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Cardiac Autonomic Neuropathy: Review for The Cardio-Diabetologist to Boost Their Clinical Practice.

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Abstract:
Coronary heart disease and diabetes are significant global health issues. Coronary heart disease (CHD) is a common complication of diabetes mellitus (DM). A frequently overlooked complication of DM is cardiac autonomic neuropathy (CAN), which significantly contributes to cardiovascular disorders. These disorders include myocardial ischemia/infarction, orthostatic hypotension, hypertension, arrhythmias, and cardiomyopathy, all of which can lead to heart failure. In patients with diabetes, both components of the autonomic nervous system (ANS)—the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS)—play essential roles in regulating cardiovascular health. They help control heart rate, cardiac output, myocardial contractility, and the constriction and dilation of blood vessels. A notable clinical manifestation of CAN in patients with coronary artery disease (CAD) is silent myocardial ischemia (SMI), which can lead to significant morbidity and mortality and increases the risk of sudden cardiac death. This review analyzes recent research on cardiac autonomic neuropathy, particularly in diabetic patients. Early and accurate diagnosis of CAN can improve patient management, enhance prognosis, and reduce the risk of major adverse cardiac events.

Keywords: cardiac autonomic neuropathy, coronary heart disease, diabetes.

1. Introduction:

Uncontrolled diabetes leads to complications in many parts of the body including heart attack, stroke, kidney failure, leg amputation, vision loss, and nerve damage. But then difficult there to access the true prevalence of diabetic adverse events, due to microvascular complications are often underdiagnosed especially cardiac autonomic neuropathy.[1] Cardiovascular autonomic neuropathy (CAN) in diabetic patients represented as hyperglycemia damages autonomic nerve fibers leading to innervating the heart and blood vessels, resulting in abnormal heart rate and vascular dynamics. CAN is known to affect multiple organ systems with higher morbidity and mortality in patients with diabetes. A more frequent & less diagnosed complication of diabetes mellitus is cardiac autonomic neuropathy (CAN) which has a major focus on cardiovascular disorders including myocardial ischemia/infarction, orthostatic hypotension, hypertension, arrhythmias & cardiomyopathy leading to heart failure.[2]In patients associated with diabetes, the two parts of the autonomic nervous system (ANS) --parasympathetic (PNS) and sympathetic (SNS) have an important influence on CVD to control heart rate, cardiac output, myocardial contractility, constriction, and dilatation of blood vessels. As per the Toronto Consensus Panel, Cardiac autonomic neuropathy is called the imbalance of cardiovascular autonomic control in DM with the exclusion of other etiology.[3]

2. Purpose of Review:

Various studies have showed the number of patients with cardiovascular autonomic neuropathy (CAN) varies from 17% to 90% in DM type 1 and 27.5% to 73% in DM type 2 across the world due to underdiagnosis.[4-7]There is huge variation in CAN about incidence & prevalence depending on different population with variable diagnostic methods and stages of disease. On the other ways of risk

to develop the cardiac autonomic neuropathy, are poor glycemic control (major risk factor), old age, morbid obesity, frequent smoking, uncontrolled hypertension, distal polyneuropathy, retinopathy and nephropathy.[4-7]According to the diabetes control and complication (DCC) trial, intensive glycemic control resulted in 50% decrease incidence of CAN with follow-up of > 6.5 years **(8)**.The life style & pharmacological intervention for hypertension, smoking, obesity, and hyperlipidemia also reduce the incidence & prevalence of CAN .[1-8] Strongly underdiagnosed, CAN explore multiple clinical manifestations, such as orthostatic hypotension, resting tachycardia, exercise intolerance, silent myocardial infarction, heart failure and intra or perioperative cardiovascular liabilities.[1-8] This review explores the fundamentals of CAN, epidemiology, pathophysiology, clinical features, diagnosis, and consequences of CAN &research as well as evidence based current treatment options may reduce the morbidity & mortality in patients with diabetes.

3. Basic Fundamentals:

The abnormalities of metabolism diabetes lead to diffuse and gross injury to peripheral and autonomic nerves and microvasculature which distresses the autonomic nervous system, it can damage the cardiovascular system and impair metabolic functions such as glucose counter-regulation resulting into. cardiac autonomic neuropathy.[9,11] This cardiac autonomic neuropathy (CAN) responds to progressive damage to the autonomic nerve nervous system and affects to the cardiovascular (the heart and blood vessels) system, resulting in abnormal heart rate, heart rate variability, and vascular dynamics. CAN is a significant cause of morbidity (coronary heart disease) and mortality associated with myocardial silent ischemia, infarction high risk of cardiac arrhythmias, heart failure, and sudden death.[9,12] Our clinical review would emphasize on cardiovascular autonomic neuropathy pathogenesis& relationship with the various inflammatory routes..[9,10]

The autonomic nervous system functions have two main branches: the sympathetic and parasympathetic nervous system, is well known physiology. First, stimulation of the sympathetic nervous system represents physiological responses of fight and flight which leads to tachycardia, hypertension, utilization of required stored energy, and jumped arousal. Responding major neurotransmitters are epinephrine, norepinephrine and dopamine, and these neurotransmitters mediate cellular responses by interacting with G-protein coupled ADRs& dopaminergic (α1, α2, β1, β2, β3 and D1, D2, D3)receptors.[9-12]The stimulation of the parasympathetic nervous system tends to produce opposite effects of the sympathetic nervous system, resulting as decrease the heart rate, cardiac contractility and increase the functions of digestive system.[9-13] Basic mechanism of CAN is based on complex interactions and involves various mechanisms and pathways those lead to neuronal ischemia followed by neuronal death.[9-12,13-14]The major cause of the pathogenic process is hyperglycaemia-induced oxidative stress and to advanced glycosylation factors lead to mitochondrial dysfunctions, decrease membrane permeability, and endothelial dysfunctions.[10-11] (See Figure-1)

The many different pathways are responsible to changes in transcription factors, expressionof gene, interruption of numerous cellular functions, and communication between the cells and surrounding matrix (Summary of the mechanisms that relate hyperglycaemia to microvascular complications such as neuropathy in patients with diabetes, PKC: protein kinase C; AGE: advanced glycation end-products; PARP: poly ADP-ribose polymerase; GSH: glutathione; NADH: nicotinamide adenine dinucleotide; GAPDH: glyceraldehyde-3 phosphate dehydrogenase; TGF-β: transforming growth factor beta; VEGF: vascular endothelial growth factor; PAI-1: plasminogen activator inhibitor-1; IL-1: interleukin 1;eNOS: endothelial nitric oxide synthase; IL-6 interleukin 6, TNF-α: tumor necrosis factor alpha; VCAM-1: vascular cell adhesion molecule 1).These inflammatory agents lead to alter neuronal function and neural death.[10-12]

The vagus nerve is affected in early stages of CAN which may increase the sympathetic tone to continues until advanced CAN. Finally, CAN is responsible for the abnormalities in heart rate and changes in heart rate variability (HRV). Recent study on the same, Cichosz et al. revealed that the

HRV parameter low frequency (LF) was significantly reduced during hypoglycaemic episodes in patients with and without CAN **(15)**.Another study; Jaiswal et al. revealed that hypoglycaemic stress decrease HRV power independently of glucose control as assessed by HbA1c **(9-13)**.Accordingto these data high glucose variability may contribute to CAN in spite of hyperglycaemia**.**[12-13]

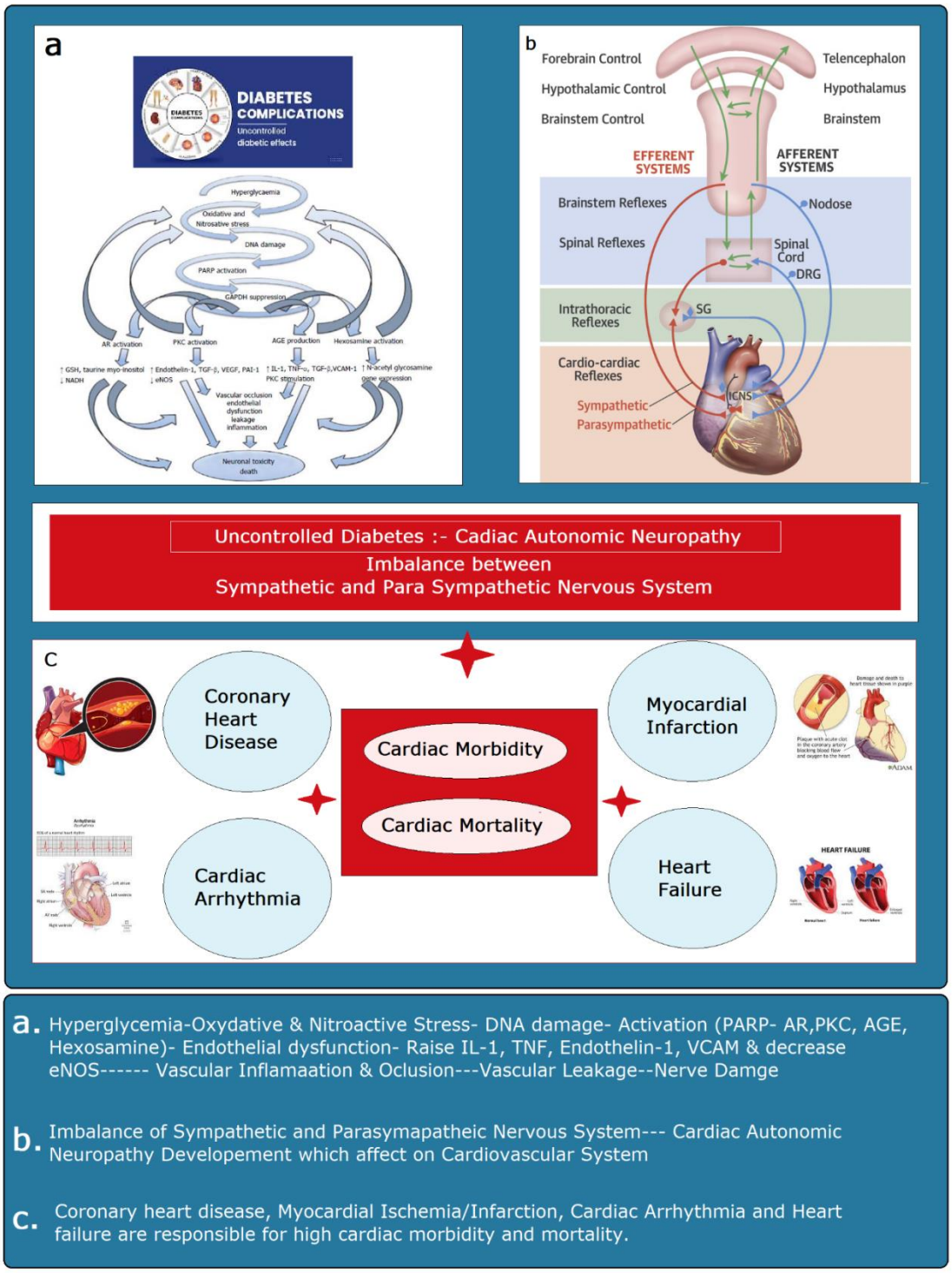


Figure-1: A- Hyperglycemia-Nerve Damage, B -CAN develop C- Cardiac Morbidity & Mortality

4. . Management:

The review article is trying to focus step by step about clinical features, diagnostic methodology with current treatment for the cardiac autonomic neuropathy.

4.1 Clinical Features

Cardiac autonomic neuropathy is found in 25 % of DM type 1 and 33% of DM type 2 patients, is associated with silent myocardial ischemia, cardiomyopathy, increased mortality and stroke. CAN has been revealed to resting tachycardia, exercise intolerance, postural hypotension, enhanced intraoperative or perioperative cardiovascular liability, raised incidence of silent ischemia, silent myocardial infarction and increased rate cardiac death after myocardial infarction and decrease life expectancy. (See Figure-2)

Clinical Manifestations of Cardiac Autonomic Neuropathy
Resting Tachycardia Abnormalities in heart rate variability (HRV) are early findings of CAN, tachycardia at rest and a static heart rate are typical late findings in diabetes with impaired vagal function. Resting heart rates of 90–100 beats/min. and occasional heart rate increments up to 130 beats/min. occur.
Exercise Intolerance The disturbed autonomic function leads to exercise intolerance, decreases response in HR and BP, and dampens increases in cardiac output in response to exercise.
Intraoperative Cardiovascular Liability Intra/ Perioperative cardiovascular morbidity and mortality are increased two- to threefold in patients with diabetes. Compared with non-diabetic subjects, diabetic patients undergoing general anesthesia might experience a greater degree of decline in heart rate and blood pressure during initiation of anesthesia, and less of an increase after tracheal intubation and extubation.
Orthostatic Hypotension Fall in BP (i.e. >20 mmHg for systolic or >10 mmHg for diastolic BP) in reply to postural change, from supine to standing is termed orthostatic hypotension**.** It is usually a result of impairment of the efferent sympathetic vasomotor fibers, predominantly in the splanchnic vasculature.
Silent Myocardial Ischemia/Cardiac Denervation Syndrome The incidence of CAD with or without symptoms is raised in diabetes, and the important cause of silent ischemia in diabetic patients is cardiac autonomic neuropathy.
Autonomic Cardiomyopathy The CAN may be associated with left ventricle (LV) dysfunction mainly, diastolic functions in the absence of cardiac disease in diabetic patients. Research has shown a significant correlation of the brutality of CAN with decreased peak diastolic filling and with an amplified atrial role to diastolic filling rate as measured by Doppler echocardiography.

Figure 2- Clinical Manifestations of Cardiac Autonomic Neuropathy

CAN may affect the daily routine activities of diabetic patients, might alter their quality of life, and may raise possibly life-threatening consequences**.**[12-13]

4.2 Diagnosis

There are few many recent investigations have suggested that autonomic dysfunction (enhanced activity of the sympathetic nervous system and decreased activity of the parasympathetic nervous system) impairs the capability of the autonomic nervous system (ANS) to control the cardiovascular system. 9see figure-3)

Test	Clinical diagnosis	Research	End-point in clinical trials
Heart rate cardiovascular tests	Yes	Yes	Yes
Orthostatic hypotension test	Yes	Yes	No (low sensitivity)
QT interval	Yes (additional information and risk stratification)	Yes	No (low sensitivity)
Ambulatory blood pressure monitoring for dipping status	Yes (risk stratification)	Yes	No (low sensitivity)
HRV time and frequency domain indices	Yes (additional information and risk stratification)	Yes	Yes
Baroreflex sensitivity measures	No (early addeddata and hazard stratification but low accessibility)	Yes	Yes
Scintigraphy studies	No (low availability, limited standardization)	Yes	Yes
Muscle sympathetic nerve activity	No (low availability, limited data in cardiovascular autonomic neuropathy)	Yes	Likely (for lifestyle intervention trials in diabesity)
Catecholamine assessment	No (low availability)	Yes	Likely (for lifestyle intervention trials in diabesity)

Figure-3 Various diagnostic tests for CAN

The factor is that one needs to distinguish the difference between autonomic imbalance and clear evidence of autonomic neuropathy. The diminished autonomic balance produces a figure of interesting and annoying clinical circumstances such as orthostatic brady-tachycardia, orthostatic hypotension and can lead to arrhythmias and sudden cardiac death**.**[15-18]

CAN assessment in clinical practice includes symptoms and signs, **cardiovascular autonomic reflex tests**(CARTs) based on HR, HR Variability, postural BP, and ABPM (24 24-hour BP monitoring)**.**[16]

- CARTs evaluate cardiovascular autonomic function by time-sphere HR response to deep breathing, postural change, and Valsalva maneuver and by gauging the end-organ response; that is, HR and BP variations. Even though indirect autonomic events, are measured as the gold standard in autonomic assessments.

- HR disparities during supine to standing, deep breathing and Valsalva maneuver (heart rate tests) are guides mainly of parasympathetic role; however, the orthostatic hypotension, the blood pressure response to maneuver of Valsalva and constant isometric muscular strain offer catalogs of sympathetic function.

These diagnostic tests are safe, clinically applicable (they compare with tests of PNS function), non-invasive, specific, reproducible, and identical and so they are considered fused gold-standard procedures of autonomic function.[16-18] (see figure-4,5)

Diagnostic Test	Methodology	Values & Normal Response
Heart rate response to standing	During Holter ECG monitoring, the R-R interval is accessed at 15-30 beats after standing.	Characteristically, tachycardia is followed by reflex bradycardia. The of 30:15 should be > 1.03.
Heart rate response to Valsalva maneuver	The subject by force exhales into the mouthpiece of a manometer to 40 mm Hg for 15 s during ECG monitoring.	Healthy subjects progress tachycardia and peripheral vasoconstriction during strain and exceed bradycardia and increase in blood pressure with release. The normal ratio from longest to shortest R-R is > 1.2.
Systolic blood pressure (SBP) response to standing	SBP is measured in the supine subject. During standing, the systolic BP is measured after 2 min.	SBP fall of < 10 mm Hg; borderline is a fall of 10–29 mm Hg as normal; SBP fall of > 30 mm Hg with symptoms as abnormal response.
Diastolic blood pressure (DBP)response to isometric exercise	The subject squeezes a handgrip dynamometer to establish a maximum. Grip is at that point squeezed at 30% maximum for 5 min.	DBP is an increase of > 16 mm Hg in the opposite limbs normal response.
Beat-to-beat HRV	With the patient at rest and supine, HR is monitored by ECG while the patient respirates at 6 breaths per minute, paced by a metronome device or like.	An alteration in HR of > 15 bpm is normal and < 10 bpm is abnormal. The lowermost normal value for the expiration-inspiration (E/I) ratio of the R-R interval is 1.17 in patients aged 20–24;

		this value declines with age.

Figure-4 Various diagnostic tests, methodology and values for CAN

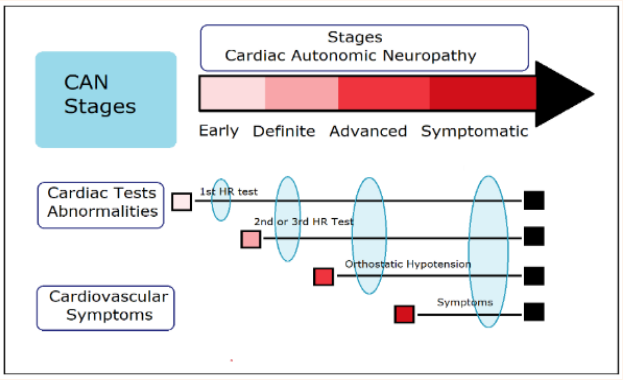
CAN Diagnosis and Staging	
Existence of one abnormal cardiovagal test result identifies the condition of possible or early CAN, to be established over time. Minimum2 abnormal cardiovagal grades are needed for a definite diagnosis. (LevelA) Existence of orthostatic hypotension in count to HR test irregularitiesfinds advanced or severe CAN (level B). CARTs permit CAN staging from early to advanced participation (level C).	

Figure-5 stages of cardiac autonomic neuropathy

Cardiac Autonomic Neuropathy Diagnostic Criteria
Subcommittee of Toronto Consensus Panel endorses CAN Four gold standard assessments for CAN are the CARTs of the heart rate response to standing, deep breathing, and Valsalva maneuver & blood pressure (BP) response to standing posture.[16,21] Numerous anomalous variable quantities in cardiac autonomic neural function catalogs are more consistent and desirable for diagnosis.[21] CAN is staged in three classes: (1) early or possible CAN (1 abnormal CART outcome), (2) confirmed or definite CAN (2–3 abnormal CART results), and (3) advanced or severe CAN (orthostatic hypotension in count to ≥2 abnormal cardiovascular reflex test grades).
The Toronto Consensus endorses universal screening for symptoms and signs of CAN in all diabetes patients.[22,] The American Association of Clinical Endocrinologists recommends screening for CAN in all type 2 diabetes patients from analysis and in all type 1 diabetes patients with a duration of > 5 years.[21] CAN screening is currently being accessed, in the UK, But in various countries, is not usually accomplished.[23]

4.3 Treatment

Initial treatment is crucial after diagnosis of CAN. Treatment must not be overdue while waiting for the symptoms and signs of cardiac autonomic neuropathy to ensue because these results appropriately specify the stages of advanced CAN, once there is a nonexistence of reversibility.[24] Initial management, counting risk factor alteration, should be started before definitive, irreversible CAN progresses. (See Figure 6, 7) Management of type 1 &2 diabetes varies due to the conflicting fundamental pathophysiology in these subpopulations.[21] Lifestyle modifications are also significant for the stoppage of CAN in prediabetes patients before onset of type 2 diabetes as seen in the study for Diabetes Prevention Programme.[25] In total, recent data propose that sodium-glucose cotransporter

2 inhibitors (SGLT2i) may have a modifying consequence on the autonomic nervous system as accessed by decreased without changes in heart rate, suggesting a decrease in sympathetic drive.[26]

Figure-6: TCP Recommendation

The recommendations from the Toronto Consensus Panel on Cardiac Autonomic Neuropathy in Diabetes.[22]
• Severe diabetes therapy slows the progression of CAN in type 1 diabetes (level A). • Severe multifactorial risk factors to CVD, Lifestyle intervention retards the progression & development of CAN in type 2 diabetes (level B). • Lifestyle modifications may improve HR Variability in prediabetes (level B) and diabetes (level B). • Indicative orthostatic hypotension can be improved by a non-pharmacological approach (level B)& midodrine (level A) and/or fludrocortisone (level B).
• In type 1 and 2 diabetes patients, medical therapy should deliberate comorbidities and specific risk profiles (class I). • Lifestyle modifications should be obtainable as a basic preventive measure (class I). • The limited evidence from very few large-scale randomized trials, approvals cannot be given for pharmacological and non-pharmacological management of CAN. (class II) • In patients of CAN, avoid medicines that may reduce HR variability, (class III) • Tachycardia at rest in patients of CAN may be managed with cardiac selective beta-blockers (class I).
• The primary approach in orthostatic hypotension with relevant symptoms should deliberate the exclusion of medicines worsening orthostatic hypotension, improvement of volume depletion (class I), and other non-pharmacological approaches (class IIa). • Pharmacotherapy in orthostatic hypotension with relevant symptoms should include midodrine (class I) or fludrocortisone, or a combo of both in refractory to monotherapy (class IIa). • Due to limited clinical evidence, the possible risk of any pharmacological management should be carefully evaluated against its likely benefit (class I). • CARTs should be used as end-points in prospective observational and clinical trials.

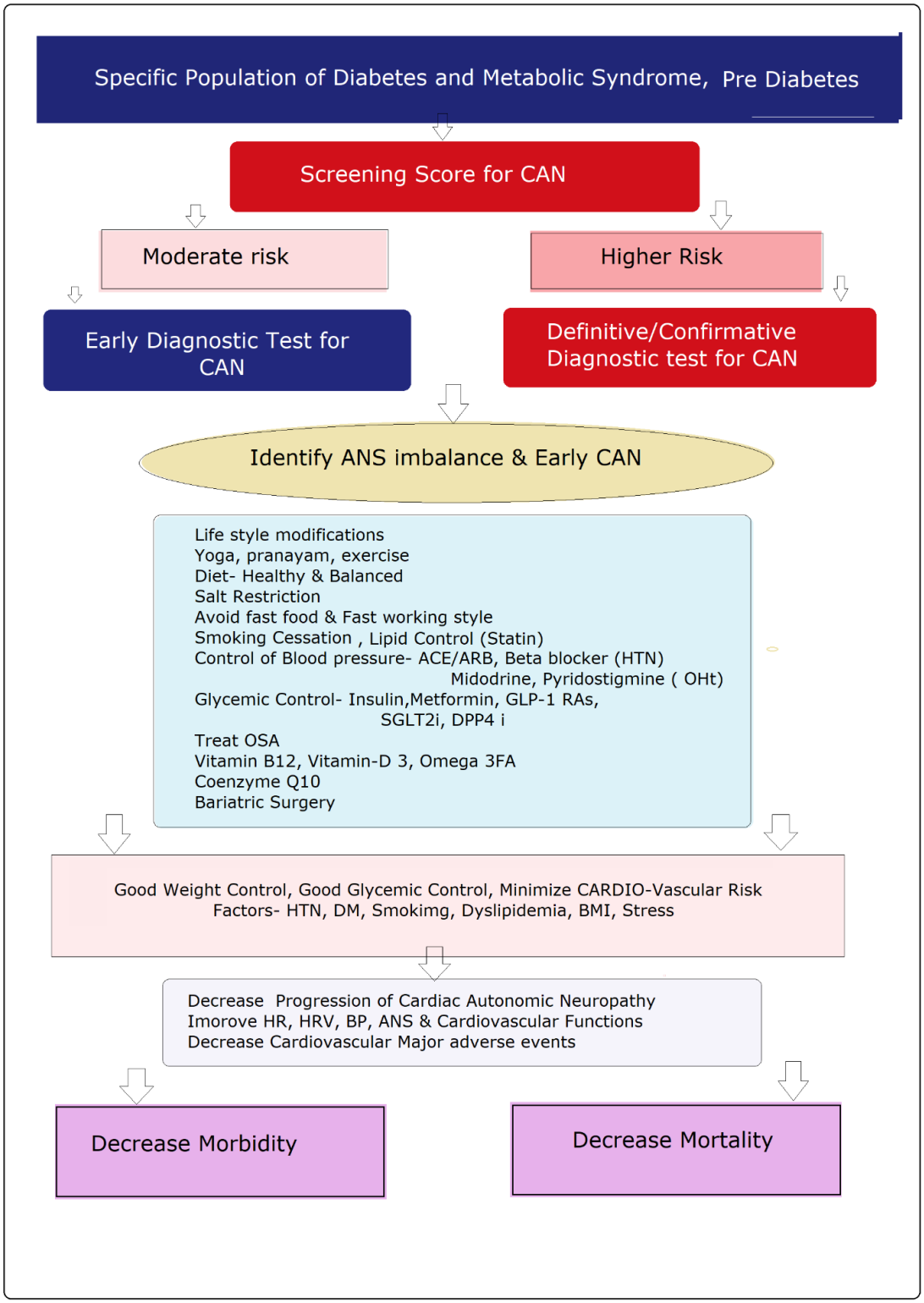


Figure-7: Management chart for reduction of Cardiac Morbidity & Mortality in CAN

Treatment of cardiac autonomic neuropathy:

The initial component of CAN management is the optimization of glycaemic control using intensive insulin therapy and early control of type 1 diabetes. According to the DCCT trial , which used an intensive insulin treatment for a mean duration of 6.5 years, and the DCCT-EDIC, follow-up to 13 to 14 years.[27] The both study found a long-term reduction in CAN prevalence to 28.9% in the intensively treated arm compared with 35.2% in the predictable conduct arm (P = 0.018) which

persevered 8 years after the original DCCTrial intervention.[27] The management of CAN requires a multifaceted approach as requires lifestyle interventions with diet modification & supportive aerobic exercise& yoga followed by pharmacologic interventions in selected patients with type 2 diabetes.[27-28]

Lifestyle Interventions

- **Dietary Interventions**

A balanced diet with reduced carbohydrates & rich protein -fiber combined with plant-unripe fruits based low caloric agenda could be benefited diabetes for the prevention of cardiac autonomic neuropathy and reduce cardiac complications. Based on a previous study in CAN prevention by dietary restriction for weight loss delivered by two differing calorie during 8 weeks in people living with diabesity.[29] The first diet used high content of cereal fibre and coffee without red meat; the second one was rich in red meat and low in fibre without coffee. Both groups of diets were used to diminish energy intake by a mean - 1198 kJ, leading weight loss about 5 to 6 kg with related enhancements in cardiac autonomic function.[29]

- **Yoga &Exercise Interventions**

Study was presented by Indian authors during annual scientific meeting of American College of Cardiology, 2018 on combination of India yoga & Chinese aerobic exercise in diabetic patients which revealed as significant reduction of heart rate, improvement of HRV, control of blood pressure, HbA1C. Data showed 2-fold reduction of CAN &2.5-fold reduction in cardiovascular risk in combined approach rather than individuals reserve .[28] Combined physical activity, including lower intensity activity, such as breathing exercise, pranayama, walking, and moderate-intensity endurance activity like jogging, running and aerobic exercise, have shown improvements in cardiac autonomic function, including HRV.[28,31] Justified improvements in HRV indexes were found in an aerobic exercise training database after 6 months which were conducted 3 times weekly to an intensity of 70% to 85% of an each individual 's HR reserve.[30]

An integrated lifestyle intervention ,a cohort study in prediabetes, counting 20 to 30 minutes of activity on as a minimum 5 days/week, with the purpose of 7-9 % weight reduction and positively amended cardiac autonomic function in the type 2 diabetic patients .[32]

- **Glycaemic Control**

Poor glycaemic status is a main key factor in developing cardiac autonomic neuropathy in diabetes patients, so optimizing glycaemic control in type 2 diabetes prevents CAN with the support of the best pharmaceutical plus alternative multi approach.[33] Warning signal to avoid excessively tight glycaemic control in patients with type 2 diabetes to develop hypoglycemia with increased cardiovascular risk (eg, ischemic heart disease) based on ACCORD trial revealed increased cardiovascular mortality in this subgroup, leading to the premature cessation of the same .[33]

- **Bariatric Surgery**

Drastic changes occur after bariatric surgery for optimized weight reduction followed by targeted HbA1C reduction with tight glycaemic control. Data suggest the use of bariatric surgery to achieve weight loss in patients with severe diabesity (n = 17) improves measurements of cardiac autonomic function using HRV and Sudo-scan testing (measure of sudo-motor function) for prevention of cardiac autonomic neuropathy.[34]

- **Control of Cardiovascular Risk Factors**

For prevention of the progression of CAN in diabetes, it is a must to address modifiable cardiovascular risk factors along with hyperglycemia, including the management of hypertension and dyslipidemia.[35-36] Patients with type 1 diabetes for more than 10 years or older than 40 years of age

besides type 2 diabetes with a QRISK2 score for developing cardiovascular disorders of ≥10% for 10 years should get treatment using lipid modification therapy with an optimized dose of statins.[35-36] Smoking cessation and stress reduction supportive & preventive programs should be provided in prone to CAN individuals .[21]

Pharmacologic Intervention with beneficial Properties on the Autonomic Nervous System in CAN.

Metformin

Metformin is an oral hypoglycaemic well-known medicine to manage hyperglycemia for improvements in heart rate variability (HRV) indexes, including a rise in mean [SD] total power 2711 [395] $msec^2$ at baseline vs 2915 [348] $msec^2$ after metformin; P = 0.05).The study showed about mean high frequency (22.4 [1.8] nu at baseline vs 23.6 [2.1] nu after metformin; P = 0.05), with a mean decrease in low frequency 68.6 [1.5] nu at baseline vs 52.1 [1.1] after metformin; P = 0.05).On the other hand, metformin also enhanced HRV central between deviations in the lifestyle versus placebo groups in QT catalogs, the SD of NN intervals in diabetic patients to decrease the progression of CAN.[35]

Glucagon-like Peptide 1 Receptor Agonists

Glucagon-like peptide 1 (GLP-1)receptor agonists (RAs) have a valuable role in the countdown progression of CAN by weight-lowering effect in type 2 diabetes & reduction in cardiovascular morbidity and mortality.[35-36]According to LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), median follow-up duration of 3.8 years, decreased in death from cardiovascular causes, nonfatal myocardial infarction & stroke in 13% with liraglutide compared with placebo group 14.9% (P = 0.01).[35-36]

Angiotensin-converting enzyme (ACE) Inhibitors &Angiotensin II Receptor Blockers (ARB)

ACE/ARB have shown their vasodilatory action with reduction of inflammation & fibrosis followed by balancing between SNS and PNS through raising parasympathetic tone resulting as suppression of CAN in diabetes. Angiotensin-converting enzyme Inhibitors **(**ACE), e.g. Enalapril have decreased in cardiac neurohormone planes of noradrenaline, which could be defensive against CAN.[35-36] The (ARB) angiotensin II receptor blocker e.g. Losartan has shown its action to an increase in parasympathetic tone, and also produced improvements in HRV spectral analysis measures of cardiac autonomic function, with an overall increase in HRV (increase in high frequency) (P < 0.01).[35-36]

SGLT2i

Sodium-Glucose Cotransport 2 inhibitors (SGLT2i) have shown better glycaemic control & reduced heart failure adverse events. Data suggest that SGLT2 inhibitor for reduction in cardiovascular death and heart failure recurrent adverse events is yet to be fully demonstrated but fairly extends beyond glycaemic control.[37-39] On empagliflozin is the class of SGLT2i, the EMPA-REG outcome (BI 10773)trial, in Type 2 Diabetes Mellitus Patients Cardiovascular Outcome Event Trial of empagliflozin revealed a modest reduction in blood pressure in the absence of increased heart rate,[38-39]signalling a sympathetic tone reduction.[37] In reality, dapagliflozin reduces the expression of the sympathetic nervous system & neurotransmitter for example noradrenaline in the cardio-renal part, refining renal blood flow self-reliantly of its glucose-countering upshot.[40] Another study on empagliflozin, EMBODY randomized controlled trial explored the significant properties of empagliflozin on cardiac sympathetic and parasympathetic nerve activity by counting HR Variability and HR turbulence in acute myocardial infarction with type 2 diabetes patients .[39]

β-Blockers

The β-Adrenoceptor antagonist medication (β-blockers) lowers the resting heart rate and improves the 24-hour ambulatory HRV and vagal function which decreases the progression of cardiac autonomic dysfunction.[41] This cardioprotective effect of beta-blocker (BB) may reduce morbidity & mortality in CAN. Selective BB as Bisoprolol produced improvements in several HRV measures of parasympathetic activity of the ANS in patients with heart failure, counting rises in the 24-hour root mean square of successive differences between daytime high-frequency power (P = 0.03)& normal heartbeats (P = 0.04) .[43]Other researchers also found enhanced HRV in CAD patients who were given beta blockers as atenolol or metoprolol.[42]

Statins

Lipid-lowering agents like atorvastatin and rosuvastatin in a group of statins are competitive inhibitors of 3-hydroy-3-methylglutaryl A reductase and decrease cardiovascular risk in diabetes through both primary and secondary prevention of cardiac autonomic neuropathy. In a rat model, Statin reduces damage to ANS and may improve sympathetic nerve function in CAN, regardless of level of blood glucose.[44] Statins also reduce the sympathetic nerve activity in muscles by 12% to 30%end resulting in as countdown of CAN in diabetes type 1 & 2 .[44]

α-Lipoic Acid

Many previous studies suggest that α-Lipoic acid is a scavenger of free radicals with a good neuroprotective role by reducing oxidative stress and controlling hyperglycemia in a supporting manner.[45] Related studies on α-Lipoic acid e.g. ALADIN (Alpha-Lipoic Acid in Diabetic Neuropathy) I & ALADIN II revealed that α-lipoic acid improved nerve conduction parameters and reduced symptoms CAN.[46]

600 mg oral dose of α-lipoic acid provided a better risk-benefit ratio for reducing neuropathic symptoms and autonomic neuropathic deficits during 5 weeks (Sydney 2 study).[45] As per Deutsche Kardiale Autonome Neuropathie (DEKAN) study guide us regarding enhancements of HR Variability in type 2 diabetes and CAN (n = 29 after dropouts) with good tolerance of α-lipoic acid for 4 months treatment.[47]

Orthostatic Hypotension

As per the definition of orthostatic hypotension is a fall in BP (i.e. SBP >20 mmHg or DBP >10 mmHg) in response to changing posture from supine to standing.[47] In cardiac autonomic neuropathy (CAN) with diabetes, orthostatic hypotension is typically an outcome of injury to the efferent sympathetic vasomotor fibers, especially in the splanchnic vasculature .[21,48] Usually late diagnosis of CAN is typically associated with orthostatic hypotension, which can be treated with fludrocortisone or midodrine as per symptoms .[48-51] Mineralocorticoid like fludrocortisone increases blood pressure and expands plasma volume, thereby reducing postural orthostatic hypotension..[49] Current Cochrane review disappointingly revealed clinical evidence about benefit of fludrocortisone in reducing postural symptoms in CAN .[49]Vasopressor like a midodrine that increases standing blood pressure, thereby reducing orthostatic hypotension in two randomized controlled trials.[50,51] It increases cardiovascular risk by increasing supine hypertension (RR = 5.1) but recovers postural symptoms in CAN..[52]

60 mg daily Pyridostigmine also improves standing blood pressure in patients with orthostatic hypotension in CAN without worsening supine hypertension.[53] It augments baroreflex-mediated increases in systemic resistance (through improving BRS) followed by controlling orthostatic hypotension and also proportional to the degree of orthostatic stress without causing supine hypertension.[53]

Combined Lifestyle Modification and Pharmacologic Interventions

Managing cardiovascular risk factors, counting and optimizing blood pressure and dyslipidemia, using both lifestyle modification & pharmacologic interventions in a multi-layered approach should be an essential approach.[16,21,28] A target-driven strengthened lifestyle and multimodal approach, including pharmacologic intervention for 7.8 years that optimized glycaemic control, cholesterol level, and blood pressure. The average 7.9 years of life added at 21.2 years of follow-up were reflected by a 68% (RR) risk reduction for progression of CAN and countdown from major cardiovascular adverse events.[54,55]

5. Clinical Research:

A recent study by Ziegler et al showed the prevalence of CAN to be 7.7% in newly diagnosed type 1 diabetes (n = 130), suggestive of an excess prevalence.[29,45,] The prevalence varies from 17% to 66%, in type 1 diabetes whereas in type 2 diabetes the prevalence is 31% to 73%.[59,35] In another recent comprehensive systematic review, CAN is also revealed in prediabetes at a higher prevalence of 9% to 38%, which is greater than in euglycemic groups (0%-18%). KORA, S4 the Cooperative Health Research in the Region of Augsburg survey for CAN in people with impaired glucose tolerance (5.9%), impaired fasting glycemia (8.1%), and combined impaired fasting glycemia and impaired glucose tolerance (11.4%). The study guides us about the excess of CAN in prediabetes when compared with the normoglycemic whose prevalence was about 4%.[56]

Typical clinical evidence of CAN in patients with **coronary artery disease** (CAD) is silent myocardial ischemia (SMI). [57]CAN is associated with SMI, according to a meta-analysis of 12 studies showed the exercise test with prevalence ratios 0.85 to 15.53 (the Mantel-Haenszel prevalence risk 1.96, 95% CI: 1.53–2.51) .[58] Another study of 120 patients with DM and absence of CAD found that CAN was a good predictor of major cardiovascular events (such as death caused by MI, nonfatal MI, heart failure, resuscitation from ventricular arrhythmia,

need for coronary revascularization & sudden death,) then the presence of SMI (OR = 4.16, 95% CI: 1.01–17.19) with a high prevalence of CAN associated with a high risk of cardiac mortality after myocardial infarction .[60]

CAN may lead to abnormalities in the left ventricular systolic and predominantly diastolic function based on 2D echocardiographic studies revealed that CAN is significantly associated with a decrease in the peak diastolic filling and an increase in the atrial component of diastole .[61]Cardiac autonomic neuropathy associated with cardiac arrhythmias like sinus tachycardia or sinus arrhythmia is a common manifestation of the early stage of CAN. This study showed HR > 90 bpm observed as a result of parasympathetic withdrawal and an impaired HR response to exercise leads to exercise intolerance .[61]

CAN associated with diabetes present, a higher number of recurrences of paroxysmal AF are observed in comparison to diabetes without CAN (47 events versus 22 events per year). The same study also revealed that the presence of CAN with a significant increase in P-wave duration followed by inhomogeneous atrial depolarization as a potential trigger of paroxysmal AF .[62]

The EURODIAB IDDM Complication Study revealed the association between QT prolongation and CAN .63 Subsequently QT prolongation predisposes to cardiac arrhythmias and sudden death. On the other hand mechanisms depending on autonomic imbalance, such as less response to a hypoxic state, decreased hypoglycaemic awareness, and prolonged hypoglycemia events, may also be responsible for malignant ventricular arrhythmias which lead to sudden cardiac death .[64]

Regarding cardiovascular mortality in CAN we realize that based on a meta-analysis of 15 studies, Maser et al. 65 revealed relative mortality risk was 2.14 (95% CI: 1.83–2.51,). In another study, EURODIAB IDMM Complications Study had cardiac mortality with strongest association of cardiac autonomic neuropathy .[66]As per the ACCORD trial, 3.5 years follow up with in height risk of cardiovascular adverse event were associated with CAN as an independent factor for risk to all-cause

mortality (HR 2.14, 95% CI: 1.37–3.37) & cardiovascular mortality (HR 2.62, 95% CI: 1.4–4.91) at significant p-value .[67]

5. Future Aspect:

Clinical research needs to continue to increase sensitivity and specificity about screening scores by different target diagnostic testing for cardiac autonomic neuropathy in the early stage. Increasing awareness about the understanding of the pathophysiology of CAN reproduces the therapeutic targets with the combination of lifestyle intervention and advanced pharmacological support including newer therapies such as SGLT2i and GLP-1RA, Ivabradine, Midodrine Vitamins, Coenzymes, Antioxidants with supportive upcoming researches on integrated yoga & breathing exercise. Upcoming research needs to access the role of sympathetic control of cardio-renal function and renal afferent nerve and the succeeding report to SGLT2is on blood pressure and HRV.[35]

6. Conclusion &Take-Home Message:

- This REVIEW is trying to focus on attributed variations about different definitions of CAN, diagnostic tests, and variations of population characteristics, age, duration& types of diabetes, with other cardiovascular risk factors existence.
- Clinical research needs to continue to increase sensitivity and specificity about screening scores by different target diagnostic testing for cardiac autonomic neuropathy in the early stage.[5,15,35]
- Few common & simple bedside tests are available to diagnose CAN using HRV, HR & BP responses to breathing, the Valsalva maneuver, and standing. There is respiratory modulation of different-frequency oscillations in HRV to access the functional abnormalities and imbalance between the SNS and PNS.[15,21,35]
- ECG suggests QT interval with support of Holter monitoring for CAN-associated cardiac arrhythmia. Echocardiograms & MRIs have more advancement to access cardiac functions in the early stages of CAN.[55]
- Also, clinical evidence of inflammation (CRP level) with activation of inflammatory cytokines like IL-1, and IL-6 in patients with diabetes are helpful to diagnosis of CAN. Inflammatory changes correlate with abnormal sympathetic-vagal balance neuroregulatory character for the ANS in CAN.[35,55]
- Cardiac Autonomic Neuropathy has been shown as a strong predictor of risk to the cardiovascular system and sudden cardiac death in type 2 diabetes patients as attributed to functional abnormality between heart & ANS or organic structural damage to the different components of ANS.[15,21,35]
- CAN is responsible for patients with severe orthostasis, postural hypotension, exercise intolerance, enhanced intra/perioperative instability, and an increased incidence of silent MI and ischemia.[35,55]
- Reversal of imbalance of ANS or restoration of autonomic neuropathy is possible on clinical evidence-based studies with **therapeutic lifestyle modification, decreased stress, increased physical activity, control diabetes treatment, ACE inhibitors /ARB, β-adrenergic blockers and potent anti-oxidants, such as α-lipoic acid**.[35]
- Increasing awareness about the understanding of the pathophysiology of CAN reproduce the therapeutic targets with the combination of lifestyle intervention and advanced pharmacological support including newer therapies such as SGLT2i and GLP-1RA, **ARNI,** Ivabradine, Midodrine Vitamins, Coenzymes, Antioxidants with supportive upcoming researches on integrated yoga & breathing exercise.[28,55]

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8. Conflict of Interest:

None

9. References:

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