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Hypothalamic-pituitary-adrenal activity in type 2 diabetes mellitus: role of autonomic imbalance

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Abstract

Symptomatic diabetic neuropathy has been found to be associated with hypothalamus-pituitary-adrenal (HPA) axis hyperfunction, but no data are available about HPA activity in diabetic patients with asymptomatic autonomic imbalance. To evaluate HPA axis activity in patients with type 2 diabetes mellitus (T2DM) in relation to the presence or the absence of subclinical parasympathetic or sympathetic neuronal dysfunction, we performed an observational study on 59 consecutive type 2 diabetic patients without chronic complications and/or symptoms of neuropathy or hypercortisolism. The following were measured: serum cortisol at 08:00 AM and at midnight (F8 and F24, respectively), post-dexamethasone suppression cortisol, 24-hour urinary free cortisol (UFC), and morning corticotropin (ACTH). Deep-breathing (DB) and LS (LS) autonomic tests were performed to assess the parasympathetic function; postural hypotension test was performed to evaluate sympathetic activity. Patients were subdivided into 4 groups: subjects with parasympathetic failure (group A), sympathetic failure (group B), both para- and sympathetic failure (group C), and without autonomic failure (group D). Hypothalamus-pituitary-adrenal activity was increased in group A compared with group D (UFC, 48.6 ± 21.4 vs 21.6 ± 9.8 μg/24 h, $P < .0001$; ACTH, 27.0 ± 8.6 vs 15.7 ± 5.7 pg/dL, $P < .01$; F8, 20.4 ± 4.5 vs 13.6 ± 3.8 μg/dL, $P < .05$; post-dexamethasone suppression cortisol, 1.2 ± 0.4 vs 0.8 ± 0.6 μg/dL, $P < .05$, respectively) and group B (UFC, 26.3 ± 11.0 μg/24 h, $P < .0001$; ACTH, 19.9 ± 8.0 pg/dL, $P < .05$). Regression analysis showed that UFC levels were significantly associated with the deep-breathing test ($\beta = -0.40$, $P = .004$) and tended to be associated with the lying-to-standing test ($\beta = -0.26$, $P = .065$), whereas body mass index, glycated hemoglobin, and duration of disease were not. Type 2 diabetic patients with asymptomatic parasympathetic derangement have increased activity of HPA axis, related to the degree of the neuronal dysfunction.

1. Introduction

Glucocorticoid secretion in diabetes has been suggested to be one of the possible missing link between insulin resistance and the manifestations of the metabolic syndrome (hypertension, obesity, coronary heart disease, hyperlipidemia, and type 2 diabetes mellitus [T2DM]) [1-4].

In the past years, several studies investigated the hypothalamic-pituitary-adrenal (HPA) axis secretion in patients with T2DM [5-11]. In particular, patients with T2DM were found to have elevated basal corticotropin (ACTH) levels [7,9], and high levels of cortisol secretion [6-8] at basal and after dexamethasone suppression [10,11]; other studies did not show any alteration of HPA secretion [12,13]. Recent data suggest that subtle autonomous ACTH independent adrenal hypersecretion of cortisol is more prevalent in patients with T2DM than previously expected [14,15]. Thus, the HPA axis involvement in T2DM has still to be fully evaluated.

Symptomatic (somatic or autonomic) diabetic neuropathy has been found to be associated with increased activity of HPA axis [16]. Consequently, diabetic neuropathy should be taken into account when investigating this topic. As far as we know, no data are available about the HPA activity in type 2 diabetic patients with asymptomatic diabetic autonomic derangement (or asymptomatic autonomic

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imbalance), particularly if associated to a prevalent parasympathetic or sympathetic neuronal activity.

In this study, we evaluate HPA axis in 59 diabetic patients without both clinically evident neuropathy and hypercortisolism, but with asymptomatic autonomic imbalance as investigated by deep-breathing (DB), lying-to-standing (LS), and postural hypotension (PH) tests.

2. Subjects and methods

2.1. Subjects

Subjects were recruited from January 2003 to January 2004 at the San Giuseppe-Fatebenefratelli Hospital in Milan, Italy. Three hundred twenty-two consecutive inpatients with T2DM referred to our unit for poor metabolic control were enrolled. The study was carried out on 59 subjects with T2DM who fulfilled the following selection criteria: age at diagnosis of older than 30 years, body mass index (BMI) of ≥ 19 and ≤ 40 kg/m^2, no need for insulin therapy in the first 2 years of disease, no history of ketoacidosis, no hypoglycemia in the last 6 months, absence of signs or symptoms of clinically evident diabetic neuropathy (ie, present or past foot ulceration; postural hypotension; dysesthesias; gastrointestinal, genitourinary, metabolic, pupillary, and sudomotor symptoms) [17], somatic neuropathy by measuring the diabetic neuropathy score [18], macrovascular disease (by ultrasonographic measuring carotidal and arterial leg flow), background or proliferative retinopathy, and overt nephropathy (by measuring microalbumin excretion). Moreover, patients with signs or symptoms of hypercortisolism (including moon facies, striae rubrae, hypertrichosis, skin atrophy, buffalo hump), hyperandrogenism, chronic renal failure, acute illnesses, alteration of sleep-wake cycle, depression, alcoholism, disease potentially affecting the autonomic nervous system, present glucocorticoid therapy (oral, inhalation, and intranasal), or intake of drugs known to interfere with the HPA axis or with the autonomic nervous system (ie, β-blockers, α-blockers, cholinergic agonists, and antagonists) were excluded from the study.

In all subjects, serum morning cortisol levels (F8; normal values, 5-25 μg/dL, 138-690 nmol/L) at 8 AM and after 1-mg overnight dexamethasone suppression test (cutoff value fixed at <1.8 μg/dL, <50 nmol/L, according to previous studies) [19]; 24-hour urinary free cortisol (UFC; normal values, 10-60 μg/24 h, 27.6-165.6 nmol/24 h), plasma ACTH at 8 AM (normal values, 10-50 pg/dL, 2.2-11 pmol/L), and plasma cortisol at midnight (F24; normal values, <7.5 μg/dL, 207 nmol/L) were measured. In all patients, DB, LS, and PH tests were performed to evaluate the possible derangement of autonomic nervous system [20-25].

Recent data suggest a high prevalence of subtle asymptomatic cortisol hypersecretion (subclinical hypercortisolism [SH]) in patients with T2DM [14,15,26]. Because SH could affect autonomic neuronal function, type 2 diabetic patients with SH were excluded from the study.

In all subjects, blood pressure was measured everyday at 08:00 AM for at least 5 consecutive days and expressed as mean of the determinations.

Subjects with systolic blood pressure (SBP) of ≥ 130 mm Hg and/or diastolic blood pressure (DBP) ≥ 85 mm Hg and/or on antihypertensive treatment were defined as hypertensive [27]. Dyslipidemia was defined as triglycerides of 150 mg/dL or higher (1.7 nmol/L), or high-density lipoprotein cholesterol of less than 40 mg/dL (1.03 mmol/L) in males and less than 50 (1.3 mmol/L) in females [27,28]. Subjects were also considered dyslipidemic if an anti-dyslipidemic treatment was given. In all subjects, data on the use of oral hypoglycemic agents (ie, sulfonylurea) and/or insulin treatment, and measurements of glycated hemoglobin (HbA_{1c}) and waist circumference were also collected.

Based on the results of DB, LS, and PH tests, patients were subdivided into 4 groups: patients with autonomic derangement leading to a prevalent parasympathetic failure (group A), sympathetic failure (group B), both para- and sympathetic failure (group C), and without autonomic imbalance (group D). Diagnosis of autonomic imbalance with prevalent parasympathetic failure was made based on altered DB or LS test, and diagnosis of autonomic imbalance with prevalent sympathetic impairment based on altered PH test [18].

All subjects gave their informed consent, and local ethical committees approved the study in accordance with Helsinki Declaration II.

2.2. Methods

In the day of the admission, all individuals had a catheter inserted in the forearm vein to avoid stress-related hypopituitary-adrenal-axis activation caused by venipuncture; all biochemical determinations were made not earlier than the second day after admission. Serum cortisol and UFC (after dichloromethane extraction) levels were determined immunometrically by chemiluminescence (Immulite, Diagnostic Products, Los Angeles, CA, and TDX-FLX Abbott Diagnostika kits, Wiesbaden-Delkenheim, Germany, respectively); plasma ACTH levels (mean of 3 determinations at 20-minute intervals) were measured immunometrically by chemiluminescence (Immulite, Diagnostic Products).

All neuro-autonomic tests were performed at 08:00 AM. Ewing's tests (DB and LS), using a Cardionomic device (Psion Organiser II, LZ64, PSICOM, Milan, Italy), were performed by a computerized system that records real-time R-R intervals and heart rate values [18-22]. In all patients, the DB and LS tests were performed after regular heart rhythm was ascertained. The DB test is performed with the patient lying in the supine position and breathing at the rate of 6 breaths per minute. The Cardionomic device calculates the ratio between the means of 3 maximum and minimum instantaneous heart rate variations during inspiration and expiration over a period of 1 minute. Three DB tests are performed for each patient, calculating the mean between

ratios, which is compared with the age-related normal values [20] and expressed as the difference (ΔDB) from age-related cutoff values.

The LS test is performed with the patient lying in the supine position quietly for at least 3 minutes: the subject is then asked to get up unaided. The ratio between the longest R-R interval (around the 30th beat) and the shortest R-R interval (around the 15th beat) is recorded; at least 2 LS tests are performed for each patient, calculating the mean between the 30th-to-15th ratios, which is compared with normal values [21] and expressed as the difference (ΔLS) from age-related cutoff values. The results of DB and LS tests are considered to reflect mainly the parasympathetic activity. Deep breathing and LS maneuvers, indeed, modulate firing rate of lung and vascular stretch receptors, respectively, consequently leading to variations of inputs to parasympathetic cardio-inhibiting central neurons in medulla oblongata; efferent vagal fibers reverberate those inputs toward the heart, thus controlling cardiac vagal tone [19,21,29].

Sympathetic function was evaluated by the PH test. The test is performed with the patient lying in the supine position until 2 consecutive blood pressure measurements are identical. The subject is then asked to get up unaided, and then blood pressure is measured 5 times (30, 60, 90, 120, and 180 minutes). The mean between the 2 biggest systolic decreases from the value in supine position (Δsystolic blood pressure) is then calculated. Two PH tests are performed for each patient, calculating the mean between Δsystolic blood pressure values (ΔPH, normal values, 10 mm Hg) [18-20]. The results of this test are considered to reflect mainly the sympathetic neuronal activity because the effect of postural variation maneuver on blood pressure is mediated only by sympathetic afferent and efferent fibers [30].

2.3. Statistical analysis

For each variable, normality of distribution was tested by the Shapiro-Wilk W statistic. The results are expressed as mean (±SD) or median (range) for not normally distributed variables. Data were compared by 1-way analysis of variance, and post hoc analysis was performed by either Bonferroni or Student-Neuman-Keuls test, as appropriate. The associations between variables were tested by either Pearson or Spearman correlation, as appropriate.

Multivariate regression analysis was used to evaluate the influence of HPA axis parameters and BMI, HbA_{1c}, and duration of disease (independent variables) on ΔDB or ΔLS as indexes of parasympathetic neuronal derangement (dependent variables).

Statistical analysis was done by using SPSS version 12.0 statistical package software (SPSS, Chicago, IL). Probability values of less than .05 were considered as significant.

3. Results

Nine patients (3 from group A, 3 from group B, 1 from group C, and 2 from group D) were excluded from the study because of the finding of at least 2 altered biochemical parameters of HPA function. These patients, indeed, were found to bear an adrenal mass and therefore they might be affected by SH of adrenal origin [26], whose prevalence is thought to be high in the diabetic population [14,15]. However, the following results were not modified even after adding data from these subjects (data not shown). Therefore, the final analysis was carried out on the remaining 50 patients. Clinical and biochemical HPA axis data of the whole group of patients are reported in Table 1.

Clinical characteristics of the subjects included in the 4 different groups (groups A-D) based on their different autonomic neuronal involvement are reported in Table 2. The 4 groups were comparable with regard to age, sex, BMI, prevalence of insulin or sulfonylurea treatment, hypertensive and dyslipidemic conditions, HbA_{1c} percentage, and waist circumference.

Patients with parasympathetic impairment (groups A and C) showed higher SBP and DBP levels as compared to patients with prevalent sympathetic failure and without autonomic derangement (Table 2).

Table 1
Clinical characteristics and parameter HPA axis activity

	All patients (n = 50)	Female patients (n = 22)	Male patients (n = 28)
Age (y)	58.2 ± 9.3 (37.0-79.0)	56.7 ± 7.7 (37.0-69.0)	59.4 ± 10.4 (39.0-79.0)
BMI (kg/m^2)	30.3 ± 4.9 (22.1-40.0)	32.3 ± 5.0 (23.7-40.0)	28.8 ± 4.3 (22.1-39.0)
WC (cm)	102.5 ± 11.7 (85.0-135.0)	105.4 ± 11.8 (85.0-129.0)	100.2 ± 11.3 (85.0-135.0)
T2DM duration (y)	9.8 ± 8.5 (0-32)	8.1 ± 6.3 (0-26)	11.1 ± 9.8 (0-32)
HbA_{1c} (%)	10.3 ± 2.2 (5.4-14.8)	10.4 ± 2.5 (5.4-14.8)	10.2 ± 1.9 (5.9-13.8)
Insulin-treated patients (%)	14 (28.0)	5 (22.7)	9 (32.1)
Dyslipidemia (n)	26 (52.0)	11 (50.0)	15 (53.6)
Hypertension (n)	33 (66.0)	15 (68.2)	18 (64.3)
UFC (μg/dL)	30.9 ± 16.3 (11.0-84.0)	28.0 ± 13.3 (14.0-72.0)	33.2 ± 18.2 (11.0-84.0)
ACTH (pg/mL)	21.1 ± 8.7 (10.0-43.0)	20.0 ± 8.2 10.0-35.0)	22.1 ± 9.2 (10.0-43.0)
F8 (μg/dL)	15.8 ± 5.8 (5.0-27.5)	16.2 ± 4.7 (8.2-26.4)	15.5 ± 6.5 (5.0-27.5)
F24 (μg/dL)	4.1 ± 1.9 (1.1-8.2)	3.7 ± 1.5 (1.1-7.2)	4.3 ± 2.2 (1.3-8.2)
F-Dex (μg/dL)	1.0 ± 0.5 (0.5-1.8)	1.1 ± 0.4 (0.5-1.7)	1.0 ± 0.5 (0.5-1.8)

Data are expressed as mean ± SD with range or percentage in parenthesis. Conversion factors are as follows: serum cortisol, 27.59; UFC, 2.759; ACTH, 0.22. F-Dex indicates serum cortisol after 1-mg overnight dexamethasone suppression test.

Table 2
Clinical characteristics of patients subdivided into different groups based on different autonomic neuronal involvement

	Group A (n = 11)	Group B (n = 15)	Group C (n = 9)	Group D (n = 15)
Age (y)	57.8 ± 7.6 (44.0-69.0)	60.2 ± 10.2 (41.0-79.0)	59.6 ± 5.9 (51-69)	55.7 ± 11.2 (37.0-71.0)
BMI (kg/m2)	30.1 ± 4.5 (23.9-36.2)	29.4 ± 5.5 (22.1-39.0)	30.2 ± 3.8 (25.0-37.6)	31.4 ± 5.4 (23.0-40.0)
WC (cm)	100.4 ± 9.5 (86.0-113.0)	100.1 ± 10.2 (85.0-117.0)	103.6 ± 13.0 (92.0-135.0)	105.9 ± 13.8 (89.0-129.0)
T2DM duration (y)	6.2 ± 6.1* (0.0-22.0)	7.1 ± 6.5* (0.0-20.0)	14.7 ± 11.4 (0.0-32.0)	12.1 ± 8.3 (0.0-30.0)
HbA_{1c} (%)	11.0 ± 2.3 (6.1-14.8)	9.7 ± 2.5 (5.4-13.8)	11.1 ± 2.3 (6.3-14.4)	9.9 ± 1.5 (7.9-13.0)
Insulin-treated patients (%)	3 (27.3)	2 (13.3)	3 (33.3)	6 (40.0)
Sulfonylurea-treated patients (%)	5 (45.5)	6 (40.0)	4 (44.4)	7 (46.6)
Dyslipidemia (n)	6 (54.5)	4 (26.7)	7 (77.8)	9 (60.0)
Hypertension (n)	8 (72.7)	11 (73.3)	6 (66.7)	8 (53.3)
SBP (mm Hg)	136.4 ± 16.8†‡ (104.0-163.0)	123.3 ± 14.6 (100.0-148.0)	136.5 ± 7.7†‡ (128.0- 150.0)	120.7 ± 12.9 (103.0-150.0)
DBP (mm Hg)	81.0 ± 7.7‡§ (65.0-90.0)	75.5 ± 7.2 (65.0-90.0)	84.3 ± 3.7‡‖ (80.0-90.0)	74.0 ± 6.1 (65.0-85.0)

Data are expressed as mean ± SD with range or percentage in parenthesis. Group A includes patients with parasympathetic neuropathy; group B, patients with orthosympathetic neuropathy; group C, patients with para- and orthosympathetic neuropathy; and group D, patients without autonomic neuropathy.

* $P < .05$ vs group C.
† $P < .01$ vs group D.
‡ $P < .05$ vs group B.
§ $P < .05$ vs group D.
‖ $P < .001$ vs group D.

Data on scores of parasympathetic (ΔDB and ΔLS) and sympathetic (ΔPH) neuronal function and HPA axis activity are presented in Table 3. As expected, the autonomic neuropathy scores were different among the 4 groups, according to type of prevalent neuronal failure. All parameters of HPA activity were increased in patients with prevalent parasympathetic failure (group A) when compared to those with prevalent sympathetic failure (group B) and without autonomic derangement (group D), even if not all reached statistical significance (Table 3). Moreover, patients from group A (with parasympathetic derangement) showed UFC and F8 levels significantly higher as compared with those from group C (with both para- and sympathetic failure) (Table 3). In patients with prevalent parasympathetic failure, parameters of HPA activity were also higher when compared with those in all other diabetic subjects without parasympathetic neuropathy (data not shown).

In the whole sample, parasympathetic neuronal function as reflected by ΔDB and ΔLS were significantly and

Table 3
Scores of prevalent parasympathetic and sympathetic neuronal derangement and parameters of HPA axis activity in patients subdivided into different groups based on different autonomic neuronal involvement

	Group A (n = 11)	Group B (n = 15)	Group C (n = 9)	Group D (n = 15)
ΔDB	−0.021 ± 0.23*† (−0.085 to −0.005)	0.146 ± 0.535 (0.055-0.215)	0.051 ± 0.198 (−0.075-0.560)	0.179 ± 0.158 (0.050-0.500)
ΔLS	0.021 ± 0.116‡ (−0.150-0.325)	0.090 ± 0.101 (0.000-0.395)	−0.008 ± 0.028§ (−0.045 to 0.055)	0.116 ± 0.099 (0.005-0.360)
ΔPH (mm Hg)	5.68 ± 4.49 (0.0-10.0)	16.83 ± 5.86 (11.0-28.0)	15.5 ± 5.68‖ (10.0-28.0)	4.50 ± 2.53 (0.0-8.0)
UFC (μg/d)	48.6 ± 21.4¶# (26.0-84.0)	26.3 ± 11.0 (11.0-50.0)	32.5 ± 6.1 (23.0-44.0)	21.6 ± 9.8 (12.0-45.0)
ACTH (pg/mL)	27.0 ± 8.6*† (14.0-43.0)	19.9 ± 8.0 (10.0-35.0)	25.0 ± 9.3§ (14.0-38.0)	15.7 ± 5.7 (10.0-32.0)
F8 (μg/dL)	20.4 ± 4.5**†† (10.8-26.4)	14.3 ± 6.2 (5.0-25.5)	16.5 ± 6.5 (5.0-27.5)	13.6 ± 3.8 (5.7-18.5)
F24 (μg/dL)	4.8 ± 2.3 (2.5-8.2)	3.4 ± 1.6 (1.1-7.5)	4.9 ± 2.2 (1.3-7.5)	3.7 ± 1.6 (1.3-7.5)
F-Dex (μg/dL)	1.2 ± 0.4§ (0.5-1.7)	1.0 ± 0.6 (0.5-1.8)	1.2 ± 0.5§ 0.5-1.8)	0.8 ± 0.4 (0.5-1.8)

Data are expressed as mean ± SD with range or percentage in parenthesis. Conversion factors are as follows: serum cortisol, 27.59; UFC, 2.759; ACTH, 0.22. Group A includes patients with parasympathetic neuropathy; group B, patients with sympathetic neuropathy; group C, patients with parasympathetic and sympathetic neuropathy; and group D, patients without autonomic neuropathy. ΔDB indicates DB score expressed as the difference from age-related normal values (35-39 years, 1.210; 40-45 years, 1.185; 45-49 years, 1.165; 50-54 years, 1.145; 55-59 years, 1.125; 60-64 years, 1.110; 65-69 years, 1.090; 70-74 years, 1.060; see Ref. [20]); ΔLS, LS score expressed as the difference from age-related normal values (35-39 years, 1.130; 40-45 years, 1.111; 45-49 years, 1.090; 50-54 years, 1.070; 55-59 years, 1.060; 60-64 years, 1.040; 65-69 years, 1.030; 70-74 years, 1.010; see Ref. [21]); ΔPH, PH score (normal values ≤10 mm Hg).

* $P < .001$ vs group D.
† $P < .05$ vs group B.
‡ $P < .05$ vs group D.
§ $P < .01$ vs group D.
‖ $P < .0001$ vs groups A and D.
¶ $P < .0001$ vs groups B and D.
# $P < .01$ vs group C.
** $P = .002$ vs group D.
†† $P = .005$ vs group B.

indirectly correlated to UFC ($R = -0.39$, $P = .006$ and $R = -0.46$, $P = .009$, respectively; Fig. 1), SBP ($R = -0.32$, $P = .025$ and $R = -0.30$, $P = .04$, respectively), and DBP ($R = -0.28$, $P = .046$ and $R = -0.32$, $P = .025$, respectively); UFC was directly associated to DBP ($R = 0.32$, $P = .025$). Multivariate linear regression analysis showed that UFC levels were significantly associated with ΔDB ($\beta = -0.40$, $P = .004$) and tended to be associated with ΔLS ($\beta = -0.26$, $P = .065$), whereas BMI, HbA_{1c}, and duration of disease were not.

4. Discussion

Several previous studies showed that type 2 diabetic patients have increased HPA axis activity measured as basal ACTH levels [5,7,9], and basal cortisol levels [6-8] or cortisol levels after dexamethasone suppression [10,11]. However, other studies failed to find such alterations [12,13]. An increased HPA axis function has been reported in symptomatic diabetic neuropathy, and it has not been clearly linked to the physical stress associated to neuropathic pain symptoms [16]. To the best of our knowledge, this is the first study that evaluates the HPA axis activity in type 2 diabetic patients with asymptomatic autonomic imbalance. The study investigates the possible association between HPA function and prevalent sympathetic and parasympathetic derangement.

The main result of the present study is that in diabetic patients without symptoms of neuropathy, the imbalance of the autonomic nervous system toward a parasympathetic failure is associated to increased HPA axis activity. Because our patients were completely asymptomatic, these modifications of HPA function should not be attributable to the physical stress usually associated to diabetic neuropathy. Moreover, in our sample the degree of HPA function activity appears to be related to the degree of the prevalent parasympathetic neuronal impairment regardless of the metabolic control (as suggested by HbA_{1c}), the duration of disease, and the presence of chronic complications of diabetes, the latter being an exclusion criteria.

The design of this study allows us to show only association but not causality. Therefore, the explanations of these findings are hypothetical. However, it is known that catecholaminergic pathways exert an excitatory [31,32] role on the corticotropin-releasing hormone–secreting neurons in the hypothalamus, whereas the cholinergic tone seems to inhibit corticotropin-releasing hormone secretion at least in humans [33]. It is possible to speculate that in diabetic patients with prevalent parasympathetic failure, the sympathetic function may not be adequately counteracted; this imbalance toward a prevalent sympathetic activity may lead to HPA axis hyperactivity. The finding of higher HPA activity in patients with both parasympathetic and sympathetic failure as compared to those without neuropathy may suggest that the normal parasympathetic activity is crucial to maintain a normal HPA function.

The association between parasympathetic autonomic failure (or a not adequately counteracted adrenergic tone) and cortisol secretion may explain why, in our sample, patients with parasympathetic failure show higher blood pressure levels correlated with the degree of neuronal impairment and HPA activity [34]. The crucial role of parasympathetic activity is confirmed by the finding that blood pressure levels were found to be increased also in patients with combined parasympathetic-sympathetic dysfunction. Moreover, the finding of association between blood pressure levels and HPA activity is in line with recent data showing that hypertension is significantly associated with impaired glucocorticoid feedback control [35].

The finding of activated HPA axis in diabetic patients with asymptomatic autonomic imbalance is of clinical interest because the prevalence of subclinical autonomous adrenal hypersecretion in diabetic subjects is now extensively investigated, and it is still a matter of debate [14,15]. Our study suggests that the presence of autonomic derangement has to be considered when investigating HPA axis in diabetic patients. If these data would be confirmed, the neuro-autonomic tests might be useful to search for patients at higher risk of developing a preclinical condition of increased HPA axis activity.

A limitation of our study may be related to the lack of longer-term tests for the evaluation of heart rate variability in our patients with T2DM. Nevertheless, DB and LS test results have been reported to closely correlate to those of the 24-hour test [36]. The lack of a matched nondiabetic control group could also be a limit of this study. Nevertheless, the observation about the association between HPA activity and parasympathetic impairment in type 2 diabetic subjects is novel, and further studies should confirm these data in respect to a nondiabetic population. Other studies are warranted to evaluate if there is a causal relationship between these alterations.

In conclusion, our study shows that diabetic patients with asymptomatic autonomic imbalance with prevalent parasympathetic failure have increased activity of HPA axis, related to the degree of the neuronal dysfunction, and higher blood pressure levels when compared to those with asymptomatic prevalent sympathetic failure or without autonomic derangement.

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