Cardiac imaging for risk stratification in asymptomatic diabetes

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Chapter 8

Diabetic cardiovascular autonomic neuropathy by ^{123}I metaiodobenzylguanidine myocardial scintigraphy and heart rate variability in asymptomatic patients with type 2 diabetes mellitus

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Abstract

Purpose

The purpose of this study was to evaluate the prevalence of cardiac autonomic neuropathy (CAN) in a cohort of truly asymptomatic patients with type 2 diabetes mellitus using heart rate variability (HRV) and ^{123}I-metaiodobenzylguanidine (^{123}I-*m*IBG) myocardial scintigraphy.

Methods

88 asymptomatic patients with type 2 diabetes mellitus were prospectively recruited from an outpatient diabetes clinic. In patients with normal myocardial perfusion CAN was assessed by HRV and ^{123}I-*m*IBG myocardial scintigraphy. Two or more abnormal tests were defined as CAN positive (ECG-based cardiac autonomic neuropathy) and one or less as CAN negative. CAN assessed by ^{123}I-*m*IBG scintigraphy was defined as abnormal if: heart/mediastinum ratio<1.8, washout>25%, or total defect score>13.

Results

The prevalence of CAN in asymptomatic patients with type 2 diabetes and normal myocardial perfusion assessed by HRV and ^{123}I-*m*IBG scintigraphy was respectively, 27% and 58%. Furthermore, in almost half of patients with normal HRV, ^{123}I-*m*IBG scintigraphy showed CAN.

Conclusion

The current study revealed a high prevalence of CAN in patients with type 2 diabetes mellitus. Secondly, disagreement between HRV and ^{123}I-*m*IBG scintigraphy for the assessment of CAN was observed.

Introduction

Diabetes mellitus is an increasing health care problem.[2, 16] Cardiovascular complications including coronary artery disease (CAD), are the most common causes of mortality and morbidity in patients with type 2 diabetes mellitus.[7] Because patients with diabetes mellitus type 2 often suffer from CAD without symptoms, risk stratification is needed to identify patients at high risk for CAD. In the DIAD (Detection of silent myocardial Ischemia in Asymptomatic Diabetic subjects) study the overall prevalence by single photon emission computed tomography (SPECT) of silent myocardial ischemia was 22%.[36] Although traditional risk factors failed to predict silent myocardial ischemia, cardiac autonomic neuropathy (CAN) assessed by heart rate variability (HRV), was a strong predictor for silent myocardial ischemia in this study. Furthermore, it is known that CAN is one of the most common diabetes-associated complications and has been associated with increased risk of mortality and major cardiovascular events.[125-129] However, although CAN assessed by HRV is a sensitive method to detect neuropathy, it is less accurate in detecting sympathetic dysfunction.[130] The sympathetic cardiac innervation can nowadays be assessed directly and noninvasively with ^{123}I-*m*IBG myocardial scintigraphy in many clinical disorders, including diabetes.[131-135]

How HRV and ^{123}I-*m*IBG myocardial scintigraphy compare in asymptomatic patients with diabetes is unknown. The current observational study evaluated the prevalence of CAN according to HRV versus ^{123}I-*m*IBG myocardial scintigraphy.

Methods

Patient population

All patients were referred from an outpatient diabetic clinic to our institution for risk stratification. This included adenosine stress SPECT myocardial perfusion imaging to assess myocardial ischemia and HRV to assess CAN. The diagnosis of diabetes was established by the referring physician and confirmed by patient history or the use of medication such as insulin or oral hypoglycaemic agents.[1] Inclusion criteria consisted of confirmed type 2 diabetes mellitus in combination with complete absence of angina or angina-equivalent symptoms. Asymptomatic status was confirmed using the Rose questionnaire for angina.[15] Exclusion criteria were: known CAD; stress test or coronary angiography before referral, history of coronary revascularization, treatment with anti-anginal medication,

electrocardiographic evidence of Q-wave myocardial infarction, ischemic ST-segment or T-wave changes or complete left bundle branch block and active bronchospasm, excluding the use of adenosine as stressor for SPECT myocardial perfusion imaging. In patients with normal myocardial perfusion (stress and rest) ^{123}I-*m*IBG myocardial scintigraphy was performed to evaluate the prevalence of sympathetic CAN compared to the prevalence of CAN assessed by HRV.

Adenosine stress SPECT myocardial perfusion imaging

Data acquisition and analysis were performed as described before.[84] Briefly, ECG-gated SPECT imaging was performed using a 2-day protocol (adenosine and rest) with technetium-99m sestamibi (99mTcMIBI). Twelve-lead electrocardiography (ECG) was recorded each minute and continuously monitored (leads aVF, V1 and V5) for the development of arrhythmia or ST-segment deviation. Imaging was performed 120 minutes after tracer injection using a triple-head SPECT camera (GCA 9300/HG, Toshiba Corporation, Tokyo, Japan) using low-energy, high resolution collimators. Image acquisition was performed using a circular 360° orbit, 60 projections and 40 second/projection[61, 62] No attenuation correction was applied. The cardiac images were processed in the usual manner and short-axis, horizontal and vertical long-axis views were reconstructed. The adenosine stress SPECT myocardial perfusion imaging study was considered normal in case of 1) both SRS and SDS <2, 2) resting LVEF ≥45%, and 3) absence of increased lung uptake, TID or flat or down sloping ST-segment depression ≥ 1mm at 80 ms after the J-point in two or more leads on the ECG during adenosine infusion.

Cardiovascular autonomic reflex tests

Data acquisition

To assess cardiovascular autonomic neuropathy (CAN), heart rate variability (HRV) was measured during the following 4 cardiovascular reflex tests and recorded with the aid of a Holter ECG .[136, 137]

1. HRV at rest over 150 consecutive beats,
2. HRV during deep breathing at 6 cycles per minute over 120 consecutive beats,
3. HRV during Valsalva manoeuvre,
4. Immediate heart rate response to standing from the recumbent position.

A final test measured the difference in systolic blood pressure between supine and upright position. No patients were receiving drugs influencing HRV, such as neuroleptic drugs or clozapine. Antihypertensive medications such as angiotensin converting enzyme (ACE)- inhibitors and angiotensin receptor blockers (ARB) were stopped one week before HRV measurements.[138, 139]

Data analysis

All Holter ECG recordings were analyzed by two experienced observers unaware of the clinical history of the patients. In case of disagreement, a joint reading was performed and a consensus decision was reached. For the evaluation of HRV at rest, coefficient of variation (CV) was used.[140] HRV during deep breathing was evaluated by calculating the E-I ratio (ratio of the mean longest to shortest R-R interval during respectively inspiration and expiration).[141] The 'Valsalva ratio' was calculated as the ratio of the longest R-R interval following release to the shortest R-R interval during the maneuver.[142] Immediate heart rate response to standing up was calculated as the '30-15 ratio', defined as the longest R-R interval of beats 20-40 divided by the shortest R-R interval of beats 5-25 with beat one being the first one during the process of getting up. The shortest R-R interval came always prior to the longest R-R interval within the calculation of the '30-15 ratio'. Age related normal ranges were used for evaluation of these 4 cardiovascular reflex tests.[143] Patients were excluded from analysis when either one or more recordings of HRV during Holter monitoring consisted of too few consecutive beats for interpretation or in case of extra systoles impairing interpretation. A decrease of systolic blood pressure equal to or greater than 30 mmHg within 2 minutes after standing was defined as an abnormal heart rate response.[144]

Thus, CAN assesses by HRV was classified according to the number of abnormal cardiovascular reflex tests. Two or more abnormal tests were defined as CAN positive (ECG-based cardiac autonomic neuropathy) and 1 or less as CAN negative.[145, 146]

^{123}I-*m*IBG myocardial scintigraphy imaging protocol

Data acquisition

Patients were instructed not to take tricyclic antidepressants drugs, sympathetic agents, or other drugs known to interfere with *m*IBG uptake. Thyroid uptake of unbound ^{123}I was blocked with sodium iodine solution given orally 60 minutes before ^{123}I-*m*IBG injection. 185 MBq of ^{123}I-*m*IBG (GE Healthcare, USA) was injected in 60 seconds intravenously at

rest. Fifteen minutes post injection anterior planar images of the chest were acquired and stored in a 256 x 256 matrix. Thereafter, a 360° SPECT study was acquired using a double-head gamma camera (GCA 9300/HG, Toshiba Corporation, Tokyo, Japan) (4˚/ step, 35 sec/projection, 128 x 128 matrix). Repeat planar and SPECT studies were acquired at approximately 4 hours post-injection. All camera heads were equipped with low-energy high-resolution collimators and all acquisitions were performed with a 15% energy window centered at the 159 keV photopeak of ^{123}I.

Data analysis and image interpretation

Planar images

Early (15 min post-injection) and late (4-hour delayed) planar images were processed to determine the heart-to-mediastinum ratio (HMR). The planar *m*IBG images were analyzed using regions of interest (ROI) to calculate the uptake ratios and washout percentages. Therefore, a ROI was drawn manually over the left ventricle. A second rectangular ROI over the upper mediastinum and opposite arm were used as a reference background region. The HMR of average counts per pixel was calculated for the early and delayed images. After correcting for the physical decay of ^{123}I, early and delayed HMR values were then used to compute the myocardial washout ratio (WR) of *m*IBG as follows:

WR= [early heart counts-early mediastinum counts] – [delayed heart counts-delayed mediastinum counts] / [early heart counts-early mediastinum counts] x 100%.

Since most available evidence supports the use of the delayed MIBG images (and the derived HMR and WR) for risk stratification, abnormal delayed HMR and WR were defined as lower than 1.8 and higher than 25%, respectively.[147, 148]

SPECT images

Polar map formats (normalized to 100%) were used for semi-quantitative and visual interpretation. The delayed myocardial SPECT images were divided into 17 segments and each segment was evaluated in consensus by two expert observers, using a 4-point scoring system (0: >70% tracer uptake, 1: 50-70% tracer uptake, 2: 30-50% tracer uptake, 3: <30% tracer uptake).[66, 85] As a result, the summed score for each study could theoretically range from 0 to 51 (17 x 3). The total defect score (TDS) was calculated as the sum of all defect scores. The TDS was converted to percentage of the total denervated myocardium. The percentage denervation in the LV was calculated as follows: (TDS/ 51 [maximum score =17x3] x 100. Based on the study by Kasama et

al, a TDS >18 was considered abnormal; when corrected for a 4-point scoring system (as used in the current study), a TDS >13 would be considered abnormal.[149] Next, the location of defects was evaluated, and categorized as inferior, apical, lateral, anterior or septal. In addition, patients were categorized as having 1 defect allocated to 1 region (see above), having ≥2 defects, or diffusely reduced MIBG uptake. Thus, CAN assessed by ^{123}I-*m*IBG scintigraphy was defined as abnormal if: HMR<1.8, WO>25%, or TDS>13.

Statistical analysis

Categorical baseline characteristics were expressed as numbers and percentages. Continuous variables were expressed as mean (± standard deviation). Statistical analyses were performed using SPSS software (version 12.0, SPSS Inc, Chicago, Il, USA) and SAS software (The SAS system, release 6.12, Cary, NC, USA: SAS Institute Inc.). A P-value <0.05 was considered as statistically significant.

Results

Patient characteristics

From the clinical registry, 110 consecutive patients with normal SPECT perfusion studies were identified and available for ^{123}I-*m*IBG scintigraphy. Of these, 22 (20%) patients were excluded due to incomplete datasets (n=13) or poor MIBG image quality (n=9).

Thus, the final patient population consisted of 88 patients (56 men, age 53 ± 10 years). The patient characteristics are shown in Table 1. The mean duration of diabetes was 9.8 ± 8.2 years. Most of the patients were on oral anti-diabetic therapy (61%). ACE inhibitors/ARB was used in 35% and 21% of patients. Twenty-eight patients had complications of diabetes, such as peripheral neuropathy and/or peripheral vascular disease.

Cardiac autonomic neuropathy assessed by HRV

Of the 88 patients, CAN was classified according to the number of abnormal cardiovascular reflex tests. Thirty (34%) of these patients had ≥1 abnormal cardiovascular reflex test. Twenty-four (27%) patients were considered to have ≥2 abnormal tests and were categorized as CAN positive.

Table 1. Patient characteristics of 88 asymptomatic patients with diabetes type 2. Data between parentheses indicate percentages.

Variables	Patients n=88
Male	56(64)
Age (years)	53±10
Diabetes-related risk factors	
Duration (years)	9.8±8.2
Age at time of diagnosis of diabetes (years)	44±12
HbA_1C	7.4±1.6
Treatment	
Oral/Insulin	54(61)/21(24)
Oral and Insulin	11(13)
Peripheral vascular disease/peripheral neuropathy	9(10)/19(22)
Peripheral vascular and neuropathy	11(13)
Body mass index (kg/m^2)	29.2±5.7
Waist circumference (cm)	103±15.0
Hypertension	47(53)
Hypercholesterolemia	46(52)
Family history of CAD	52(59)
Current Smoking	12(14)
Medication	
Aspirin	18(21)
ACE inhibitors/ARB	31(35)/18(21)
Statins	45(51)
Total cholesterol (mmol/l)	4.9±1.1
LDL (mmol/l)	3.2±.1.1
HDL (mmol/l)	1.4±0.6
Cholesterol/HDL ratio	3.8±1.3
Triglycerides (mmol/l)	2.0±1.2
Creatinine (mmol/l)	78.5±20.0
Urine albumin-creatinine ratio	12.4±32.8
CRP (mg/l)	8.3±5.8
Apolipoprotein A1 (g/l)	1.4±0.30
Apolipoprotein B (g/l)	0.9±0.30
Fibrinogen (g/l)	3.9±0.90

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; CAD, coronary artery disease; CRP, chain reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Cardiac autonomic neuropathy assessed by ^{123}I-*m*IBG

Of the 88 patients, 37 patients (42%) had a normal ^{123}I-*m*IBG study. In the remaining 51 patients (58%), the ^{123}I-*m*IBG study was abnormal. Of these 51 patients, 22 patients (43%) had 1 criterium for an abnormal ^{123}I-*m*IBG study; the remaining 30 patients (57%) had ≥2 criteria. In the total 88 patients, 36 (41%) patients had a HMR<1.8 (mean 1.62±0.13) and 32 (36%) patients had a WO>25% (mean 34± 8). A TDS>13 (mean 43±18) was observed in 25 (28%) patients.

Location of ^{123}I-mIBG defects on SPECT

Thirty-nine patients (44%) had no defects on the delayed ^{123}I-*m*IBG images. The majority (n=22, 25%) of the innervation defects were located in the inferior wall. Seven patients showed defects in the apex, whereas 3 patients had defects in the anterior wall. Eight patients had diffuse diminished tracer uptake over the entire LV and 9 patients had defects in more than 2 regions. In the 25 patients with a TDS>13 the location of the defects were as follows: inferior wall n=7, apex n=4, diffuse diminished n=7 and ≥ 2 regions n=6.

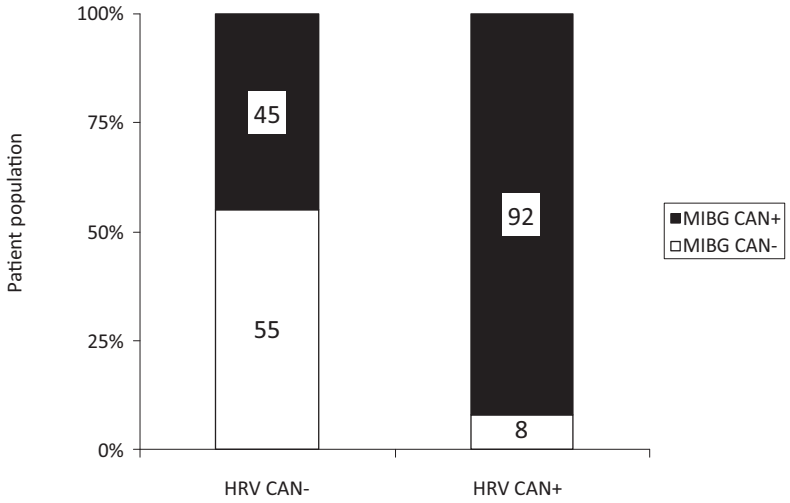
Cardiac autonomic neuropathy assessed by ^{123}I-*m*IBG versus HRV

The agreement and disagreement between HRV and ^{123}I-*m*IBG for the assessment of CAN is shown in Figure 1. Of the 64 patients without CAN according to HRV, 35 patients (55%) had a normal ^{123}I-*m*IBG study. Of the 24 patients with CAN according to HRV, 22 (92%) had an abnormal ^{123}I-*m*IBG study. In particular, 15 (63%) patients had HMR<1.8 (mean 1.57±0.16), 13 (54%) patients had a WO>25% (mean 35±10) and 12 (50%) patients had a TDS>13 (mean 51±24). 12 patients (50%) had ≥2 criteria for an abnormal ^{123}I-*m*IBG study. However, in the remaining 29 patients (45%) with normal HRV, ^{123}I-*m*IBG scintigraphy was abnormal. In particular, twenty-one patients (72%) had a HMR<1.8 (mean 1.66±0.10), 18 patients (62%) had a WO>25% (mean 34±7) and 13 patients (45%) had a TDS>13 (mean 26±11). 15 patients (52%) had ≥2 criteria for an abnormal ^{123}I-*m*IBG study.

Discussion

In the present study, the prevalence of CAN in asymptomatic patients with type 2 diabetes and normal myocardial perfusion was assessed by HRV and ^{123}I-*m*IBG scintigraphy;

Figure 1. Agreement and disagreement between HRV and ^{123}I-*m*IBG scintigraphy for the assessment of cardiovascular autonomic neuropathy



CAN, cardiac autonomic neuropathy; HRV, heart rate variability.

the prevalence of CAN was 27% according to HRV and 58% on ^{123}I-*m*IBG scintigraphy. Importantly, in almost 50% of the patients with normal HRV, ^{123}I-*m*IBG scintigraphy showed CAN, suggesting that ^{123}I-*m*IBG imaging may be more sensitive for the assessment of CAN than HRV.

CAN is one of the most important complications of diabetes mellitus. It results from damage to the autonomic nerve fibers innervating the heart and blood vessels, which causes abnormalities in heart rate control and impairs vascular dynamics. Clinical manifestations of CAN include exercise intolerance, intra-operative cardiovascular instability, orthostatic hypotension, asymptomatic ischemia and painless myocardial infarction.[150] Furthermore, CAN is associated with poor outcome related to ventricular arrhythmias and sudden cardiac death.[125-129] [151] In clinical practice, CAN is generally assessed using HRV. When CAN has progressed significantly, it may result in a reduction of HRV.[152] Measuring the HRV has shown to be a simple, noninvasive method to evaluate the sympatheticovagal balance at the sinoatrial level and can identify patients at elevated risk for cardiac arrhythmias and sudden death.[153, 154]

Therefore, assessing HRV is potentially important in the management of patients with diabetes. In the current study, a series of simple bedside tests that are fairly sensitive in detecting CAN were used.[126] In 1976 already, Ewing et al published the results of 37 diabetic patients with symptoms and clinical features suggestive of autonomic neuropa-

thy who were followed for 33 months.[125] The authors concluded that simple autonomic function tests provided significant prognostic information, with abnormal tests being associated with a high mortality. These results were confirmed in a larger population (n=605) of the Hoorn study with a follow-up period of 9 years.[127] Mortality during the follow-up was 17% (n=101 patients); patients with diabetes and impaired autonomic function had a twofold mortality risk.

^{123}I-*m*IBG is an analog of the false neurotransmitter guanethidine. It is taken up by adrenergic neurons in a similar fashion to norepinephrine and does not undergo intracellular metabolism. When labelled with ^{123}I, it can be used to visualize adrenergic receptors in the myocardium using scintigraphic imaging.[155] At present, cardiac ^{123}I-*m*IBG imaging has mainly been used for prognostification of patients with heart failure. In a pooled analysis, including almost 1800 patients derived from 8 studies, a decreased late H/M ratio or increased myocardial ^{123}I-*m*IBG washout was associated with a worse outcome compared to patients with normal ^{123}I-*m*IBG scintigraphy parameters.[156] In patients with diabetic neuropathy and/or CAN, Ziegler et al investigated prospectively the effect of glycemic control on myocardial sympathetic innervation using ^{123}I-*m*IBG scintigraphy, at baseline and at 4 year follow-up.[157] Among the patients with a poorly controlled HbA1c, (mean ≥7.6%) ^{123}I-*m*IBG uptake deteriorated after 4 years.

Conversely, Schnell and co-workers reported that global and regional ^{123}I-*m*IBG uptake in 22 asymptomatic patients with type 1 insulin-dependent diabetes did neither significantly regress nor progress on average ^{123}I-*m*IBG uptake over 3 year follow-up. These results suggested hat CAN seemed to be a persistent phenomenon in intensive treated diabetic patients.[158] Recently, Nagamachi et al investigated retrospectively the long-term (mean 7.2 ± 3.2 years) prognostic value of ^{123}I-*m*IBG scintigraphy for both cardiac events and mortality in 144 patients with type 2 diabetes and normal myocardial perfusion.[131] A decreased delayed H/M ratio (<1.7) was an independent predictor of long-term mortality. A combination of ^{123}I-*m*IBG scintigraphy parameters (delayed H/M ratio <1.7, WR >25%) and HRV was independently predictive of cardiac events.

Previous data have suggested that ^{123}I-*m*IBG scintigraphy may be more sensitive than HRV for detection of CAN in diabetic subjects.[137, 157] Schnell and colleagues demonstrated that 14 (93%) of 15 diabetic patients without CAN according to HRV had an abnormal ^{123}I-*m*IBG study.[137]

The role of CAN in asymptomatic diabetic patients has been described by Valensi et al.[159] In this study, 75 patients with at least two cardiovascular risk factors, were evaluated for silent myocardial ischemia and CAN with a 3-7 years follow-up period. Eleven (15%)

patients had a major cardiovascular event and multivariate analysis demonstrated that CAN was a better predictor of major cardiac events than silent myocardial ischemia. Furthermore, Langer et al investigated CAN according to HRV and ^{123}I-*m*IBG scintigraphy in 23 normal subjects and 65 asymptomatic patients with diabetes type 2 and silent myocardial ischemia.[160] The authors showed that ^{123}I-*m*IBG uptake was largely diminished in diabetic patients, especially in those with clinically detectable CAN; moreover diffuse abnormalities in ^{123}I-*m*IBG uptake were observed in patients with silent myocardial ischemia.

In the present study, we performed a systematic, head-to-head comparison between HRV and ^{123}I-*m*IBG scintigraphy in 88 asymptomatic patients with type 2 diabetes to evaluate the presence of CAN. The current study has included much more patients than the previous studies, but although the inclusion criteria were different, our results are in line with previous reports observing a significantly higher proportion of CAN with ^{123}I-*m*IBG scintigraphy compared to HRV.[137, 161, 162] The fact that more patients exhibit abnormalities in ^{123}I-*m*IBG imaging as compared to HRV, underscores the suggestion that abnormalities in cardiac sympathetic innervation occur prior to ECG-based (HRV) cardiac autonomic dysfunction.[137] An alternative explanation is that ^{123}I-*m*IBG scintigraphy mainly reflects sympathetic innervation, whereas HRV may be more related to parasympathetic function.[163] It remains to be determined which of these two parameters may be more useful to predict long-term outcome.

While HRV and other traditional parameters provide an impression of global innervation abnormalities, ^{123}I-*m*IBG scintigraphy with SPECT provides information on regional innervation. The findings in the current study indicated that regional abnormalities occur often in patients with asymptomatic diabetes. Other studies using ^{123}I-*m*IBG scintigraphy, in populations with varying cardiovascular diseases, have also shown regional innervation abnormalities.[137, 161, 162, 164] For example, Langer et al evaluated 65 diabetic patients and noted significantly impaired ^{123}I-*m*IBG uptake in the inferior wall and apex.[160] Additional studies have shown that abnormalities in CAN tend to occur first in the inferior regions of the myocardium and then progressively spread to adjacent segments.[165, 166] It may well are that these regions of reduced innervation may be more prone to cardiac arrhythmias, but this remains to be determined.

It is noteworthy that reduced ^{123}I-*m*IBG uptake has also been reported (to a lesser extent) in normal subjects and was related to attenuation artefacts; although we did not correct for attenuation in the current study, only individuals with normal SPECT perfusion studies were included, which reduces the likelihood of attenuation artefacts.[167]

Clinical implications

Diabetic CAN is a serious and common complication of diabetes. It is related to an increased risk of cardiovascular mortality and morbidity. Therefore, early detection of CAN in diabetic patients is of importance for appropriate risk stratification. Of all established diabetes-related and cardiac risk factors in patients with asymptomatic diabetes, poor glycemic control is of great importance in the development and progression of CAN.[157, 165] At the same time, poor glycemic control is associated with poor outcome.[168] Accordingly, early detection of CAN is of utmost importance. As observed in the current study, ^{123}I-*m*IBG scintigraphy appears more sensitive than HRV to detect CAN in asymptomatic diabetic patients, without myocardial perfusion abnormalities; identification of these patients may permit risk factor modification, and intensive medical treatment, aiming at better glycemic control, which in turn may favourably affect outcome.[169-172] Indeed, several studies have shown that improvement of CAN (as evidenced by HRV) can be achieved by weight loss with regular exercise.[173, 174] Furthermore, progression of CAN can also be delayed by intensive medical therapy, thereby reducing the risk of premature mortality.[175]

Conclusion

The poor long-term prognosis of asymptomatic diabetic patients and CAN justifies early risk stratification. In the current head-to-head comparison between ^{123}I-*m*IBG scintigraphy and HRV, ^{123}I-*m*IBG scintigraphy identified significantly more patients with CAN as compared to HRV. These findings suggest that ^{123}I-*m*IBG myocardial scintigraphy may be suited for early detection of CAN. Prospective studies are needed to evaluate the prognostic value of ^{123}I-*m*IBG myocardial scintigraphy in asymptomatic diabetic patients.