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Detection of Undiagnosed Ischemic Heart Disease in Hemodialysis Patients Using Myocardial Perfusion Imaging

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Background: Coronary artery disease (CAD) is prevalent but very difficult to diagnose in hemodialysis (HD) patients compared with non-uremic individuals.

Objectives: The aim of this study was to detect undiagnosed ischemic heart disease (IHD) using dipyridamole myocardial perfusion imaging (MPI) in HD patients.

Patients and Methods: In this cross-sectional descriptive study, HD patients who met the inclusion criteria were selected. Demographic, clinical, and paraclinical data were obtained via interviews and medical records. Bedside electrocardiography, resting echocardiography, and nuclear MPI with dipyridamole were done. The data were analyzed using descriptive statistical methods for detecting the prevalence of undiagnosed IHD in the HD patients. The chi-square test and the independent t-test were used to identify the high-risk HD patients.

Results: Sixty-nine HD patients were studied using dipyridamole MPI with Tc 99 m sestamibi. The mean age, body mass index, and mean duration of HD were 52.1 ± 13.8 years, 21.23 ± 4.79 kg/m^2, and 48.2 ± 34.9 months, respectively. The patients were divided into two groups based on MPI: IHD-positive group (21.7%) and IHD-negative group (78.3%). IHD was more prevalent in the patients with diabetes mellitus, hypertension, positive family history of CAD, low HD adequacy index (Kt/V < 1.2), left ventricular hypertrophy, high intact parathyroid hormone levels, electrocardiographic abnormalities, and low ferritin levels. A statistically significant correlation was also detected between IHD and aging ($P < 0.05$).

Conclusions: The prevalence of undiagnosed IHD in the HD patients was considerable. We, therefore, suggest that IHD be assessed in HD patients, especially those at high risk due to positive family history of CAD, hypertension, left ventricular hypertrophy, diabetes mellitus, Kt/V < 1.2, low ferritin levels, and high levels of intact parathyroid hormone.

Keywords: Hemodialysis Patients; Ischemic Heart Disease; Dipyridamole Myocardial Perfusion Imaging (MPI)

1. Background

Despite advancements in dialysis technology, coronary artery disease (CAD) is still one of the most common causes of morbidity and mortality among hemodialysis (HD) patients (1-3). The prevalence of asymptomatic undiagnosed ischemic heart disease (IHD) in HD patients appears to rise commensurately with the increasing age and prevalence of diabetes in the HD population. The absence of ischemic symptoms is generally attributed to diabetic and uremic autonomic neuropathy, although it is especially driven by reduced exercise capacity in the dialysis population. Unlike in the general population, the lack of angina does not imply the absence of hemodynamically significant stenosis. The continuous presence of silent ischemia may be responsible for the development of heart failure, arrhythmias, and sudden death in HD patients (4).

Hypertension and other CAD risk factors such as diabetes mellitus, hyperlipidemia, aging, male gender, and physical inactivity are more common in HD patients. These traditional CAD risk factors are found in a large proportion of HD patients (1, 5-7). HD patients are also susceptible to IHD because of other additional risk factors such as anemia, hyperuricemia, homocysteinemia, hypoalbuminemia, and chronic oxidative stress (7-9). Whereas these medical conditions are not common in non-HD IHD patients, they are prevalent among IHD patients with HD and play a well-documented role in the development of IHD in this group of patients (1, 10-14).

Screening of HD patients for IHD has not been considered a standard medical practice so far. However, such screening is applied not only to patients with abnormal

electrocardiograms (ECG) or clinical coronary sign awaiting a kidney allograft but also to those with diabetes mellitus (8, 11, 14). Coronary angiography remains the most effective method for the detection of CAD; and despite the remarkable risk of side-effects in this group of patients and its high expenses, it is still generally deemed a standard method (2, 3). Noninvasive methods for CAD evaluation have yielded different results in HD patients (15). Using chest pain and other symptoms or ECG abnormalities in dialyzed patients does not seem to be sufficient because chest pain is a particularly poor marker. Significant numbers of dialyzed patients with IHD have no symptom, and one-third of those suffering from chest pain show normal coronary arteries in angiography (3). The exercise test even with myocardial perfusion imaging (MPI) is limited due to the inability of HD patients to do exercise. Considering the increase in blood pressure during exercise and problems in the interpretation of ECG tracing obtained via the exercise test in the presence of left ventricular hypertrophy (LVH), MPI with dipyridamole or adenosine or stress echocardiography for patients unable to exercise (e.g. HD patients) can be useful (15-17). Moreover, some studies have shown that for the prediction of cardiac mortality or fatal IHD in HD patients, MPI with dipyridamole is more accurate than that with dobutamine (8, 16). A meta-analysis by Rabbat et al. (17) in 2003 reported that stress imaging was practical and useful for predicting CAD mortality and morbidity in the dialyzed patients selected for kidney transplantation. Yet, it is not clear whether this method is as accurate as coronary angiography.

Dahan et al. evaluated the prognostic value and diagnostic accuracy of the combined dipyridamole exercise imaging in their diabetic patients and concluded that this method was accurate for determining coronary artery stenosis in order to predict future coronary events (8). Hase et al. (10) in Japan utilized MPI and reported a CAD rate of 25%.

2. Objectives

Thus, the current study aimed to detect IHD using MPI with dipyridamole and its related factors among HD patients.

3. Patients and Methods

3.1. Study Population

One hundred twenty-five HD patients with more than a one-year history of HD in a tertiary center, Iran, in 2011, were screened for undiagnosed IHD. The inclusion criteria were comprised of: 1) candidacy for kidney transplantation; 2) age > 45 years for men and > 55 years for women; 3) positive history of diabetes mellitus; 4) chronic hypertension; 5) current smoking habit; and 6) triglyceride > 200 mg/dL or high-density lipoprotein < 35 mg/dL. Patients who had a history of angiography, proven myocardial infarction, history of dipyridamole MPI in the preceding year, and typical chest pain were excluded from the study. All the patients were on bicarbonate-based HD.

Totally, 107 out of the 125 HD patients met the criteria. Among the 107 participants, 3 individuals opted out, 6 received kidney transplantation, 9 died, 13 were non-cooperative, and 7 were unable to complete the perfusion scan because of asthma or severe pulmonary hypertension. Finally, a complete scan was performed in 69 patients.

3.2. Stress Technetium Procedure

MPI was carried out at rest and stress stages. Using a standardized protocol, calcium channel blockers and nitrate were stopped 24 - 72 and 24 - 48 hours before the stress stage of the procedure, respectively, and beta blockers were stopped 48 hours before it. The patients were also advised to limit their caffeine, nitrate (existing in preserved foods), and methylxanthine consumption in the 24-hour period and to fast 4 hours before the stress stage. A day after HD, the study population underwent examination. All the patients had 2-day dipyridamole stress/rest Tc 99 m sestamibi single-photon emission computed tomography (SPECT). On the first day, 560 - 740 MBq of Tc 99 m sestamibi was injected intravenously 4 minutes after the infusion of 0.56 mg/kg of dipyridamole during 4 minutes.

Post-stress tomographic images were obtained 60 - 90 minutes later in the supine position using a single-head gamma camera (Single Head Genesys®, ADAC) equipped with a low-energy, high-resolution collimator, setting the energy photopeak to 140 keV with a 20% symmetric window. Thirty-two projections were acquired for 25 sec per view over a 180°-arc commencing from the left posterior oblique view to the right anterior oblique view.

A zoom factor of 1.45 was used. The rest images were obtained on a separate day 60 - 90 minutes after an intravenous injection of 560 - 740 MBq of Tc 99 m sestamibi in the supine position with the same acquisition protocol. The images were stored in a 64 × 64 matrix in the computer and reconstructed by filtered back-projection using a Butterworth filter (cut-off value was 0.35 cycle/cm and order was 5). No attenuation correction was applied. All the reconstructed images were interpreted by one experienced nuclear medicine specialist without knowledge of the clinical and ECG data.

The stress and rest tomograms were evaluated visually with respect to defect reversibility and considered as normal, completely reversible, fixed, and partially reversible. All the scans with completely or partially reversible perfusion defects or fixed defects (except those due to breast or diaphragmatic attenuation effect, specified as a negative scan by the nuclear medicine specialist) were considered positive for IHD. The normal scans and those with defects due to attenuation effects were considered negative for IHD.

The 17-segment model (including 6 basal, 6 mid-ventricular, and 4 apical segments in the short-axis slices and 1 additional mid-ventricular apical slice in the vertical

long-axis) was used for describing the extension of the defects on MPI. However, no semi-quantitative assessment of perfusion or gated study for the evaluation of the functional parameters was performed.

3.3. Other Parameters

Dialysis adequacy (Kt/V) was estimated using the following Daugirdas Equation:

$$\text{(1)}\quad \frac{\text{Kt}}{V}\text{Daugirdas} = -\ln\left(\frac{\text{BUN}_{\text{post}}}{\text{BUN}_{\text{pre}}} - (0.008 \times h)\right) + \left(4 - \frac{3.5 \times \text{BUN}_{\text{post}}}{\text{BUN}_{\text{pre}}}\right) \times \left(\frac{UF_{\text{vol}}}{\text{Weigh}t_{\text{post}}}\right)$$

Kt/V is defined as the dialyzer clearance of urea (K, obtained from the manufacturer in mL/minute, and periodically measured and verified by the dialysis team) multiplied by the duration of the dialysis treatment (t, in minute) divided by the volume of the distribution of urea in the body (V, in mL), which is approximately equal to the total body water (18).

All the patients were evaluated via ECG (specific and nonspecific ischemic change) and echocardiographic examinations. All the laboratory variables are reported as means of 6 months' measurements.

3.4. Statistical Methods

Descriptive analysis was conducted to process the descriptive outcomes such as the prevalence of CAD and its related factors among the HD patients. The frequency method was calculated to describe the categorical variables. The estimation of the means and standard deviation was performed to describe the continuous variables. Then, analytical methods such as the independent t-test and the chi-square test were used to estimate any significant differences in some factors between the IHD-positive and IHD-negative groups. All the statistical analyses were carried out using IBM SPSS Statistics 20 for Windows (IBM Inc., Armonk, NY).

4. Results

Sixty-nine out of the 125 HD patients with no proven history of CAD were assessed. The mean age of the study population was 52.1 ± 13.8 years. Men accounted for 47.8% of the study population. The duration of HD was 48.2 ± 34.9 months. The etiologies of renal failure were glomerular disease (7.2%), polycystic kidney disease (2.9%), diabetes mellitus (33%), and hypertension (18%). Moreover, 18.8% of the patients were categorized as having undefined etiologic conditions. The prevalence of a positive family history of CAD and history of smoking, as two important risk factors for renal disease, were 28.5% and 9%, respectively. Seventy-three per cent of the patients had Kt/V < 1.2 (Table 1).

According to the perfusion scan results, 21.7% of the study population had IHD. To explore the potential effects of some clinical characteristics (Table 1) on the IHD results, we compared the IHD and non-IHD patients concerning some clinical data. There were some differences in the laboratory findings between the two groups (Table 2). The results showed that Kt/V < 1.2 (86.7% vs. 54%; P < 0.05), diabetes mellitus (31% vs. 26%; P < 0.05), ECG abnormalities (QRS, ST, and T), and, importantly, low ferritin levels and high intact parathyroid hormone (iPTH) levels were more prevalent in the HD patients with IHD. Hypertension (P = 0.012) and LVH (P = 0.001) were significantly higher in the IHD group as well (Table 3).

Table 1. Baseline Characteristics of the Hemodialysis Patients [a]

Characteristics	Descriptive Results
Age, y	52.1 ± 13.8
Male	33 (47.8)
Dialysis duration, mo	48.2 ± 34.9
Glomerular disease	5 (7.2)
Polycystic kidney	2 (2.9)
Diabetes mellitus	21 (30)
Hypertension	12 (18)
Smoking	6 (9)
Undefined conditions	13 (18.8)
Positive family history	20 (28.5)
Low hemodialysis adequacy index, Kt/V < 1.2	50 (73)
Left ventricular hypertrophy according to echocardiography	40 (58)
Body mass index, kg/m^2	21.23 ± 4.79

[a] Values are presented as mean ± SD or No. (%).

Table 2. Comparison of the Mean of Some Clinical and Laboratory Data Between the IHD and Non-IHD Groups [a]

	Ischemic Heart Disease		P Value
	Yes (n=27)	No (n=98)	
Hematocrit (mg/dL)	16.38 ± 6.59	16.15 ± 6.50	0.24
Low hemodialysis adequacy index, Kt/V < 1.2	0.92 ± 0.25	1.14 ± 0.50	0.01
Blood pressure before dialysis, mm Hg	129.3 ± 22.9	142.2 ± 19.4	0.02
Age, y	58.20 ± 9.41	50.88 ± 14.10	0.001
Duration of dialysis, mo	30.6 ± 23.1	53.2 ± 36.2	0.006
Hemoglobin, mg/dL	8.80 ± 1.43	8.97 ± 1.46	0.88
Fasting blood sugar, mg/dL	141.7 ± 76.3	116.9 ± 60	0.001
Triglyceride, mg/dL	128.2 ± 63.9	124.8 ± 85.4	0.01
High-density lipoprotein, mg/dL	36.07 ± 10.00	39.30 ± 15.27	0.023
Low-density lipoprotein, mg/dL	93.01 ± 38.99	80.56 ± 29.49	0.03
Total cholesterol, mg/dL	159.3 ± 52.8	144.0604 ± 39.6	0.01
Ferritin, mg/dL	202.18 ± 244.50	441.19 ± 464.04	0.001
Intact parathyroid hormone, pg/mL	318.23 ± 479.16	252.34 ± 250.51	0.001
Left ventricular ejection fraction in echocardiography, %	50.7 ± 10.3	53.7 ± 9.7	0.012
Body mass index, kg/m^2	22.21 ± 6.21	18.87 ± 4.27	0.01

[a] Abbreviation: IHD, Ischemic heart disease.
[b] Values are presented as mean ± SD.

Table 3. Frequency of Some Important Risk Factors in the IHD and Non-IHD Groups [a]

Risk Factors	IHD Group (n=27) [b]	Non-IHD Group (n=98) [b]	P Value
Male	10 (66.7)	23 (42.6)	0.001
HTN	12 (80)	39 (72)	0.012
Positive family history	5 (33.3)	10 (18.5)	0.016
Diabetes	7 (31)	14 (26)	0.04
ECG abnormality	11 (73.8)	14 (26.2)	0.001
LVH in echocardiography	9 (59.3)	18 (33.3)	0.001
Low hemodialysis adequacy index, Kt/V < 1.2	13 (86.7)	30 (56)	0.001

[a] Abbreviations: ECG, Electrocardiography; HTN, Hypertension; IHD, Ischemic heart disease; and LVH, Left ventricular hypertrophy.
[b] Values are presented as No. (%).

5. Discussion

The present study showed that Kt/V < 1.2, diabetes, ECG abnormalities, and, crucially, low ferritin levels and high iPTH levels were more prevalent in the HD patients with IHD detected by dipyridamole MPI. Also significantly prevalent among the IHD patients, by comparison with the non-IHD patients, were hypertension and LVH.

Almost half of the deaths reported in patients with end-stage renal disease (ESRD) are due to cardiovascular diseases, and CAD can be found in 38% - 40% of the patients who start HD (19). The risk of death due to cardiovascular diseases is reported to be 100 times higher in ESRD patients who have received a kind of HD than that in age-, gender-, and race-matched healthy people (6). In a prospective study on 130 HD asymptomatic patients, significant coronary artery stenosis was reported in 71% of the study population (19).

There is no clearly approved accurate method to analyze zIHD in HD patients. Angiography is a standard diagnostic method to diagnose IHD, but its use is limited by its prohibitive costs, especially for HD patients (8). The exercise test is also restricted in HD patients with IHD owing to their diminished capability to exercise secondary to anemia and muscular atrophy and non-cardiac exercise limitations (e.g. peripheral vascular disease). In addition, the rise in blood pressure during activity in hypertensive patients and difficulty in interpreting the electrical tracings in patients with LVH render the use of the exercise test limited (19). Noninvasive tests can provide useful information for risk stratification in chronic IHD patients (19). Currently, the sensitivity and specificity of the diagnosis of occlusive IHD with gated SPECT is 91% and 72%, respectively (16).

In the present study, the incidence rate of IHD in the study group was approximately 21.7%, whereas this rate in other studies such as those by Resic et al. (1) and Hase et al.

(10) in Japan was reported at around 25%. What needs to be taken into consideration is that the purpose of the current study was to detect undiagnosed IHD using dipyridamole MPI in HD patients; accordingly, patients having undergone angiography or MPI study in the preceding year were excluded. This seems to be the main reason for the difference between the current study and the other ones.

Our results demonstrated that the diabetic patients and those with Kt/V < 1.2 had more positive IHD results, which is compatible with the results of the study by Soubassi et al. (20). It means that these two HD patient groups need further assessment for CAD. Repeated clinical assessments with short interval follow-ups for these groups are, therefore, strongly advised. This finding was compatible with the low level of blood pressure before HD in the IHD-positive group found in our study and may be the cause of hypotensive episodes during HD, which could compromise the quality of HD. Our two study groups were not statistically significantly different in terms of the body mass index, which may be secondary to low HD quality and high prevalence of underweight patients in both groups.

The high iPTH and C-reactive protein levels were higher in our IHD-positive group, but the levels of the former were significantly different between the two study groups (P = 0.001), which is consistent with the findings of the study by Soubassi et al. (20). The difference regarding C-reactive protein may be due to the lower number of patients in our study.

HD duration was lower in our IHD-positive group. This finding may be in consequence of the higher age in this group and delay in starting HD. This finding was not compatible with the results of the study by Soubassi et al. (20). The frequency of LVH in echocardiography was significantly higher in our IHD-positive group (59.3% vs. 33.3%; P = 0.05), which chimes in with the findings reported by Soubassi et al. (20).

ECG abnormalities (ST, T, and QRS) were evaluated in our study because ECG changes mimicking myocardial ischemia or myocardial infarction may also occur in ESRD patients. For example, ST depression and T-wave inversion may be caused by LVH or electrolyte abnormalities and shifts. Elevation of the ST segment may occur with pericarditis or LVH. In addition, Q waves may be caused by LVH resulting from septal hypertrophy (19). The prevalence of ECG abnormalities was higher in our IHD-positive group (P = 0.001). Anemia was not significantly different between our two study groups, which may be due to the high incidence of anemia in our patients secondary to multifactorial causes. Nevertheless, the ferritin level was lower in the IHD-positive group significantly. It may be due to poor evaluation and follow-up by physicians and higher rates of malnutrition in these patients. There was no statistically significant association between CAD and the presence of other traditional risk factors.

Accordingly, noninvasive MPI methods, including dipyridamole MPI, are suggested in HD patients for the evaluation of IHD, especially in high-risk groups with male gender, hypertension, positive family history of premature CAD, high levels of iPTH, and Kt/V < 1.2. Given the unreliability of ECG and even echocardiography in the detection of IHD in patients whose disease could be silent, a better approach for the screening and diagnosis of IHD seems necessary.

5.1. Limitation

The salient limitation in the present study is its small population, which precludes the generalizability of its results to all ESRD patients. The findings, therefore, require confirmation by future studies with larger sample volumes.

Given the prevalence of asymptomatic undiagnosed IHD in HD patients owing to atypical chest pain, silent ischemia, and infeasibility of functional capacity assessment, it is vitally important that IHD be diagnosed in this group of patients early so that CAD-related mortality and morbidity could be decreased. HD patients with diabetes mellitus, hypertension, Kt/V < 1.2, LVH, positive family history of CAD, lower ferritin levels, and high iPTH levels have a larger burden of coronary risk factors, rendering them susceptible to IHD. The traditional risk factors are not completely useful indictors of IHD in HD patients. Consequently, our efforts should be focused on measurable improvements in cardiovascular outcomes in these patients.

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