Abstract

Rationale - Diabetes is by far, the leading cause of vegetative neuropathy in the world. Dysautonomia is one of the major complications of diabetes, it is responsible for very diverse manifestations that can, in advanced forms, be responsible for major dysautonomia affecting several organs. Nevertheless, it has been suggested recently, that a sympathetic hyperactivity would be predictive of the onset of type 2 diabetes. Our goal was to examine the relationship between type 2 diabetes and dysautonomia.

Patients and methods - This is a prospective descriptive study that took place over 5 years from June 2013 to June 2018, involving 300 non-hypertensive diabetic patients recruited at the endocrinology department of diabetology Mohammed V military hospital in Rabat.

Results – The association between sympathetic hyperactivity and type 2 diabetes in non-hypertensives diabetics was confirmed in our study (p ≤ 0.05). Male subjects were found to develop more sympathetic hyperactivity than female subjects (p ≤ 0.05). Also, there was a significant correlation between vagal impairment and the age of diabetes (p ≤ 0.05).

Conclusion – The responsibility for sympathetic dysfunction in the genesis or aggravation of metabolic disorders is currently confirmed.

Keywords: Dysautonomies, Diabetes type 2.

Introduction

The autonomic nervous system (ANS) controls unconscious activities, ensures the normal progress of the vegetative functions of the body (breathing, heart rate, blood pressure, digestion, secretions, body temperature, water balance ...), and responds instantly to all the physical and emotional solicitations. It is a system of adaptation of the body to its environment. It consists of two parts functionally and, for the most part, morphologically distinct: the sympathetic system and the parasympathetic system.

Its dysregulation, called dysautonomia, is a frequent affection, often unknown, very unpleasant for the patient and which is accompanied by polymorphic functional manifestations.

Exploration of SNA has been renewed in recent years because of the major role of its alterations in the genesis and aggravation of several diseases. The major abnormalities encountered may be an exaggeration or a deficiency of central or peripheral sympathetic and / or parasympathetic systems.

If the involvement of sympathetic hyperactivity in the genesis of several pathologies such as abdominal obesity or arterial hypertension is currently proven by several publications. To date, there is little research on the role of sympathetic hyperactivity in the physiopathology of type 2 diabetes.

Objectives of our Study

Main Objective

- Demonstrate dysautonomia in Moroccan patients with type 2 diabetes who are not hypertensive.

Secondary Objectives

- Evaluate the impact of age of type 2 diabetes on this autonomic dysfunction.

Materials And Methods

This is a prospective descriptive study that took place over 5 years from June 2013 to June 2018, involving 300 subjects recruited at the endocrinology department of diabetology Mohammed V military hospital in Rabat.

Patients

a. Inclusion criteria: We included in our study 300 Moroccan diabetics, 150 men and 150 women; under different therapeutics namely mono, tritherapy or under insulin (bedtime schema, basalotherapy or insulin premixes).

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b. Exclusion criteria: Will be excluded from the study:
- Hypertensive patients.
- Patients treated with molecules acting on the autonomic nervous system.

**Explorations**

Exploration of the ANS was carried out at the Exploration Unit of the Autonomic Nervous System, Cardiology Department "A" of Ibn Sina University Hospital in Rabat, in collaboration with the Autonomous Nervous System Research Team.

- The fasting subject is quietly settled with at least 15 minutes rest before the start of each test.
- The proofs used in their order of progress are as follows:
  - Deep Breathing test.
  - Hand grip test.
  - Mental stress.
  - Test of passive orthostatism on tilting table or tilt-test.

**Results**

**Characteristics of the groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Average ± D.S</th>
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<tbody>
<tr>
<td>Age (Years)</td>
<td>48.5 ± 15.1</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>88.6 ± 17.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>1.72 ± 0.19</td>
</tr>
<tr>
<td>IMC (Kg/m2)</td>
<td>31.15 ± 3.20</td>
</tr>
<tr>
<td>Fasting glucose (g/l)</td>
<td>1.88 ± 0.71</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.9 ± 1.54</td>
</tr>
<tr>
<td>Seniority of diabetes (Years)</td>
<td>12.5 ± 8.12</td>
</tr>
</tbody>
</table>

**Descriptive results of ANS exploration Tests**

**Evaluation of vagal activity** In Deep Breathing, 60% of patients had vagal deficiency with a result almost similar to the orthostatic test during the first few seconds evaluating vagal activity with vagal deficiency predominating at 55%. Second finding, if type 2 diabetes is older, vagal impairment is more important.

**Evaluation of the sympathetic activity** For the "Hand Grip", there is sympathetic hyperactivity in 70% of patients. Similarly, for the "mental stress" test, 65% of patients have sympathetic hyperactivity.

It is also noted that 20% of patients had orthostatic hypertension versus 50% who had orthostatic hypotension while 30% kept blood pressure within normal limits. And finally, we note that 60% of patients have orthostatic tachycardia versus 30% kept a heart rate within the limit of normal.

**Correlated Results**

- The association between sympathetic hyperactivity and type 2 diabetes in non-hypertensive diabetics was confirmed in our study (p ≤ 0.05).
- Male subjects were found to develop more sympathetic hyperactivity than female subjects (p ≤ 0.05).
- Also, there was a significant correlation between vagal impairment and the age of diabetes (p ≤ 0.05).

**Discussion**

Considered difficult, the assessment of ANS activity was greatly facilitated by the development of systems for non-invasive clinical exploration based primarily on continuous recording of blood pressure and heart rate.6,7

Our study attempted to identify the responsibility of dysautonomies in the genesis or aggravation of type 2 diabetes.

Indeed, skeletal muscles play a major role in insulin resistance, the base of the physiopathology of type 2 diabetes. Sympathetic hyperactivity is responsible for the installation of insulin resistance via8–11:

- Activation of adrenergic receptors, particularly β-adrenergic receptors, can transform the phenotype of muscle cells into insulin-resistant cells.
- Adrenaline can also reduce insulin-induced glucose uptake.
- The above mentioned anomalies are associated with a rarefaction of the capillaries which reduces the nutrient supply of the muscles.

In a longitudinal study, Flaa A. et al. studied the relationship between sympathetic activity and future insulin resistance in Caucasian healthy subjects with 18 years of follow-up. They found that sympathetic activity was a predictor of insulin resistance measured by Homeostasis Model Assessment (HOMA-IR). In our study, 70% of patients had sympathetic hyperactivity12–14.

These results provide new insights into the physiopathological mechanisms of insulin resistance, suggesting that sympathetic hyperactivity may be a predisposing factor for future insulin resistance.

As a result, sympathetic hyperactivity is incriminated in various symptoms or pathologies including type 2 diabetes12–17. (Figure 1).

**Figure 1.** Schematic Representation of The Association Between Sympathetic Hyperactivity And The Different Metabolic And Cardiovascular Pathologies16,19
Alvarez et al.\textsuperscript{20,21} observed greater sympathetic hyperactivity in men with abdominal obesity compared to men with peripheral obesity. In our study we found a sympathetic hyperactivity more common in men than in women.

The origin of this sympathetic activation is unknown. It may be related to increased insulin plasma concentrations\textsuperscript{22–24}, leptin\textsuperscript{25}, and especially stimulation of sympathetic activity at the central level.

Another explanation is possible; Obstructive sleep apnea is commonly associated with obesity. The nocturnal apnea episodes are characterized by a very strong sympathetic stimulation\textsuperscript{26,27}.

Conclusion
The responsibility for sympathetic dysfunction in the genesis or aggravation of metabolic disorders is currently confirmed.

The consequences could vary according to the genotypic and phenotypic characteristics of individuals and their environment, which our Moroccan study confirms.

These data can also lead to the proposal of new therapeutic approaches in type 2 diabetes to reduce degenerative complications and perhaps even better act in the prediabetes phase.

References
24. Diet LL. obesity and hypertension: an hypothesis involving insulin, the sympathetic nervous system, and adaptive thermogenesis; 1986.