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Original Article

Myocardial sympathetic innervation in patients with impaired glucose tolerance: relationship to subclinical inflammation

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Abstract

Aim: This study was designed to assess cardiac adrenergic nerve activity, using iodine (I)-123-labeled metaiodobenzylguanidine (MIBG), in patients with impaired glucose tolerance (IGT) and to investigate its relation to circulating levels of proinflammatory cytokines. **Methods:** We studied 22 patients with IGT (aged 34–68 years) and 18 age-matched healthy controls, using I-123 MIBG cardiac imaging. The early (10 min) and late (4 h) heart to mediastinum MIBG uptake (H/M) ratio and washout were calculated. Levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a), and its soluble receptor [soluble TNF receptor II (sTNFRII)] were measured by immunoassay of blood samples from patients and controls. **Results:** The early and late MIBG uptake was lower (both $P<.001$) and the WR was higher ($P<.001$) in patients than in controls. The analysis showed innervation defects in 20 of the 22 patients. Nearly half (45.4%) showed severe adrenergic innervation defects in both the inferior wall and the apex. Regarding cytokines, patients showed significantly elevated TNF-a ($P=.005$), sTNFRII ($P<.001$), and IL-6 ($P<.001$) levels compared to controls. IL-6 and sTNFRII were found to correlate with the WR ($r=0.468$, $P=.028$ and $r=0.455$, $P=.034$, respectively). **Conclusion:** Patients with IGT show reduced MIBG cardiac uptake with a segmental pattern. The reduced cardiac sympathetic innervation was related to the elevated proinflammatory cytokine levels and could be considered an index of early atherosclerotic process in these patients.

Keywords: Sympathetic innervation; Impaired glucose tolerance; TNF-a; interleukins

As impaired glucose tolerance (IGT) belongs to the insulin resistance syndrome, it is important to identify diabetes mellitus (DM) as early as possible, since both patients with DM and prediabetic state patients such as those with IGT run an increased risk of cardiovascular disease [1–4].

The involvement of the heart in complications specific for diabetes is mainly twofold: (i) cardiac innervation impairment by autonomic neuropathy and (ii) specific diabetic cardiomyopathy.

Previous studies have shown that the sympathetic nervous system is stimulated in the early stages of diabetes [5,6], and the extended exposure of the adrenergic receptors to increased catecholamine levels, together with hyperglycemia and insulin deficiency, is believed to lead to diabetic cardiac autonomic neuropathy.

Abnormalities of the autonomous nervous system are associated with cardiovascular mortality and morbidity and have been proven to be strong predictors of the progression of focal coronary atherosclerosis [7–10], while the presence of diabetic autonomic neuropathy also increases the morbidity and mortality rates in patients with diabetes [11,12].

The heart is an organ rich in sympathetic innervation. Iodine-123 meta-iodobenzylguanidine (MIBG) was developed to display this sympathetic innervation and has been used to study myocardial adrenergic nerve activity [13]. It

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has been reported that myocardial imaging with MIBG, an analogue of noradrenalin, provides information on the severity of altered sympathetic innervation in patients with diabetes mellitus, while previous studies have shown the potential value of MIBG for assessing the cardiac sympathetic innervation in patients with DM [14].

Increased clearance of MIBG from the heart is consistent with increased sympathetic nervous activity, and reduced MIBG uptake is related to poor prognosis. In patients with DM, MIBG abnormalities were nearly 40% more common than diabetic autonomic neuropathy when assessed by conventional means [15,16]. Furthermore, MIBG defects were present in the absence of coronary atherosclerosis or stress-induced perfusion defects [17].

Inflammation also plays a significant role in the pathogenesis and progression of atherosclerosis, and inflammation markers have proved to correlate with cardiovascular mortality and morbidity [18].

However, the clinical significance of myocardial MIBG imaging in relation to subclinical inflammation in patients with IGT has not been established.

The aims of this study were thus to (a) assess features of MIBG cardiac imaging and serum levels of inflammation markers in patients with IGT, in comparison to healthy controls, and (b) identify the relationship between MIBG cardiac imaging and serum inflammation markers in these patients.

1. Methods

1.1. Study population

Over a period of 36 months, 22 patients (15 men and 7 women) with a diagnosis of IGT, mean age 50.3±6.6 years (range 34–68), were included in this study. Patients were selected from our university-based outpatient vascular disease prevention clinic. They all had fasting serum glucose between 100 and 126 mg/dl, and their serum glucose levels 2 h after glucose loading (oral glucose tolerance test) were between 140 and 200 mg/dl. Seventeen of them had a family history of DM [19].

The control group consisted of 18 healthy volunteers from the hospital staff (12 men and 6 women), mean age 51.4±6.1 years (range 39–62), with normal fasting serum glucose (<100 mg/dl).

All 40 subjects were asymptomatic, with no history of hypertension [mean systolic blood pressure (SBP) <140 mm Hg, mean diastolic blood pressure (DBP) <90 mm Hg]. Other exclusion criteria included the presence of hyperlipidemia (fasting cholesterol levels >200 mg/dl, LDL cholesterol >160 mg/dl, and triglygerides >150 mg/dl), any medication intake, the daily consumption of >2 cups of coffee, daily intake of >2 glasses of an alcoholic drink per day, and obesity [body mass index (BMI) >27 kg/m^2].

Thus, patients with clinical covariates that might have had an obvious effect on autonomic function such as hypertension, obesity, dyslipidemia, smoking, coffee intake, alcohol consumption, patients with chronic inflammatory disease or acute infection were excluded.

All patients and control subjects underwent a physical examination, electrocardiographic and 2-D transthoracic echocardiographic examinations, and an exercise test (Bruce protocol). No indications of arrhythmias, systolic–diastolic dysfunction, or heart valve disease were detected. All subjects had a low probability of coronary artery disease based on the absence of cardiovascular symptoms and on normal 201 thallium scintigraphy. All subjects gave their consent to participate in the study. The ethics committee of the University of Crete approved the protocol.

1.2. I-123 MIBG imaging protocol

On the day of MIBG scintigraphy, all patients and control subjects were instructed to fast for 6 h. One milliliter of Lugol's solution was given orally 2 h before the slow intravenous injection of 185 MBq I-123 MIBG (Mallinackrodt, St. Louis, MO, USA; specific activity, 74 MBq /mg) for thyroid gland blocking. A dual-head gamma camera (GE Medical Systems, Milwaukee, WI, USA) provided with low-energy, general purpose collimators (LEGP) was used to obtain the I-123 MIBG scintigram. A 20% energy window centered on 157 keV and a 128×128 matrix size were used. Anterior static images were obtained 10 min (early images) and 4 h (delayed images) postinjection. Immediately after the delayed planar image, single photon emission computed tomography images (SPECT) were also recorded. Thirty-two projections (50 s each) were obtained over a 180° arc, starting at the left posterior oblique position, and images were stored by means of a 64×64 matrix. Transaxial, sagittal, and oblique tomograms were obtained through the use of a nuclear medicine computer.

1.3. Data processing

Qualitative, semi-quantitative, and quantitative analyses were performed. Qualitative and semi-quantitative analysis were based on visual evaluation of the intensity of the uptake of MIBG on SPECT images. To evaluate regional adrenergic dysfunction on SPECT imaging, the left ventricle was divided according to the five-segment model as in the echocardiographic study. A four-point scoring system was used to determine a defect score for visual interpretation of I-123 MIBG uptake in the five regions of the left ventricular myocardium as follows: 1=*normal radioisotope uptake* (>75% of peak activity); 2=*mildy reduced uptake* (50–75% of peak activity); 3=*moderately reduced uptake* (25–50% of peak activity); and 4=*absence or severe reduction in radioisotope uptake* (<25% of peak activity).