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THE MAGNETIC RESONANCE IMAGING FINDINGS OF MYOCARDIAL MICROVASCULAR CIRCULATORY DISORDER IN PATIENTS WITH IMPAIRED GLUCOSE TOLERANCE

BOZULMUŞ GLUKOZ TOLERANS HASTALARINDA MYOKARDİAL MİKROVASKÜLER DOLAŞIM BOZUKLUĞUNUN MANYETİK REZONANS GÖRÜNTÜLEME BULGULARI

Karabekir Ercan[1], Abdullah Kandemir[2]
[1]Ankara City Hospital, Department of Radiology, Ankara
[2]Merzifon Kara Mustafa Pasa Hospital, Department of Radiology, Amasya

Yazışma Adresi / Correspondence:
Karabekir Ercan (e-mail: karabekirercan@gmail.com)

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Ankara Yıldırım Beyazıt University Faculty of Medicine
Department of Family Medicine

Öz

Amaç: Bozulmuş glukoz toleransı (BGT) olan hastalarda manyetik rezonans görüntüleme (MRG) ile MRG-perfüzyon ile miyokardiyal kan akımı değerlendirildi. Mikrovasküler obstrüksiyon varlığı ve iskemik kalp hastalığı sıklığı araştırıldı.
Materyal ve Metot: Çalışmamıza IGT'li 20, tip 2 diabetes mellituslu (DM) 16 hasta ve normal MR bulguları olan 15 hasta dahil edildi. Tüm hastalar supin pozisyonda 1.5 Tesla MR ile vücut koili kullanılarak muayene edildi. İlk olarak, duvar hareketlerini görmek, duvar kütlesini ve sol ventrikül ejeksiyon fraksiyonunu hesaplamak için B-TFE sine sekansları elde edildi. Daha sonra diğer kardiyak miyokard hastalıklarını dışlamak için "siyah kan" T2 ağırlıklı ve STIR sekansları alındı. İlk geçiş perfüzyonunu değerlendirmek için 0.2 mmol/kg Gd-DTPA'nın intravenöz uygulanmasıyla bazal, midventriküler ve apikal kısa aks sekansları elde edildi. Ardından "inversiyon recovery GRE" sekansı ile enjeksiyondan 10 dakika sonra geç opaklanma bulguları elde edildi.
Bulgular: Miyokard dokusunda ilk geçiş perfüzyonunda tepe kontrastlanma ve birikmiş kontrastlanma araştırıldığında, BGT ve tip 2 DM'li olgularda benzerlik saptandı. Ancak sağlıklı kontrol grubuna göre anlamlı farklılıklar tespit edildi. İlk geçiş perfüzyonunda; kontrast madde gelme zamanı ile miyokard dokusunda kontrast madde artışının tepe noktası karşılaştırıldığında, bu gruplar arasında fark görülmedi. Ayrıca sol ve sağ ventrikül sistolik fonksiyonları gruplar arasında benzerdi.
Sonuç: BGT'li olgularda miyokardiyal mikrovasküler dolaşım bozuklukları koroner arter hastalığı olmaksızın erken evrelerde ortaya çıkabilir. Bu tür vakalarda kardiyak MRG önemli bir seçim olabilir.

Anahtar Kelimeler: Manyetik rezonans görüntüleme, miyokardiyal mikrovasküler dolaşım bozukluğu, bozulmuş glukoz tolerans.

Abstract

Objectives: Myocardial blood flow was evaluated with magnetic resonance (MR) perfusion in the patients with impaired glucose tolerance (IGT), and the existence of microvascular obstruction and risk for cardiac diseases were researched. In addition, the wall motion, wall mass (gram), and viability of the left ventricle, and the systolic function of both ventricles were evaluated.
Materials and Methods: Twenty patients with IGT, 16 patients with type 2 diabetes mellitus (DM) and 15 patients with normal MR findings were included in our study. All patients were examined in the supine position using a body coil with 1.5 Tesla MR. Firstly, images B-TFE cine sequences to see the wall motions, calculate the wall mass and the left ventricular ejection fraction. "Black blood" T2-weighted and STIR sequences were then taken to exclude other cardiac myocardial diseases. Basal, midventricular, and apical short-axis sequences were obtained by intravenous administration of 0.2 mmol/kg Gd-DTPA to evaluate first-pass perfusion. And late opacification findings were obtained 10 minutes after the injection with the "inversion recovery GRE" sequence.
Results: When peak enhancement and accumulated enhancement in the first pass perfusion of myocardial tissue were investigated, the similarity was found in cases with IGT and type-2 DM. However, significant differences were found compared to the healthy control group. In the first pass perfusion; When contrast agent arrival time and the peak of contrast agent increase in myocardial tissue were compared, no difference was observed between these groups. In addition, left and right ventricular systolic functions were similar between groups.
Conclusion: In the cases with IGT, myocardial microvascular circulation disorders can emerge in early phases without the presence of coronary artery disease. In these kinds of cases, cardiac MRI can be an important choice.

Keywords: Magnetic resonance imaging, myocardial microvascular circulatory disorder, impaired glucose tolerance.

Introduction

Diabetes Mellitus (DM) is an important risk factor for cardiovascular diseases. Silent myocardial ischemia, painless myocardial infarct (MI), and heart failure are more common in diabetic patients when compared to the normal population. DM increases morbidity and mortality by facilitating atherosclerosis with several mechanisms.[1] The patients with impaired glucose tolerance (IGT) are accepted as prediabetic patients, and it was established that the risk of coronary artery disease (CAD) is increased in these patients with coronary angiography.[2, 3, 4] The first finding of CAD is macrovascular obstruction, and this can not be demonstrated with coronary angiography. The microvascular obstruction could be evaluated by cardiac magnetic resonance (MR) imaging with the "first pass" perfusion technique, and as we know, there is no published paper about the evaluation of microvascular obstruction in patients with IGT.[5-7]

In this study, the existence of a microvascular obstruction and the risk for cardiac diseases are searched by evaluating the microvascular blood flow with cardiac MRI in patients with IGT.

Materials and Methods

Study Groups

Forty-three patients who had not any known coronary artery disease, dyspnea, hypertension, or abnormal ECG findings were referred for cardiac MR imaging from endocrinology to radiology department, one obese patient and three patients with claustrophobia were excluded from the study, and three patients did not accept MR imaging. Patients' HbA1c levels, blood pressures, and blood lipid levels were reviewed from past records, and patients with normal values were included in the study. No abnormal findings were found in the echocardiographic examinations of the patients.

Eventually, 16 diabetic patients and 20 patients with IGT were included in the study. For the control group, 15 normal patients who had cardiac MRI for different indications were included. Twelve of the patients with IGT were men, and 8 of them were women; 10 of diabetic patients were men, and 6 of them were women, 9 of control group patients were man and 6 of them were women. The smoking history was asked of the selected patients.

MRI protocol

All of the patients were examined in the supine position by using a body coil (SENSE body coil) with 1.5 Tesla MRI (Philips Achieva, Philips Medical Systems, Best, The Netherlands). The contrast material administration was done via the right antecubital vein in all study patients. 25 mg beta-blocker (Beloc, metoprolol) was given to the patients in whom heart rate was >80 beats/min before the examination. The heart rate, ECG, and respiration of patients were observed during the process. [8,9]

First, reference images in axial, coronal, and sagittal planes were obtained by the Balanced Turbo Field Echo (B-TFE) sequence. A parallel imaging technique was used for all sequences. The long and short axis of the left ventricle and four-chamber cine images were achieved with ECG triggered and breath-hold B-TFE sequence (TR/TE: 3.2/1.6 flip angle: 60°) to see the wall motions and to calculate the wall mass and ejection fraction. Then, "black blood" T2 weighted (TR/TE: 2000/60, flip angle: 90°) and STIR (TR/TE: 2000/60, flip angle: 90°) sequences were obtained to exclude the other cardiac myocardial diseases.

ECG-triggered and breath-hold "balance" TFE (TR/TE: 2.4/1.2 flip angle: 50°) sequence was obtained by administration of 0.20 mmol/kg Gd-DTPA intravenously to evaluate the first-pass perfusion. Long and short-axis images of basal, midventricular, and apical segments were achieved with ECG-triggered and breath-hold inversion recovery GRE sequence by selecting the optimal "time of inversion" (TI: 220-300ms) of each patient 10 minutes after the injection to suppress the myocardial signals.[5,10,11]

Data analysis

The MR images were transferred to the work station (Philips View Forum Extended MR Workspace), and analytic processes were done with the "Cardiac MR Package" program. The values of EF, SV, cardiac output, cardiac index, and wall mass of left ventricle were obtained by drawing the endocardial and epicardial contour manually on left ventricle short-axis cine images and by analyzing the results automatically (Figure 1).

The values of end-diastolic volume, end-systolic volume, and EF of the right ventricle were obtained by drawing the endocardial contour manually on the four-chamber images and by analyzing the results with the ALEF (Area Length of EF) technique automatically. The viability, cine images, and first-pass perfusion images were evaluated with the short axis 18 segments (left ventricle basis 6, midventricular six, and apical 6) (Figure 2 and 3). The inner and outer parts of each segment were evaluated one by one. The values of time to arrive, time to peak, peak enhancement, and accumulated enhancement were measured quantitatively (Figure 4).

Statistical Analysis

The demographic features of the patients were summarized with fundamental statistics. Mean and standard deviation values were used for numerical parameters, and if necessary, minimum and maximum values were also used. Categorical variables were indicated with the number and percentage of the patients.

P < 0.05 was accepted as statistically significant. The statistical analysis was made with the "SPSS 16.0" program.

Post-hoc analysis

Kolmogorov-Smirnov test was used to determine the distribution of continuous variables, ANOVA test was used to compare the parameters which show a normal distribution, and posthoc Tukey test was used for secondary comparisons. Cross-table statistics were used for the comparison of categoric variables (Chi-square and Fischer tests).

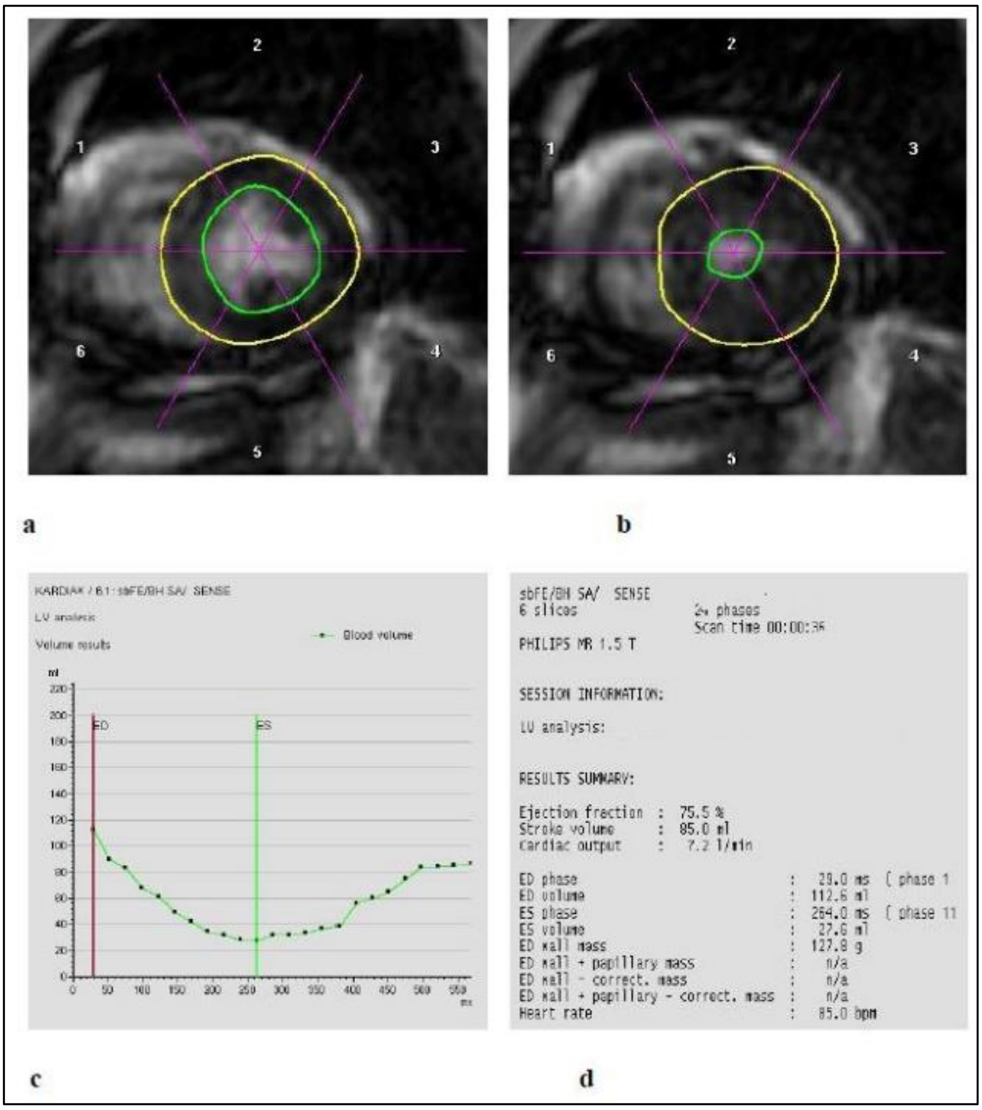

Figure 1. a, b. Contour detection of the left ventricle at systolic and diastolic phase, c. systolic function curve of the left ventricle, d. the values of systolic functions and the wall mass of the left ventricle.

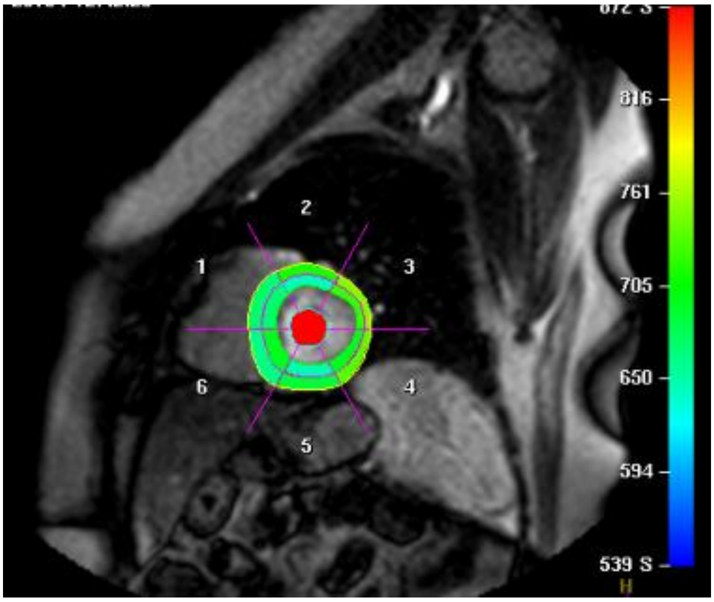

Figure 2. Midventricular perfusion of the healthy individual. (Blue color indicates the perfusion restriction. The red and yellow colors represent normal and near-normal perfusion.) Blue color coding was not seen due to the normal perfusion.

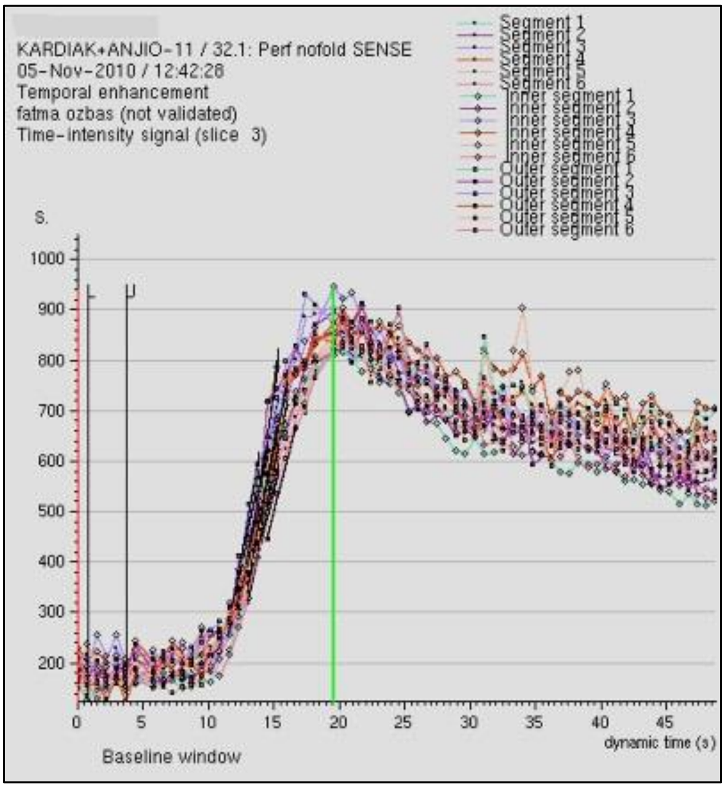

Figure 3. The curve of first-pass perfusion at the midventricular level of a healthy individual. It shows the intensity of contrast material passing through the inner and outer walls of each segment.

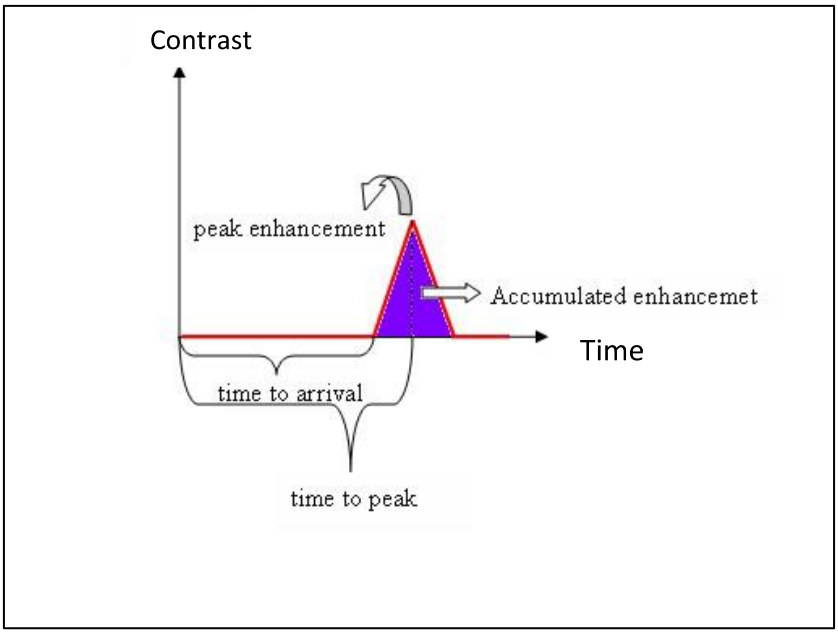

Figure 4. The contrast-time graphic of myocardial tissue on the first pass perfusion examination.

Results

Cardiac MR examination was performed on 20 patients with IGT, 16 diabetic patients, and 15 normal individuals successfully. The mean age was 53.90±7.25 in patients with IGT, 51.69±8.81 in diabetic patients, and 48.60±6.76 in the control group, respectively. The mean BMI value was 29.65±4 in patients with IGT, 30.19±3.51 in diabetic patients, and 30.34±3.07 in the control group, respectively. Male patients consist of 60.78 % (n=31) and female patients consist of 39.22 % (n=20) in study group. The smoking rate was 25% in patients with IGT, 31.25 % in diabetic patients, and 20% in the control group, respectively.

There was no statistically significant difference in terms of the mean age between the groups (p=0.138). The groups were similar in terms of gender distribution (p=0,986). There was no significant statistical difference between the groups in terms of smoking rates (p=0.771). The groups were similar in terms of the mean BMI (p=0.835) (Table 1).

The Value of Peak Enhancement at First Pass Perfusion

When the values of peak enhancement of contrast material at myocardium were evaluated after the first pass perfusion study of the patients, the cut-off signal value was detected as 418s by using the ROC analysis.

When the inner part measures of the apical wall of the patient groups were compared, 6.66% of 120 segments were below the normal values in the IGT group, and this ratio was 6.25% of 96 segments in the DM group.

Table 1. The demographic features of groups (data: mean ± the standard deviation, percent of the case)

	IGT	DM	Control group	p
Age	53.90±7.25	51.69±8.81	48.60±6.76	0.138
Gender (man/woman)	12/8 (60/40)	10/6 (62.50/37,50)	9/6 (60/40)	0.986
Smoking (smoker/non-smoker)	5/15 (25/75)	5/11 (31.25/68.75)	3/12 (20/80)	0.771
BMI	29.65±4	30.19±3.51	30.34±3.07	0.835

Table 2. Comparison of peak enhancement of myocardium (data; percent of the case)

	IGT	DM	The control group	p
Inner apical Wall (normal/patient)	112/8 (93.33/6.66)	90/6 (93.75/6.25)	90/0 (100/0)	IGT- DM=0.902 IGT-C=0.011 DM-C=0.029
Outer apical wall (normal/ patient)	114/6 (95/5)	88/8 (91.66/8.33)	90/0 (100/0)	IGT- DM=0.323 IGT-C=0.039 DM-C=0.007
Inner midventricular wall (normal/ patient)	112/8 (93.33/6.66)	91/5 (94.79/5.20)	90/0 (100/0)	IGT- DM=0.902 IGT-C=0.011 DM-C=0.029
Outer midventric. wall (normal/ patient)	120/0 (100/0)	96/0 (100/0)	90/0 (100/0)	1.000
Inner basal wall (normal/ patient)	110/10 (91.66/8.33)	88/8 (91.66/8.33)	90/0 (100/0)	IGT- DM=1.000 IGT-C=0.006 DM-C=0.007
Outer basal wall (normal/ patient)	110/10 (91.66/8.33)	90/6 (93.75/6.25)	90/0 (100/0)	IGT- DM=0.561 IGT-C=0.006 DM-C=0.029

There was not an abnormal value in any segments of the control group. The difference between the control group and patient group, including DM and IGT groups, was statistically significant since there was not any statistical difference between IGT and DM groups (p=0.011, p=0.029).

There was also not a significant statistical difference between IGT and DM groups in terms of the outer part values of apical walls (p=0.323). The abnormal values of IGT and DM were higher than those of the control group significantly (p=0.039 and p=0.007, respectively).

There was not any statistical difference between IGT and DM groups in terms of the inner part values of midventricular walls since the difference between both of these groups, and the control group was statistically significant (p=0.011 and p=0.029, respectively). There was not any statistically significant difference between the groups in terms of the outer part of the midventricular walls (p=1.000).

When the inner part values of basal walls were evaluated, there was not a significant statistical difference between BGT and DM groups since the difference was statistically significant between both these groups and the control group (p=0.006 and p=0.007, respectively). There was also not any significant statistical difference between the IGT and DM groups in terms of the outer part values of the basal walls since the difference between both these groups and the control group was statistically significant (p=0.006 and p=0.029) (Table 2).

The Value of Accumulated Enhancement at First Pass Perfusion

When the values of peak enhancement of contrast material at myocardium were evaluated after the first pass perfusion study of the patients, the cut-off signal value was detected as 2412s by using the ROC analysis. When the inner part measures of the apical wall of the patient groups were compared, 6.70% of 120 segments were below the normal values in the IGT group, and this ratio was 6.20% of 96 segments in the DM group. There was not an abnormal value in any segments of the control group. The difference between the control group and patient group, including DM and IGT groups, was statistically significant since there was not any statistical difference between IGT and DM groups (p=0.011, p=0.029).

The Value of Accumulated Enhancement at First Pass Perfusion

When the values of peak enhancement of contrast material at myocardium were evaluated after the first pass perfusion study of the patients, the cut-off signal value was detected as 2412s by using the ROC analysis. When the inner part measures of the apical wall of the patient groups were compared, 6.66% of 120 segments were below the normal values in the IGT group, and this ratio was 6.25% of 96 segments in the DM group. There was not an abnormal value in any segments of the control group. The difference between the control group and patient group, including DM and IGT groups, was statistically significant since there was not any statistical difference between IGT and DM groups (p=0.011, p=0.029).

There was also not a significant statistical difference between IGT and DM groups in terms of the outer part values of apical walls (p=0.323). The abnormal values of IGT and DM were higher than those of the control group significantly (p=0.039 and p=0.007, respectively).

There was not any statistical difference between IGT and DM groups in terms of the inner part values of midventricular walls since the difference between both of these groups and the control group was statistically significant (p=0.031 and p=0.014, respectively). There was not any statistically significant difference between the groups in terms of the outer part of the midventricular walls (p=0.561).

When the inner part values of basal walls were evaluated, there was not a significant statistical difference between IGT and DM groups since the difference was statistically significant between both these groups and the control group (p=0.021 and p=0.002, respectively). There was also not any significant statistical difference between the IGT and DM groups in terms of the outer part values of the basal walls since the difference between both these groups and the control group was statistically significant (p=0.005 ve p=0.003)

Since there was not any significant difference between IGT and DM groups in terms of the outer part values of the basal wall, there was a statistically significant difference between the control group and both of those groups (Table3).

Table 3. Comparison of the accumulated contrast amount values (data, percent of case)

	IGT	DM	The control group	p
Inner apical wall (normal/ patient)	112/8 (93.33/6.66)	90/6 (93.75/6.25)	90/0 (100/0)	IGT - DM=0.902 IGT -C=0.011 DM-C=0.029
Outer apical wall (normal/ patient)	114/6 (95/5)	88/8 (91.66/8.33)	90/0 (100/0)	IGT - DM=0.323 IGT -C=0.039 DM-C=0.007
Inner midventricular wall (normal/ patient)	112/8 (93.33/6.66)	89/7 (92.70/7.30)	90/0 (100/0)	IGT - DM=0.858 IGT -C=0.031 DM-C=0.014
Outer midventricular wall (normal/ patient)	118/2 (98.33/1.66)	92/2 (97.87/2.13)	90/0 (100/0)	0.561
Inner basal wall (normal/ patient)	113/7 (94.16/5.83)	86/10 (89.58/10.41)	90/0 (100/0)	IGT- DM=0,214 IGT-C=0.021 DM-C=0.002
Outer basal wall (normal/ patient)	101/9 (91.81/8.19)	87/9 (90.62/9.38)	90/0 (100/0)	IGT- DM=0.762 IGT-C=0.005 DM-C=0.003

Time to peak and time to arrive at first pass perfusion

When "time to arrival" and "time to peak" were evaluated after the first pass study of patients, there was not a significant statistical difference between the groups.

Delayed Enhancement

There was not any statistically significant difference between the groups in the evaluation of delayed enhancement (10th min) by using the transmural index of the study patients. The enhancement of contrast of more than 50% was adopted as abnormal.

The evaluation of cine images

The left ventricle EF, left ventricle SV, left ventricle cardiac output, left ventricle cardiac index, left ventricle wall mass, right ventricle EDV, right ventricle ESV and right ventricle EF were assessed in study patients by cardiac MR. There was not a significant difference between the groups.

Discussion

Cardiac MR examination provides a comprehensive assessment of the heart since it is non-invasive, has high tissue contrast and spatial resolution, and has no risk of ionizing radiation exposure.[11,12] Cardiac MRI examination allows the characterization of myocardial tissue, evaluation of left ventricle volume and mass, the distinction between the infarct area and the live tissue.[21] It could evaluate the transmural extension of the non-viable tissue, regional wall motion abnormalities, and systolic diastolic wall thickness.[13, 14]

The first pass perfusion is important in ischemic diseases. Al-Saadi et al. studied first-pass perfusion MRI with 15 patients who had coronary artery disease and five normal individuals. According to the study results, first, pass perfusion has high diagnostic accuracy in terms of the diagnosis of coronary artery disease.[7,15,16] To the best of our knowledge, there is not any published report which evaluates microvascular circulation with cardiac MR examination in patients with DM or IGT, and our study will be the first study on this topic.[9,17,18]

Contrast accumulation decreased in some myocardial segments that had perfusion defects due to microvascular obstruction.[7,10] As a result of this condition, contrast enhancement decreased in those segments, and peak enhancement and accumulated enhancement values were below the cut-off values.

However, perfusion defects did not affect the "time to arrival" and "time to peak" values. In our study, there was no significant statistical difference in accumulated enhancement, and peak enhancement values between the patients with IGT and diabetic patients since the difference was significant between the normal group and both of those two groups. These findings indicate a perfusion defect in the early phase due to microvascular obstruction in patients with IGT and in diabetic patients. Thus, myocardial supply could be impaired in patients with IGT before the development of DM, and these patients should be followed up in terms of cardiac risk. Schinner et al. performed coronary angiography in 1,394 patients without the diagnosis of DM. They identified coronary artery disease (CAD) in 76% of those patients. They detected DM in 15% of patients, impaired fasting glucose (IFG) in 20% of patients, IGT in 13% of them, and both IFG and IGT in 20% of the patients. They indicated that the risk of CAD increase with the rise of fasting and postprandial blood glucose.[2] Sourij et al. performed coronary angiography in 1090 patients with the diagnosis of CAD or with suspicious CAD. Those patients were followed up for 46 months. Three hundred ninety-four of the patients had normal glucose tolerance, 280 of them had the diagnosis of IGT or DM during the follow-up, and 366 of those patients were known as diabetic patients. They demonstrated that the frequency of microvascular diseases is significantly higher in patients with DM or IGT when compared with normal individuals.[3] In a prospective cohort study of Anand et al., 18,990 individuals were followed up in terms of cardiac risk existence during 3.5 years in 21 different countries. As a result, they indicated that 2.52 mmol/l of glucose increase in plasma increases the risk of cardiovascular disease and death by 17%.[4]

Our study has some limitations. Our first limitation was the small number of patients. We could include 16 patients with DM, 20 patients with IGT, and 15 healthy individuals, and it would be proper to study with large series. The second limitation is that we could not use stress agents because monitoring observations could not be done. A study that was made by using stress agents would be more sensitive. Our third limitation is that coronary artery disease was diagnosed just by the anamnesis of angina pectoris and ECG findings. Also, the left ventricle apex could not be evaluated due to technical insufficiency, and it was excluded.

Microvascular circulation failure is developed in the early phase in patients with IGT and in diabetic patients.[23] The changes of peak enhancement and accumulated enhancement which indicate the microvascular obstruction remains parallel in patients with IGT and in diabetic patients.[4.19.20,22] The findings of time to arrive, time to peak, and delayed enhancement were not statistically significant in diabetic patients and in the patients with IGT. Our study indicated that cardiovascular diseases could be seen in the prediabetic stage. Cardiac MRI examination could be used in the assessment of microvascular obstruction when the deterioration of glucose homeostasis begins.

Ethical considerations

Our study was designed in accordance with the principles of the Helsinki Declaration and regulation of patient rights and approved by the clinical research Ethics Committee of Ankara Ataturk Training and Research Hospital Non-interventional Clinical Researches with the date of 30.09.2010 and the number of 2010-09-118.

Conflict of Interest

The authors declare no conflict of interest.

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