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Dysautonomia in Diabetic Patients: A Study of 20 Cases

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Abstract | **Case Series**

Introduction: Diabetes mellitus currently represents a major public health issue due to its numerous degenerative and functional complications. Among these, dysautonomia, long underdiagnosed, constitutes a frequent and potentially severe condition that may compromise patient prognosis. ***Patients and Methods:*** This prospective study involved 20 diabetic patients who underwent systematic autonomic nervous system evaluation. Assessments were conducted in a specialized cardiology unit using validated tests for heart rate variability, orthostatic response, and baroreflex sensitivity. ***Results:*** Results highlighted a predominantly parasympathetic impairment with:

- Vagal deficit observed in 90% of patients,
- Peripheral alpha-adrenergic failure and sympathetic hyperactivity in 50%,
- Orthostatic hypotension in 30%,
- Orthostatic hypertension in 10%,
- Postural Orthostatic Tachycardia Syndrome (POTS) in 2% of cases.

Discussion: This study reveals the vulnerability of diabetic patients to cardiac autonomic neuropathy (CAN), mainly characterized by vagal deficit. Sympathetic hyperactivity, often associated with hypertension, increases cardiovascular risk. POTS mainly affects young type 1 diabetic patients with low BMI. These results advocate for early and systematic screening of dysautonomia to improve management and quality of life of patients.

Keywords: Diabetes Mellitus, Dysautonomia, Cardiac Autonomic Neuropathy (CAN), Vagal Deficit, Orthostatic Hypotension.

INTRODUCTION

The autonomic nervous system (ANS), also called the vegetative nervous system, is an essential component of the nervous system responsible for innervating most visceral organs. It regulates their functioning involuntarily, outside conscious control [1]. Its main mission is to maintain homeostasis and provide rapid and efficient adaptation to internal and external perturbations. The ANS thus plays a fundamental role in overall physiological balance and also contributes to the regulation of motor functions and social interactions [1]. Among the major etiologies of dysautonomias, diabetes holds a predominant place. Beyond the well-established microvascular and macrovascular complications, it is also responsible for autonomic nervous system dysfunction that may compromise patient prognosis [2]. It is therefore imperative to perform an autonomic function assessment in every diabetic patient, at diagnosis for type 2 diabetes, and after five years of evolution for type 1 diabetes [3]. Early recognition of dysautonomia signs allows prompt and appropriate management, essential for improving prognosis and quality of life.

PATIENTS AND METHODS

In a retrospective study, we analyzed a series of 20 type 2 diabetic patients followed in endocrinology consultation and referred to the cardiology department of the Military Hospital of Rabat, within the unit specialized in autonomic nervous system exploration. All patients presented clinical manifestations suggestive of dysautonomia, justifying a thorough autonomic assessment.

MATERIALS AND METHODS

- A Dynamap (CRITIKON, 1846 XP) for blood pressure monitoring
- A display screen (LCD CS 503 E, HELLIGE, EK 512 E) for heart rate (HR) and blood pressure monitoring
- An electrocardiogram (ECG) recording device

- A handgrip dynamometer for manual effort
- A tilt table or Tilt test

Procedure of Autonomic Nervous System Tests

Since the first observations by Cyon and Ludwig on the influence of sympathetic fibers on the cardiovascular system, numerous techniques have been developed over the decades to evaluate autonomic nervous system function. Among classically used tests, some induce variations in blood pressure (BP), such as orthostatic and isometric contraction tests, while others modify heart rate, such as the deep breathing test. These tests, initially standardized by Ewing, provide a global assessment of autonomic function by investigating both the sympathetic and parasympathetic branches of the ANS. Each cardiovascular autonomic test measures the physiological response relative to a basal state, with results generally expressed as percentage variation.

The explorations were carried out according to a standardized protocol, in the following order:

- Deep Breathing Test (DB),
- Isometric forearm contraction test (Hand Grip, HG),
- Hyperventilation test,
- Mental stress test (or stress echocardiography),
- Orthostatic test.

These tests evaluate autonomic system reactivity to different stimuli and contribute to the diagnosis of cardiac autonomic neuropathy.

1. Deep Breathing Test (DBT)

This test is a key tool for evaluating parasympathetic activity, especially vagal response. It relies on measuring RR interval variability (interval between two consecutive QRS complexes on the ECG) during deep and regular respiratory cycles.

METHODOLOGY

The patient is invited to perform slow and deep breathing at a rate of 6 cycles per minute (5 seconds inspiration, 5 seconds expiration) for one minute. RR interval variations are then analyzed. Interpretation of results:

- Normal vagal response: = 30%
- Vagal hyperactivity (HAV): > 30%
- Vagal deficiency: < 30%

2. Isometric Contraction or Hand Grip Test

- This is a manual contraction effort performed to determine modifications of blood pressure and heart rate during static effort.
- Increased sympathetic activity at the muscular level is effort- and time-dependent.
- It helps specify vagal response (heart rate variations) and peripheral alpha-sympathetic response (blood pressure ariations). It allows evaluation and measurement of blood pressure changes.

✓ Vagal or peripheral alpha-sympathetic hyperactivity (> 10%).

✓ Vagal or peripheral alpha-sympathetic deficiency (< 10%).

3. Mental Stress or Stress Echo

Mental stress (various methods, e.g., subtracting 7 successively starting from 200 down to 4).

Central sympathetic activity increase causes elevation of heart rate and blood pressure.

Beta sympathetic response (%) = (max HR - min HR) / min HR × 100. Allows specifying central alpha and beta sympathetic responses.

✓ Normal response = 10%

✓ Central alpha and beta sympathetic hyperactivity (> 10%)

✓ Central alpha and beta sympathetic deficiency (< 10%)

4. Hyperventilation

Shallow breathing for 15 seconds, where an increase in heart rate and a decrease in blood pressure (normal: 10 mm Hg) are noted.

5. Orthostatic Test

During standing, blood pressure and heart rate evolve in two phases:

- Immediate or primo-orthostatic phase (up to the 15th second): blood pressure decreases, heart rate increases.
- Second phase (beyond the 20th second): blood pressure correction by vasoconstriction, heart rate decreases.

Allows specifying vagal response and beta/alpha peripheral adrenergic sympathetic responses.

Study Results

Personal data (age, sex, medical history) and clinical data (diabetes type, duration, treatments, dysautonomia symptoms) were collected using a specifically designed data sheet.

Table 1: Characteristics of diabetic patients

Patient Characteristics	N = 20
Age (years)	46 ± 14
Sex ratio	1
Duration of diabetes	5–20 years
Diabetes control	55% uncontrolled
Presence of vascular complications	60%

Symptoms that motivated autonomic nervous system exploration were predominantly:

- Excessive fatigue (70%)
- Sensation of dizziness, presyncope, visual disturbances (45%)
- Pallor, intense thirst (37%)
- Morning malaise (40%)
- Sensation of well-being in cold climate (45%)
- Daytime or nighttime sweating (30%)
- Nausea, vomiting (23%)
- Episodes of tachycardia and/or bradycardia (27%)

Results of Autonomic Nervous System Exploration

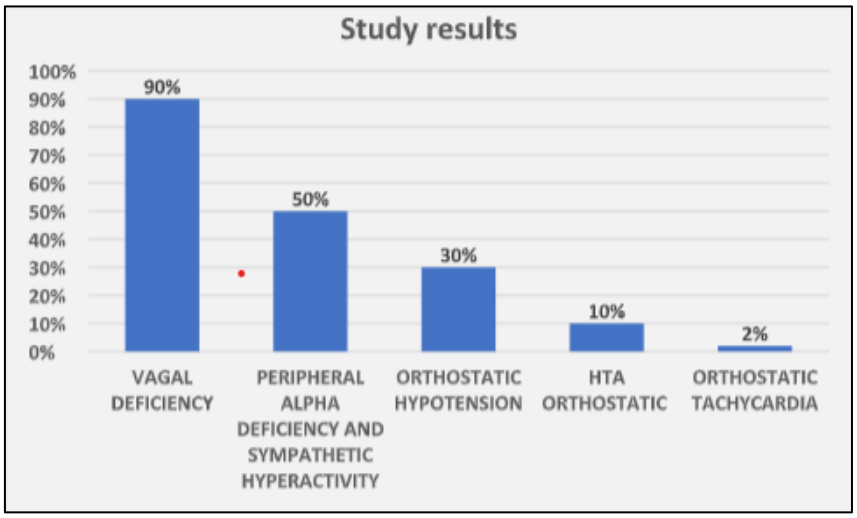

Figure 1: Autonomic response of diabetic subjects to Ewing tests

DISCUSSION

In this study, vagal nerve impairment, expressed as vagal deficiency, was found in nearly all patients assessed. This predominance of parasympathetic tone alteration is a central finding, highlighting the importance of systematically screening for autonomic nervous system involvement in diabetic patients [4]. These results should prompt proactive screening for cardiac autonomic neuropathy (CAN), one of the main forms of diabetes-related dysautonomia. Its prevalence varies greatly among studies, ranging from 9% to 91% in type 1 diabetes patients, and from 25% to 75% in type 2 diabetes patients [5,6]. CAN is one of the principal manifestations of dysautonomia in diabetic patients. It results from progressive damage to autonomic nerve fibers, particularly parasympathetic then sympathetic, responsible for cardiovascular regulation. Clinically, it typically presents with two major manifestations: orthostatic hypotension (OH) and resting sinus tachycardia [7]. OH is defined, according to international consensus criteria, as a drop in systolic blood pressure (SBP) ≥ 20 mmHg and/or diastolic blood pressure (DBP) ≥ 10 mmHg within the first three minutes after standing [8]. This results from impaired reflex vasoconstriction normally induced by orthostasis due to sympathetic nervous system dysfunction. The prevalence of OH among diabetic patients varies widely in the literature, ranging from 6% to 32%, depending on diagnostic criteria, diabetes type, disease duration, and screening methods [9]. This variability reflects heterogeneity among studied populations and underlines the importance of systematic screening, especially in patients with long-standing diabetes or cardiovascular comorbidities.

Resting sinus tachycardia is another early CAN sign, indicating initial parasympathetic system involvement, which is generally the first component affected in diabetic dysautonomia. It manifests as an abnormally high resting heart rate, often > 80 bpm, in the absence of secondary causes like fever, anemia, hyperthyroidism, or dehydration [10]. Loss of heart rate variability (HRV), measured by standardized autonomic tests (e.g., deep breathing or Valsalva maneuvers), is also recognized as a highly sensitive marker of early parasympathetic impairment. A study by Prashanth *et al*. demonstrated a statistically significant increase in resting

heart rate in diabetic subjects compared to a healthy control group, suggesting early vagal withdrawal related to parasympathetic tone alteration [11]. This supports the hypothesis of a progressive imbalance between parasympathetic and orthosympathetic systems in CAN. Identification of these early signs allows earlier diagnosis of CAN and targeted therapy to slow progression and prevent associated cardiovascular complications such as arrhythmias, reduced exercise tolerance, and sudden cardiac death. Symptoms of orthostatic intolerance are markers of poor prognosis in CAN patients and are linked to increased cardiovascular morbidity and mortality risk [8]. OH results mainly from two complementary pathophysiological mechanisms:

- Impaired baroreceptor sensitivity, leading to inadequate autonomic response to blood pressure changes during postural shifts;
- Damage to sympathetic efferent fibers, causing reduced catecholamine (mainly norepinephrine) release and decreased or absent peripheral reflex vasoconstriction upon standing.

Furthermore, the coexistence of diabetes and arterial hypertension (HTN) exerts a deleterious synergistic effect on cardiovascular autonomic function. This comorbidity, frequent in diabetic populations, accelerates autonomic nerve fiber damage and worsens baroreflex dysfunction. It is strongly involved in OH genesis among these patients [12]. Multiple studies confirmed that diabetes and HTN coexistence is associated with increased CAN prevalence, greater reduction of HRV, and earlier impairment of cardiovascular orthostatic responses. This pathological interaction promotes silent but significant dysautonomia progression, increasing risk of severe cardiovascular complications [13].

These data emphasize the importance of early and systematic CAN screening in patients with both diabetes and HTN, even without symptoms, to initiate appropriate preventive measures [14].

Our study also revealed sympathetic hyperactivity in one out of two diabetic patients. This sympathetic nervous system overactivation is clinically significant, often manifesting as sustained hypertension defined as persistent BP elevation ≥140/90 mmHg in consultations, confirmed by repeated measurements. In other subtler cases, clinical expression appears as masked hypertension, characterized by normal clinic BP (<140/90 mmHg) but elevated values outside medical settings, particularly during ambulatory BP monitoring or home self-measurement. Masked hypertension, often underdiagnosed, is common in diabetic patients and represents a silent but harmful form of neurovegetative dysregulation involving sympathetic-parasympathetic imbalance. Many studies demonstrated a close pathophysiological relationship between hyperinsulinism, often observed in early type 2 diabetes stages, and sympathetic nervous system hyperactivation, contributing to cardiovascular complications such as hypertension and CAN [15,16]. These data underscore the importance of systematic and multimodal hypertension screening in diabetic patients, considering non-apparent forms to detect early underlying cardiovascular dysautonomia and prevent associated complications.

POTS has also been observed in diabetic patients. In our series, 2% had this particular dysautonomia type, especially among type 1 diabetics, often associated with low BMI and high fasting glucose, consistent with literature data [17,18].

Several studies highlighted that these metabolic factors may contribute to POTS emergence in diabetic patients via autonomic imbalance characterized by parasympathetic hypoactivity and compensatory sympathetic hyperactivity [19].

Therapeutic Considerations

Therapeutic strategies have been proposed to improve quality of life, considering the type and severity of dysautonomia. Management of OH primarily relies on hygienic-dietary measures including adequate hydration, avoiding abrupt posture changes, and wearing peripheral venous compression (elastic stockings). Increasing salt intake can be considered in some cases but carries a risk of worsening supine hypertension, particularly in elderly or diabetic subjects [20]. Avoidance of diuretics and long-acting antihypertensives, which may exacerbate postural hypotension, is recommended. Pharmacologically, midodrine is a first-choice option. It is a selective alpha-adrenergic peripheral receptor agonist that increases peripheral arterial resistance and venous return, thereby improving standing blood pressure. It is typically prescribed at doses of 2.5 to 10 mg in three daily doses [21]. In diabetic patients with both supine hypertension and daytime OH, short-acting antihypertensive treatment at bedtime can be administered to control nocturnal blood pressure without compromising daytime hemodynamic stability [22]. Phenobarbital, a barbiturate class drug, has been proposed at low doses as a regulator of sympathetic hyperactivation. Its central action might reduce excitability of supraspinal autonomic centers, including bulbar centers responsible for sympathetic response, acting as a buffer against sympathetic discharge [23]. Though its therapeutic use in this context remains marginal and poorly documented, this approach could represent an interesting pharmacological avenue in patients with severe dysautonomia and marked hyperadrenergic state, if no contraindications exist.

Treatment of POTS in diabetic patients involves a comprehensive approach combining non-pharmacological measures and appropriate medication. Increasing fluid and salt intake, wearing compression stockings, and encouraging regular physical activity

adapted to deconditioning are first steps. Glycemic control is crucial to limit progression of autonomic neuropathy. Pharmacological agents such as fludrocortisone, midodrine, low-dose beta-blockers, or ivabradine may be used according to patient profile. Management should be individualized, considering comorbidities, especially renal and cardiovascular [24,25].

Cardiac autonomic neuropathy (CAN) is associated with increased cardiovascular morbidity. Its treatment mainly relies on prevention, strict metabolic control, and symptomatic management. Optimizing glycemic balance, especially in type 1 diabetes, significantly reduces the risk of CAN development or progression. Symptomatic patients receive non-pharmacological care (rehydration, compression stockings, exercise training) and targeted treatments depending on clinical presentation: beta-blockers for resting tachycardia, midodrine or fludrocortisone for orthostatic hypotension, and cholinesterase inhibitors in some cases. Cardiovascular monitoring is essential due to sudden death risk. A multidisciplinary, individualized approach is recommended to improve quality of life and limit complications [26,27].

CONCLUSION

Autonomic nervous system exploration in diabetic patients should become routine, alongside degenerative assessments, accessible to all diabetics. Early detection of dysautonomia, even at subclinical stages, is essential to promptly identify abnormalities that could compromise patient prognosis. Moreover, several therapeutic options currently exist to modulate autonomic responses, offering diabetic patients' better quality of life.

Declarations

Ethics approval and consent to participate

The study did not require approval from an ethics committee. Verbal consent was obtained from all patients involved.

Consent for publication

Verbal consent for publication was obtained from all patients.

Competing interests: The authors declare that they have no competing interests.

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