisligil, G.S. Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. Cell 2010, 140, 900–917. [Google Scholar] [CrossRef]
12. Cullinan, S.B.; Diehl, J.A. Coordination of ER and oxidative stress signaling: The PERK/Nrf2 signaling pathway. Int. J. Biochem. Cell Biol. 2006, 38, 317–332. [Google Scholar] [CrossRef]
13. Pedersen, D.J.; Guilherme, A.; Danai, L.V.; Heyda, L.; Matevossian, A.; Cohen, J.; Nicoloro, S.M.; Straubhaar, J.; Noh, H.L.; Jung, D. A major role of insulin in promoting obesity-associated adipose tissue inflammation. Mol. Metab. 2015, 4, 507–518. [Google Scholar] [CrossRef] [PubMed]
14. Campos, S.; Baumann, H. Insulin is a prominent modulator of the cytokine-stimulated expression of acute-phase plasma protein genes. Mol. Cell. Biol. 1992, 12, 1789–1797. [Google Scholar] [CrossRef] [PubMed]
15. Ye, J. Emerging role of adipose tissue hypoxia in obesity and insulin resistance. Int. J. Obes. 2009, 33, 54–66. [Google Scholar] [CrossRef] [PubMed]
16. Kushner, I. Regulation of the acute phase response by cytokines. Perspect. Biol. Med. 1993, 36, 611–622. [Google Scholar] [CrossRef]
17. Samad, F.; Uysal, K.T.; Wiesbrock, S.M.; Pandey, M.; Hotamisligil, G.S.; Loskutoff, D.J. Tumor necrosis factor α is a key component in the obesity-linked elevation of plasminogen activator inhibitor 1. Proc. Natl. Acad. Sci. USA 1999, 96, 6902–6907. [Google Scholar] [CrossRef]
18. Cinti, S.; Mitchell, G.; Barbatelli, G.; Murano, I.; Ceresi, E.; Faloia, E.; Wang, S.; Fortier, M.; Greenberg, A.S.; Obin, M.S. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans. J. Lipid Res. 2005, 46, 2347–2355. [Google Scholar] [CrossRef]
19. Weisberg, S.P.; McCann, D.; Desai, M.; Rosenbaum, M.; Leibel, R.L.; Ferrante, A.W. Obesity is associated with macrophage accumulation in adipose tissue. J. Clin. Investig. 2003, 112, 1796–1808. [Google Scholar] [CrossRef]
20. Meier, B.; Radeke, H.; Selle, S.; Younes, M.; Sies, H.; Resch, K.; Habermehl, G. Human fibroblasts release reactive oxygen species in response to interleukin-1 or tumour necrosis factor-α. Biochem. J. 1989, 263, 539–545. [Google Scholar] [CrossRef]
21. Bandeira, D.M.; Da Fonseca, L.J.S.; Guedes, D.S.; Rabelo, L.A.; Goulart, M.O.; Vasconcelos, S.M.L. Oxidative stress as an underlying contributor in the development of chronic complications in diabetes mellitus. Int. J. Mol. Sci. 2013, 14, 3265–3284. [Google Scholar] [CrossRef]
22. Downs, C.A.; Faulkner, M.S. Toxic stress, inflammation and symptomatology of chronic complications in diabetes. World J. Diabetes 2015, 6, 554. [Google Scholar] [CrossRef]
23. Pliquett, R.; Fasshauer, M.; Blüher, M.; Paschke, R. Neurohumoral stimulation in type-2-diabetes as an emerging disease concept. Cardiovasc. Diabetol. 2004, 3, 1–8. [Google Scholar] [CrossRef] [PubMed]
24. Rafeh, R.; Viveiros, A.; Oudit, G.Y.; El-Yazbi, A.F. Targeting perivascular and epicardial adipose tissue inflammation: Therapeutic opportunities for cardiovascular disease. Clin. Sci. 2020, 134, 827–851. [Google Scholar] [CrossRef] [PubMed]
25. Etchegoyen, M.; Nobile, M.H.; Baez, F.; Posesorski, B.; González, J.; Lago, N.; Milei, J.; Otero-Losada, M. Metabolic syndrome and neuroprotection. Front. Neurosci. 2018, 12, 196. [Google Scholar] [CrossRef] [PubMed]
26. Pop-Busui, R.; Ang, L.; Holmes, C.; Gallagher, K.; Feldman, E.L. Inflammation as a therapeutic target for diabetic neuropathies. Curr. Diabetes Rep. 2016, 16, 29. [Google Scholar] [CrossRef]
27. Mauro, C.; De Rosa, V.; Marelli-Berg, F.; Solito, E. Metabolic syndrome and the immunological affair with the blood–brain barrier. Front. Immunol. 2015, 5, 677. [Google Scholar] [CrossRef]
28. Van Dyken, P.; Lacoste, B. Impact of Metabolic Syndrome on Neuroinflammation and the Blood–Brain Barrier. Front. Neurosci. 2018, 12. [Google Scholar] [CrossRef]
29. Thomsen, M.S.; Routhe, L.J.; Moos, T. The vascular basement membrane in the healthy and pathological brain. J. Cereb. Blood Flow Metab. 2017, 37, 3300–3317. [Google Scholar] [CrossRef]
30. Muriach, M.; Flores-Bellver, M.; Romero, F.J.; Barcia, J.M. Diabetes and the brain: Oxidative stress, inflammation, and autophagy. Oxid. Med. Cell. Longev. 2014, 2014, 102158. [Google Scholar] [CrossRef]
31. Sifuentes-Franco, S.; Pacheco-Moisés, F.P.; Rodríguez-Carrizalez, A.D.; Miranda-Díaz, A.G. The role of oxidative stress, mitochondrial function, and autophagy in diabetic polyneuropathy. J. Diabetes Res. 2017, 2017, 1673081. [Google Scholar] [CrossRef]

32. Román-Pintos, L.M.; Villegas-Rivera, G.; Rodríguez-Carrizalez, A.D.; Miranda-Díaz, A.G.; Cardona-Muñoz, E.G. Diabet ic polyneuropathy in type 2 diabetes mellitus: Inflammation, oxidative stress, and mitochondrial function. J. Diabetes Re s. 2016, 2016, 3425617. [Google Scholar] [CrossRef] [PubMed]

33. Tilg, H.; Zmora, N.; Adolph, T.E.; Elinav, E. The intestinal microbiota fuelling metabolic inflammation. Nat. Rev. Immuno l. 2019, 1–15. [Google Scholar] [CrossRef] [PubMed]

34. Jonsson, A.L.; Bäckhed, F. Role of gut microbiota in atherosclerosis. Nat. Rev. Cardiol. 2017, 14, 79. [Google Scholar] [CrossRef] [PubMed]

35. Muscogiuri, G.; Cantone, E.; Cassarano, S.; Tuccinardi, D.; Barrea, L.; Savastano, S.; Colao, A. Gut microbiota: A new path to treat obesity. Int. J. Obes. Suppl. 2019, 9, 10–19. [Google Scholar] [CrossRef]

36. Cani, P.D.; Van Hul, M.; Lefort, C.; Depommier, C.; Rastelli, M.; Everard, A. Microbial regulation of organismal energy h omeostasis. Nat. Metab. 2019, 1, 34. [Google Scholar] [CrossRef]

37. Lu, Y.-C.; Yeh, W.-C.; Ohashi, P.S. LPS/TLR4 signal transduction pathway. Cytokine 2008, 42, 145–151. [Google Schol ar] [CrossRef]

38. Caesar, R.; Tremaroli, V.; Kovatcheva-Datchary, P.; Cani, P.D.; Bäckhed, F. Crosstalk between gut microbiota and dieta ry lipids aggravates WAT inflammation through TLR signaling. Cell Metab. 2015, 22, 658–668. [Google Scholar] [Cross Ref]

39. Takeuchi, O.; Hoshino, K.; Kawai, T.; Sanjo, H.; Takada, H.; Ogawa, T.; Takeda, K.; Akira, S. Differential roles of TLR2 a nd TLR4 in recognition of gram-negative and gram-positive bacterial cell wall components. Immunity 1999, 11, 443–45 1. [Google Scholar] [CrossRef]

40. Cani, P.D.; Bibiloni, R.; Knauf, C.; Waget, A.; Neyrinck, A.M.; Delzenne, N.M.; Burcelin, R. Changes in gut microbiota co ntrol metabolic endotoxemia-induced inflammation in high-fat diet–induced obesity and diabetes in mice. Diabetes 200 8, 57, 1470–1481. [Google Scholar] [CrossRef]

41. Ziegler, D.; Strom, A.; Bönhof, G.; Püttgen, S.; Bódis, K.; Burkart, V.; Müssig, K.; Szendroedi, J.; Markgraf, D.F.; Roden, M. Differential associations of lower cardiac vagal tone with insulin resistance and insulin secretion in recently diagnose d type 1 and type 2 diabetes. Metabolism 2018, 79, 1–9. [Google Scholar] [CrossRef] [PubMed]

42. Xu, W.; Zhu, Y.; Yang, X.; Deng, H.; Yan, J.; Lin, S.; Yang, H.; Chen, H.; Weng, J. Glycemic variability is an important ris k factor for cardiovascular autonomic neuropathy in newly diagnosed type 2 diabetic patients. Int. J. Cardiol. 2016, 215, 263–268. [Google Scholar] [CrossRef]

43. Ceriello, A.; Esposito, K.; Piconi, L.; Ihnat, M.A.; Thorpe, J.E.; Testa, R.; Boemi, M.; Giugliano, D. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. Diabetes 2008, 57, 1349–1354. [Google Scholar] [CrossRef]

44. Bhati, P.; Alam, R.; Moiz, J.A.; Hussain, M.E. Subclinical inflammation and endothelial dysfunction are linked to cardiac autonomic neuropathy in type 2 diabetes. J. Diabetes Metab. Disord. 2019, 18, 419–428. [Google Scholar] [CrossRef]

45. Alaaeddine, R.; Elkhatib, M.A.; Mroueh, A.; Fouad, H.; Saad, E.I.; El-Sabban, M.E.; Plane, F.; El-Yazbi, A.F. Impaired e ndothelium-dependent hyperpolarization underlies endothelial dysfunction during early metabolic challenge: Increased ROS generation and possible interference with NO function. J. Pharmacol. Exp. Ther. 2019, 371, 567–582. [Google Sc holar] [CrossRef]

46. Alaaeddine, R.A.; Mroueh, A.; Gust, S.; Eid, A.H.; Plane, F.; El-Yazbi, A.F. Impaired cross-talk between NO and hyperp olarization in myoendothelial feedback: A novel therapeutic target in early endothelial dysfunction of metabolic disease. Curr. Opin. Pharmacol. 2019, 45, 33–41. [Google Scholar] [CrossRef]

47. Matsutani, D.; Sakamoto, M.; Iuchi, H.; Minato, S.; Suzuki, H.; Kayama, Y.; Takeda, N.; Horiuchi, R.; Utsunomiya, K. Gl ycemic variability in continuous glucose monitoring is inversely associated with baroreflex sensitivity in type 2 diabetes: A preliminary report. Cardiovasc. Diabetol. 2018, 17, 36. [Google Scholar] [CrossRef]

48. Tarvainen, M.P.; Laitinen, T.P.; Lipponen, J.A.; Cornforth, D.J.; Jelinek, H.F. Cardiac autonomic dysfunction in type 2 dia betes–effect of hyperglycemia and disease duration. Front. Endocrinol. 2014, 5, 130. [Google Scholar] [CrossRef]

49. Verma, S.; Alam, R.; Ahmad, I.; Singla, D.; Ali, K.; Hussain, M.E. Effect of glycemic control and disease duration on car diac autonomic function and oxidative stress in type 2 diabetes mellitus. J. Diabetes Metab. Disord. 2018, 17, 149–158. [Google Scholar] [CrossRef]

50. Vinagre, I.; Sánchez-Quesada, J.L.; Sánchez-Hernández, J.; Santos, D.; Ordoñez-Llanos, J.; De Leiva, A.; Pérez, A. Inf lammatory biomarkers in type 2 diabetic patients: Effect of glycemic control and impact of LDL subfraction phenotype. Cardiovasc. Diabetol. 2014, 13, 1–7. [Google Scholar] [CrossRef] [PubMed]

51. Bakkar, N.-M.Z.; Mougharbil, N.; Mroueh, A.; Kaplan, A.; Eid, A.H.; Fares, S.; Zouein, F.A.; El-Yazbi, A.F. Worsening bar oreflex sensitivity on progression to type 2 diabetes: Localized vs. systemic inflammation and role of antidiabetic therap

y. Am. J. Physiol.-Endocrinol. Metab. 2020, 319, E835–E851. [Google Scholar] [CrossRef] [PubMed]

52. Warram, J.H.; Martin, B.C.; Krolewski, A.S.; Soeldner, J.S.; Kahn, C.R. Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. Ann. Intern. Med. 1990, 113, 909–915. [Google Scholar] [CrossRef] [PubMed]

53. Angelis, K.D.; Senador, D.D.; Mostarda, C.; Irigoyen, M.C.; Morris, M. Sympathetic overactivity precedes metabolic dysfunction in a fructose model of glucose intolerance in mice. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2012, 302, R950–R957. [Google Scholar] [CrossRef] [PubMed]

54. Low, P.A.; Walsh, J.; Huang, C.; McLeod, J. The sympathetic nervous system in diabetic neuropathy: A clinical and pathological study. Brain 1975, 98, 341–356. [Google Scholar] [CrossRef] [PubMed]

55. Sacre, J.W.; Franjic, B.; Jellis, C.L.; Jenkins, C.; Coombes, J.S.; Marwick, T.H. Association of cardiac autonomic neuropathy with subclinical myocardial dysfunction in type 2 diabetes. JACC Cardiovasc. Imaging 2010, 3, 1207–1215. [Google Scholar] [CrossRef] [PubMed]

56. Thackeray, J.T.; Radziuk, J.; Harper, M.-E.; Suuronen, E.J.; Ascah, K.J.; Beanlands, R.S.; DaSilva, J.N. Sympathetic nervous dysregulation in the absence of systolic left ventricular dysfunction in a rat model of insulin resistance with hyperglycemia. Cardiovasc. Diabetol. 2011, 10, 75. [Google Scholar] [CrossRef]

57. Poliakova, N.; Després, J.-P.; Bergeron, J.; Alméras, N.; Tremblay, A.; Poirier, P. Influence of obesity indices, metabolic parameters and age on cardiac autonomic function in abdominally obese men. Metabolism 2012, 61, 1270–1279. [Google Scholar] [CrossRef] [PubMed]

58. Ellulu, M.S.; Khaza'ai, H.; Rahmat, A.; Patimah, I.; Abed, Y. Obesity can predict and promote systemic inflammation in healthy adults. Int. J. Cardiol. 2016, 215, 318–324. [Google Scholar] [CrossRef] [PubMed]

59. Kurajoh, M.; Koyama, H.; Kadoya, M.; Naka, M.; Miyoshi, A.; Kanzaki, A.; Kakutani-Hatayama, M.; Okazaki, H.; Shoji, T.; Moriwaki, Y. Plasma leptin level is associated with cardiac autonomic dysfunction in patients with type 2 diabetes: HSCAA study. Cardiovasc. Diabetol. 2015, 14, 117. [Google Scholar] [CrossRef] [PubMed]

60. Grigoropoulou, P.; Eleftheriadou, I.; Zoupas, C.; Makrilakis, K.; Papassotiriou, I.; Margeli, A.; Perrea, D.; Katsilambros, N.; Tentolouris, N. Effect of atorvastatin on baroreflex sensitivity in subjects with type 2 diabetes and dyslipidaemia. Diabetes Vasc. Dis. Res. 2014, 11, 26–33. [Google Scholar] [CrossRef] [PubMed]

61. Hong, L.-Z.; Hsieh, P.-S. Hyperinsulinemia instead of insulin resistance induces baroreflex dysfunction in chronic insulin-infused rats. Am. J. Hypertens. 2007, 20, 451–458. [Google Scholar] [CrossRef] [PubMed]

62. Lieb, D.C.; Parson, H.K.; Mamikunian, G.; Vinik, A.I. Cardiac autonomic imbalance in newly diagnosed and established diabetes is associated with markers of adipose tissue inflammation. Exp. Diabetes Res. 2012, 2012, 878760. [Google Scholar] [CrossRef]

63. Herder, C.; Schamarek, I.; Nowotny, B.; Carstensen-Kirberg, M.; Straßburger, K.; Nowotny, P.; Kannenberg, J.M.; Strom, A.; Püttgen, S.; Müssig, K. Inflammatory markers are associated with cardiac autonomic dysfunction in recent-onset type 2 diabetes. Heart 2017, 103, 63–70. [Google Scholar] [CrossRef]

64. Hansen, C.S.; Vistisen, D.; Jørgensen, M.E.; Witte, D.R.; Brunner, E.J.; Tabák, A.G.; Kivimäki, M.; Roden, M.; Malik, M.; Herder, C. Adiponectin, biomarkers of inflammation and changes in cardiac autonomic function: Whitehall II study. Cardiovasc. Diabetol. 2017, 16, 153. [Google Scholar] [CrossRef]

65. Herder, C.; Schamarek, I.; Nowotny, B.; Carstensen-Kirberg, M.; Straßburger, K.; Nowotny, P.; Kannenberg, J.M.; Strom, A.; Püttgen, S.; Müssig, K. Inflammatory markers are associated with cardiac autonomic dysfunction in recent-onset type 2 diabetes. Heart 2017, 103, 63–70. [Google Scholar] [CrossRef]

66. Al-Assi, O.; Ghali, R.; Mroueh, A.; Kaplan, A.; Mougharbil, N.; Eid, A.H.; Zouein, F.A.; El-Yazbi, A.F. Cardiac autonomic neuropathy as a result of mild hypercaloric challenge in absence of signs of diabetes: Modulation by antidiabetic drugs. Oxid. Med. Cell. Longev. 2018, 2018, 9389784. [Google Scholar] [CrossRef]

67. Herder, C.; Schamarek, I.; Nowotny, B.; Carstensen-Kirberg, M.; Straßburger, K.; Nowotny, P.; Kannenberg, J.M.; Strom, A.; Püttgen, S.; Müssig, K. Inflammatory markers are associated with cardiac autonomic dysfunction in recent-onset type 2 diabetes. Heart 2017, 103, 63–70. [Google Scholar] [CrossRef]

68. Hansen, C.S.; Vistisen, D.; Jørgensen, M.E.; Witte, D.R.; Brunner, E.J.; Tabák, A.G.; Kivimäki, M.; Roden, M.; Malik, M.; Herder, C. Adiponectin, biomarkers of inflammation and changes in cardiac autonomic function: Whitehall II study. Cardiovasc. Diabetol. 2017, 16, 153. [Google Scholar] [CrossRef]

69. Al-Assi, O.; Ghali, R.; Mroueh, A.; Kaplan, A.; Mougharbil, N.; Eid, A.H.; Zouein, F.A.; El-Yazbi, A.F. Cardiac autonomic neuropathy as a result of mild hypercaloric challenge in absence of signs of diabetes: Modulation by antidiabetic drugs. Oxid. Med. Cell. Longev. 2018, 2018, 9389784. [Google Scholar] [CrossRef]