

NUCLEAR MEDICINE IN THE DIAGNOSIS OF RENAL AND CORONARY ANGIOPATHIES IN PATIENTS WITH TYPE 2 DIABETES AND IMPAIRED GLUCOSE TOLERANCE

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The number of patients suffering from diabetes mellitus (DM) is increasing necessitating the development of new strategies for early detection of the disease. Here, radionuclide imaging may be a promising diagnostic technique. We have conducted a retrospective analysis of medical records and scintigrams of patients with type 2 diabetes ($n = 83$) and impaired glucose tolerance ($n = 52$) to evaluate the effectiveness of dynamic renal scintigraphy and myocardial perfusion scintigraphy at rest (single-photon emission computed tomography, SPECT) in detecting coronary and renal angiopathies. The control group consisted of patients with normal levels of blood sugar. To evaluate the functional state of the renal parenchyma, we conducted a qualitative analysis of patients' scintigrams and renographic curves; the glomerular filtration rate (GFR) was evaluated using Gates and Cockcroft-Gault methods; myocardial scarring was evaluated using perfusion SPECT images synchronized with ECG. The functional activity of the renal parenchyma was shown to decrease significantly in patients with type 2 DM (Pearson's chi-squared test was applied, p -value was 0.03). With Gates method applied, GFR in both experimental groups was significantly lower than in the controls (Mann-Whitney U was calculated; p -value was 0.0004 and 0.0002, respectively). In patients with type 2 DM, GFR was lower than in patients with impaired glucose tolerance ($p = 0.0004$). With Cockcroft-Gault method applied, we observed the same GFR pattern; however, the difference between patients with impaired glucose tolerance and the controls was insignificant ($p = 0.08$). The correlation between GFR values obtained using different methods was moderate in all groups (Spearman's rank correlation coefficient $r_s = 0.53$, with $p = 0.038$).

Keywords: diabetes mellitus, impaired glucose tolerance, dynamic renal scintigraphy, myocardial perfusion scintigraphy

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ВОЗМОЖНОСТИ ЯДЕРНОЙ МЕДИЦИНЫ В ДИАГНОСТИКЕ АНГИПАТИЙ ПОЧЕК И СЕРДЦА У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА И НАРУШЕНИЕМ ТОЛЕРАНТНОСТИ К ГЛЮКОЗЕ

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Число больных сахарным диабетом (СД) растет, и требуется разработка эффективных подходов к ранней диагностике заболевания. Перспективными являются радионуклидные методы диагностики. Проведен ретроспективный анализ историй болезни и скинтиграмм пациентов с СД 2 типа ($n = 83$) и нарушением толерантности к глюкозе ($n = 52$) для оценки эффективности динамической нефросцинтиграфии и перфузионной томосцинтиграфии (одnofотонной эмиссионной компьютерной томографии, ОФЭКТ) миокарда в покое при выявлении ангиопатий почек и сердца. В группу сравнения ($n = 45$) включили пациентов с нормальным содержанием глюкозы в крови. Оценивали функциональное состояние паренхимы почек путем качественного анализа скинтиграмм и ренографических кривых, скорость клубочковой фильтрации (СКФ) — по методам Gates и Кокрофта–Голта, наличие и площадь повреждений миокарда — по данным перфузионной ОФЭКТ, синхронизированной с эхокардиографией. Функциональная активность почечной паренхимы значимо снизилась только у пациентов с СД 2 типа (критерий χ^2 Пирсона, $p = 0,03$ при сопоставлении с группой сравнения). СКФ по Gates в обеих опытных группах была значимо ниже, чем в группе сравнения (U-критерий Манна–Уитни, $p = 0,0004$ и $p = 0,0002$ соответственно), а в группе пациентов с СД 2 типа — ниже, чем в группе пациентов с нарушением толерантности к глюкозе ($p = 0,0004$). Для показателя СКФ по Кокрофту–Голту наблюдали те же закономерности, но различия при сопоставлении группы пациентов с нарушением гликемии и группы сравнения были недостоверными ($p = 0,08$). Корреляция между значениями СКФ, полученными разными методами, во всех группах была средней силы (коэффициент корреляции Спирмена $r = 0,53$ при $p = 0,038$). Рубцовые повреждения миокарда в обеих опытных группах выявлялись достоверно чаще, чем в группе сравнения, но различия по показателю между опытными группами были незначимыми.

Ключевые слова: сахарный диабет, нарушение толерантности к глюкозе, динамическая нефросцинтиграфия, перфузионная томосцинтиграфия миокарда

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Diabetes mellitus (DB) is a common chronic disease. Its main symptom is hyperglycemia induced by defective insulin synthesis/secretion, insulin deficiency or a combination of both [1–3]. DB is a serious medical and social issue due to its high prevalence, increasing incidence, chronicity and worrying disability rates. According to World Health Organization reports, there are currently about 250 million diabetics worldwide. This number is expected to reach 380 million by the year 2025 [4].

DB can be classified based on various criteria, including its complications, such as diabetic micro- and macroangiopathy, arthro-, polyneuro-, ophthamo-, retino-, nephro-, and encephalopathy [5]. Microvascular and macrovascular pathologies are among the most common DB complications; the former occur in smaller blood vessels and induce nephropathy, the latter occur in medium and large vessels and are equivalent to coronary artery disease [6–9].

Early detection of diabetic complications requires a complex approach. Renal damage is most often discovered by clinical laboratory tests (manifesting through microalbuminuria) or by ultrasound imaging (altered parenchymal echogenicity or enlarged kidneys). Macroangiopathy (affected coronary arteries) can be detected using standard diagnostic techniques normally employed to detect coronary artery disease, such as cardiac markers, functional techniques (electrocardiography, echocardiography, exercise tolerance tests) and radiation techniques (coronary angiography, or in other words imaging of coronary arteries). These methods are used to assess structural and morphological changes in the organs and tissues in symptomatic patients. To verify angiopathies in asymptomatic patients with inconspicuous structural changes, state-of-art imaging techniques are used, such as single-photon emission computed tomography (SPECT) and positron emission tomography [10, 11].

Patients with impaired glucose tolerance constitute a separate group. A 2-hour glucose tolerance test reveals elevated glucose blood levels (from 7.8 to 11.1 mmol/L). Temporary increase in blood sugar leads to micro- and macroangiopathy occurring even before patients can be diagnosed with diabetes [12]. Therefore, individuals with impaired glucose tolerance should be monitored very closely as they are at risk of renal pathology: as the disease progresses and type 2 diabetes develops, the vessels of the kidneys will be affected in the first place [13]. The left ventricular myocardium may also be affected even if macroangiopathy has not yet been detected by routine tests [14]. Besides, in patients with impaired glucose tolerance, temporary increase in blood sugar can be sufficient to cause damage to the endothelium of small vessels [15]. Also, there is a risk of late cardiac events, such as silent myocardial ischemia, early infarction, etc. [16]. In patients with impaired glucose tolerance, results of radionuclide scans such as myocardial perfusion imaging (scintigraphy) can influence the choice of treatment. It is known that radionuclide diagnostic techniques are assistive in detecting functional damage to the organs in the early stages of the disease [17].

In light of the above, the aim of our study was to detect the diagnostic effectiveness of radionuclide technique, namely dynamic renal scintigraphy and myocardial perfusion SPECT synchronized with ECG at rest, for the detection of micro- and macroangiopathy of the kidneys and the heart in patients with impaired glucose tolerance and type 2 diabetes.

METHODS

We conducted a retrospective analysis of medical records and scintigrams of 180 patients who had been admitted to

the Central Clinical Hospital of RAS in 2011–2016. The study included patients diagnosed with type 2 diabetes mellitus or with impaired glucose tolerance who had undergone dynamic renal scintigraphy (DRS) and myocardial perfusion imaging (SPECT). Exclusion criteria applied were as follows: previously diagnosed myocardial infarction, signs of myocarditis, chronic renal insufficiency, the absence of one kidney, congenital renal anomalies (horseshoe kidney, L- and S-shaped kidney), tumors and severe co-morbidities (multiple metastases, stage 4–5 chronic kidney disease).

Of 180 patients (mean age of 69.0 ± 11.6 years, male to female ratio of 1 : 0.8), 83 were diagnosed with type 2 diabetes mellitus (group 1) and 52 had impaired glucose tolerance and were not diagnosed with diabetes (group 2); 45 patients with normal blood sugar referred to hospital for other reasons (pain associated with angina, arrhythmias of unclear etiology, difficulty urinating, girdling pain in the loin) were included in the control group. The participants were divided into subgroups depending on the type of radionuclide imaging technique applied; their demographic characteristics are presented in Table 1. Scans were performed using the Infinia 4 Hawkeye SPECT/CT scanners (General Electric, USA). Blood chemistry tests were performed 3 days before and after the scan to measure troponin, creatinine and glycated hemoglobin levels. Also, echocardiography (ECG) records were analyzed to obtain information about the ejection fraction (EF).

Dynamic renal scintigraphy can be used to assess individual renal function and to study the concentrating ability and excretory function of the kidneys impaired by defective microcirculation. We used DRS to measure relative renal uptake of a radiotracer (RT), glomerular filtration rate (GFR) by Gates method [18], the maximum amplitude of the time-activity curves for both kidneys normalized to the administered RP dose, and its mean value. To estimate the volume of the functional parenchymal tissue, scintigrams and renogram curves were analyzed; the curve peak indicated maximum RT accumulation [19]. Based on the obtained data, the volume of the functional renal tissue was considered normal or reduced.

Prior to DRS, patients received an i. v. bolus injection of 200 MBq technetium-labeled diethylenetriamine pentaacetate, or ^{99m}Tc -DTPA (Pentatech, ^{99m}Tc by Diamed, Russia). DRS was recorded for 30 minutes at 1 frame per minute; renal angiography was performed in parallel. In total, 60 frames (1 second long each) of the vascular phase were recorded immediately after RT administration [18]. To calculate GFR, pre- and post injection syringe activity was recorded for 10 seconds (a 128×128 matrix was used); the difference in the activity was calculated from the obtained scintigrams. The total accumulation of RT was estimated based on the renogram curve between minutes 2 and 3 after the injection [18, 19]. Dynamic kidney images were reconstructed using Xeleris 2.1 workstation (General Electric) and Renal Analysis software (Emory University Hospital, USA). An example of the reconstruction process is shown in Fig. 1.

In addition, GFR was calculated based on serum creatinine using the Cockcroft–Gault equation:

$$\text{GFR} = K \times \frac{(140 - \text{age}) \times \text{weight}}{\text{serum creatinine}},$$

where K is 1.23 for men and 1.05 for women [20].

Patients who were ordered a myocardial perfusion scan received 750 MBq of methoxyisobutyl isonitrile (Technetrit, ^{99m}Tc by Diamed) 40 min before the scan. ECG-gated SPECT images were acquired from 120 projections (60 per detector); acquisition time per projection was 32 seconds. Images were

Table 1. Demographic characteristics of patient subgroups based on the radionuclide diagnostic technique applied

Parameter	Dynamic renal scintigraphy			Myocardial perfusion SPECT		
	Group 1 (type 2 DM)	Group 2 (IGT)	Controls	Group 1 (type 2 DM)	Group 2 (IGT)	Controls
Number of patients n	25	17	20	58	35	25
Mean age, years (M ± SD)	71.7 ± 9.0	67.0 ± 14.4	67.0 ± 11.9	69.0 ± 9.8	67.9 ± 11.9	70.7 ± 12.3
Male to female ratio	1 : 0.4	1 : 0.7	1 : 0.6	1 : 0.9	1 : 0.4	1 : 1.1

Abbreviations: type 2 DM — type 2 diabetes mellitus; IGT — impaired glucose tolerance; M — arithmetic mean; SD — standard deviation.

reconstructed using Quantitative Gated SPECT/Quantitative Perfusion SPECT software (Cedar-Sinai Hospital, USA). Myocardial pathologies were indicated by perfusion defects on polar maps, reduced regional contractility in the same area and myocardial damage >5 %. An example of the reconstruction process is shown in Fig. 2. The same software was used to evaluate blood flow in the coronary arteries by measuring end systolic (ESV) and end diastolic (EDV) volumes (ml) and ejection fraction calculated as (EDV-ESV)/ESV.

Data were statistically processed using STATA-13 MP (StatCorp LP, USA). Due to a small size of the samples and the absence of normal distribution in them evaluated by the Shapiro–Wilk test, we used nonparametric statistical methods (Mann–Whitney U, Wilcoxon matched-pairs test, Spearman’s correlation, Pearson’s chi-squared test; see RESULTS for further details). Difference was considered significant at $p < 0.05$.

RESULTS

The analysis of scintigrams revealed reduced amount of functional renal parenchyma in almost all patients with type 2 DB (group 1) in contrast to the controls (Pearson’s chi squared test was applied; $p = 0.03$); while patients with impaired glucose tolerance (group 2) demonstrated no significant reduction of the renal parenchymal volume (Pearson’s chi squared test was applied; $p = 0.23$).

The Gates GFR was lower in groups 1 and 2 than in the controls (Mann–Whitney U-test was applied; p was 0.0004 and 0.0002, respectively). It was also lower in patients from group 1 compared to patients from group 2 (42.7 ± 15.9 vs. 50.4 ± 16.5 at $p = 0.0004$) (Table 2). The Cockcroft–Gault GFR was lower in patients from group 1 than in the controls (Mann–Whitney U-test was applied; $p = 0.003$). Group 2 also demonstrated lower values but the difference between this group and the controls was insignificant ($p = 0.08$). The Cockcroft–Gault GFR was lower in patients with type 2 DB in comparison with group 2 patients (58.2 ± 23.3 vs. 73.1 ± 25.9 at $p = 0.005$).

In group 1, the Cockcroft–Gault GFR was significantly higher than the Gates GFR (Wilcoxon test was applied; $p = 0.023$). The same pattern was observed in group 2 ($p = 0.02$). Inside the control group, the difference was statistically insignificant ($p = 0.243$). The correlation between GFR values obtained by different techniques was moderate and statistically significant in all groups (Spearman’s $r = 0.53$ at $p = 0.038$).

The Mann–Whitney U-test showed that group 1 patients had higher levels of glycated hemoglobin and troponin than the controls (p was 0.01 and 0.0007, respectively) (Table 3). The same pattern was observed when comparing group 2 and the controls (p was 0.027 and 0.0069, respectively). When comparing groups 1 and 2, slightly higher levels of glycated hemoglobin were observed in patients with type 2 diabetes (6.96 ± 2.03 vs. 6.10 ± 0.80 at $p = 0.025$). Within these groups, the difference in troponin levels was unreliable ($p = 0.38$).

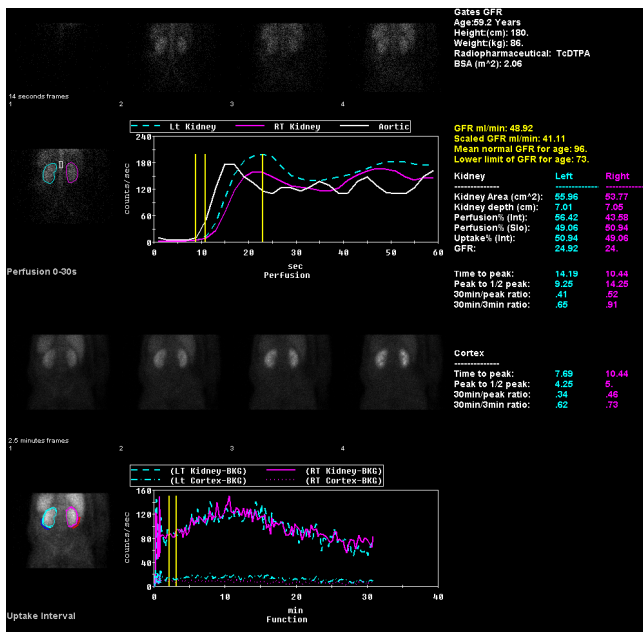


Fig. 1. Reconstruction of kidney images obtained by dynamic renal scintigraphy using Xeleris 2.1 working station (General Electric, USA) and Renal Analysis software (Emory University Hospital, USA)

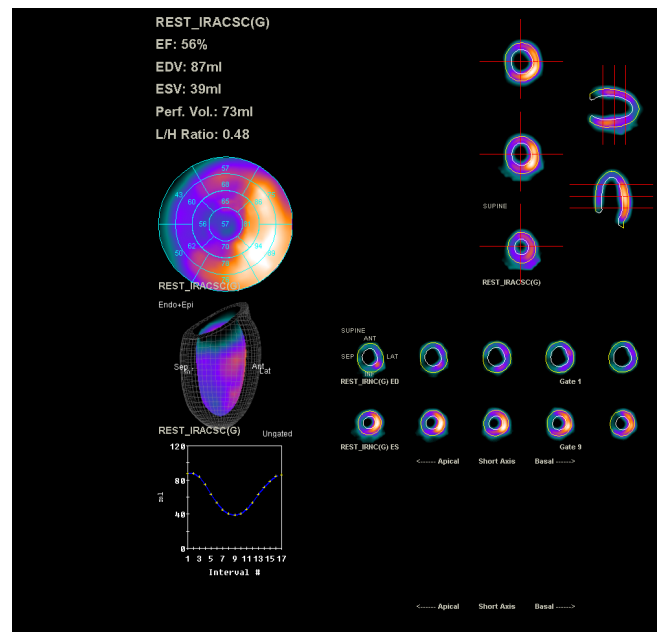


Fig. 2. Reconstruction of myocardium images obtained by perfusion SPECT using Quantitative Gated SPECT/Quantitative Perfusion SPECT software (Cedars-Sinai Hospital, USA)

Myocardial perfusion SPECT and ECG revealed no significant difference between patients with normal glucose levels and patients with impaired glucose tolerance with respect to the ejection fraction used to assess the myocardial contractile function (Table 3). ECG revealed a statistically significant EF reduction in patients with type 2 DM compared to the controls (Mann-Whitney U was applied; $p = 0.01$). Myocardial perfusion SPECT did not reveal any significant difference between the groups in this respect. Also, no significant difference in EF was observed when comparing groups 1 and 2 using the data from both scan types.

The results of myocardial perfusion SPECT showed that patients with type 2 DM had a higher prevalence of myocardial scarring (30 %) and greater lesion extent (6.4 ± 10.8 %) than the controls (0 and 0.06 ± 1.1 % $p = 0.02$ with Pearson's chi-squared test applied and at $p = 0.02$ with Mann-Whitney U-test applied, respectively) (Table 3). The same pattern was observed when comparing patients with impaired glucose tolerance and the controls ($p = 0.001$ for both statistical methods). When comparing groups 1 and 2, no significant difference was observed.

DISCUSSION

Similar patterns of changing glomerular filtration rates in patients with impaired glycemia and patients with type 2 diabetes prove our hypothesis about the renal endothelial dysfunction in the early stages of the disease, which is also confirmed by other works [9, 13, 15, 16].

The assessment of the renal function by means of dynamic renal scintigraphy in patients with impaired glucose tolerance revealed a tendency for reduced GFR (based on the analysis of time-activity curves), while their creatinine levels remained normal. It means that the Cockcroft-Gault equation for GFR calculation in such patients is of no informative value. We believe that such patients should undergo DRS (fasting is required) for the primary assessment of the renal dysfunction and deciding on the adequate protective therapy. It is advisable to consider

other renal conditions besides microangiopathy that may be present in a patient and lead to reduced functional activity of the kidneys, which in our case was a limitation. It is also known that in cases of severe renal dysfunction with GFR <15 ml/min, the outcome of the Gates measurement is unreliable due to decreasing count rates [18, 21].

In our study, myocardial perfusion SPECT detected even minimal damage to the left ventricular myocardium and helped to assess lesion sizes in the earliest stages of the disease in patients with impaired glucose tolerance; note that in those patients troponin levels were normal. However, ECG-gated perfusion SPECT can also detect defective perfusion, lesions and scars unrelated to impaired glycemia, which means that additional diagnostic techniques will be required to verify the diagnosis and medical records will have to be considered. This restricts the use of myocardial perfusion SPECT.

Due to the exposure to radiation during radionuclide scans, it is important to make sure they are really necessary. Here, the criteria may be such risk factors for cardiovascular disease as elevated cholesterol levels, smoking, arterial hypertension, obesity, hypersthenic habitus.

CONCLUSIONS

In the course of our study that employed dynamic scintigraphy and myocardial perfusion SPECT, we discovered changes in renal and cardiac tissues in patients with type 2 diabetes, as well as in patients with impaired glucose tolerance. We recommend that dynamic renal scintigraphy should be ordered for patients with impaired glucose tolerance for early detection of renal tissue dysfunction and vascular pathologies. Myocardial perfusion SPECT may be recommended for patients at risk of cardiovascular disease.

A limitation to this study was strict inclusion criteria resulting in small patient samples. Our research continues. So far, the prognostic role of radionuclide diagnostic techniques and their application as a treatment monitoring tool remain unclear. A multicenter prospective study of sufficient duration would be a solution.

Table 2. Glomerular filtration rates calculated using Gates method (dynamic renal scintigraphy) and Cockcroft-Gault equation

Method	Group 1 (type 2 DM, n = 25)	Group 2 (IGT, n = 17)	Controls (n = 20)
Glomerular filtration rate calculated using Cockcroft-Gault equation, ml/min	58.2 ± 23.3 (56.9)	73.1 ± 25.9 (71.4)	80.1 ± 23.7 (79.0)
Glomerular filtration rate calculated using Gates method (dynamic renal scintigraphy), ml/min	42.7 ± 15.9 (44.0)	50.4 ± 16.5 (57.3)	71.9 ± 25.7 (69.8)

Abbreviations: type 2 DM — type 2 diabetes mellitus; IGT — impaired glucose tolerance. Data are presented as M ± SD (μ), where M is arithmetic mean, SD is standard deviation, μ is median.

Таблица 3. Результаты биохимического анализа крови и перфузионной ОФЭКТ миокарда

Group	Parameter					
	Glycated hemoglobin (HbA1C), %	Troponin (Tns), pg/ml	Ejection fraction measured by echocardiography, %	Ejection fraction measured by myocardial perfusion SPECT, %	Scarring prevalence, %	Lesion extent, %
Group 1 (type 2 DM)	6.96 ± 2.03 (6.90)	30.9 ± 104.8 (8.8)	50.2 ± 8.8 (52.0)	56.5 ± 14.2 (59.0)	30	6.4 ± 10.8 (1.0)
Group 2 (IGT)	6.10 ± 0.80 (6.10)	29.6 ± 82.5 (10.0)	52.9 ± 9.2 (56.0)	59.9 ± 15.9 (66.0)	36.3	6.2 ± 10.5 (1.0)
Controls	5.07 ± 0.60 (5.10)	6.6 ± 3.6 (5.5)	56.7 ± 4.4 (58.0)	64.2 ± 10.6 (61.0)	0	0.6 ± 1.1 (0)

Abbreviations: type 2 DM — type 2 diabetes mellitus; IGT — impaired glucose tolerance. Data are presented as M ± SD (μ), where M is arithmetic mean, SD is standard deviation, μ is median.

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