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Clinical significance of technetium-99m methylene diphosphonate myocardial uptake: association with carcinoma of the prostate

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Abstract. Benign myocardial uptake of technetium-99m labelled phosphates, not related to cardiac or metabolic disorders, has been documented except in the case of ^{99m}Tc-methylene diphosphonate (MDP). The aim of this study was to assess the frequency of myocardial uptake and its possible association with malignant tumours in general and prostatic carcinoma in particular. We reviewed bone scintigrams performed with either ^{99m}Tc-hydroxydiphosphonate (HDP) or ^{99m}Tc-MDP over a period of more than 2 years for all patients with prostatic carcinoma and a matching group of patients suffering from other malignant and non-malignant disorders. A total of 965 scintigrams of 812 patients (males=559, females=253; age range 50–91 years, average age 69.2 years) were reviewed. Increased myocardial uptake was detected in 19 scintigrams (MDP=13, HDP=6) of 18 patients (17 males, one female). Most of the male patients with increased myocardial uptake had prostatic carcinoma (13/17) and were over 80 years of age (12/17). All patients were free of any cardiac or non-cardiac disorder that might account for such uptake. When scintigraphy was repeated in the same patient, the uptake of ^{99m}Tc-HDP was more diffuse and of higher grade than that of ^{99m}Tc-MDP. "Benign" myocardial uptake of ^{99m}Tc-MDP is more common than previously thought. Although uptake of radiophosphates is attributed to asymptomatic atherosclerotic changes associated with old age, a strong association with prostatic carcinoma exists which may indicate variations in the bone: soft tissue affinity of different MDP complexes.

Key words: Myocardial uptake – Technetium-99m methylene diphosphonate – Technetium-99m hydroxydiphosphonate – Bone scintigraphy – Prostatic carcinom

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Introduction

Technetium-99m labelled bone-seeking phosphates are known to localize in the myocardium after myocardial damage [1–3], in hypercalcaemia and in other clinical, biochemical and iatrogenic conditions [4–11]. Diffuse myocardial uptake of ^{99m}Tc-pyrophosphate (PYP) and ^{99m}Tc-hydroxydiphosphonate (HDP) in apparently healthy people who had no obvious cardiac or non-cardiac disorder, thus termed "benign" myocardial uptake [2–3, 12], has also been documented. Repeat ^{99m}Tc-methylene diphosphonate (MDP) scintigrams were reported as discordant, showing no myocardial uptake [12].

Our observation that such uptake can also be detected with ^{99m}Tc-MDP is new. We also observed such uptake to occur more frequently in patients with prostatic carcinoma. This study was performed to determine the frequency of this uptake in patients with malignant disorders in general and prostatic carcinoma in particular.

Materials and methods

Bone scintigrams performed over a period of 26 months between 1991 and 1993, for all cases of prostatic carcinoma, were reviewed for myocardial uptake. A group of patients of both sexes, who were over 50 years of age and suffering from a variety of malignant and non-malignant conditions during the same period, were chosen at random for comparison. Patients who had an obvious reason for decreased soft tissue attenuation of the anterior chest wall, such as those with left mastectomy, were excluded. The patients were grouped as follows (Table 1):

Group A. Patients with prostatic carcinoma: a total of 322 scans in 244 patients (age range 55–89, average age 74.4 years).

Group B. Patients with other malignant diseases: a total of 427 scans in 361 patients (199 males, 162 females; age range 50–91, average age 66.9 years) (Table 2).

Group C. Patients with benign musculoskeletal disorders referred for bone scintigraphy: a total of 216 scans of 207 patients (116 males, 91 females; age range 50–88, average age 65.9 years) (Table 3).

Table 1. The three patient categories selected for entry into the study

Group	Category	No. of patients	No. of scintigrams	Mean age (years)
A	Prostatic carcinoma	244	322	74.4
B	Other malignancies[a]	361	427	66.9
C	Benign disorders[b]	207	216	65.9
Total		812	965	69.2

[a] Including other malignant disorders (see Table 2)
[b] Including benign disorders (see Table 3)

Table 2. Distribution of positive results in patients with malignant conditions other than prostatic carcinoma (group B)

Diagnosis	No. of patients	Positive scintigrams	
		MDP	HDP
Breast carcinoma	115	1	0
Lung carcinoma	98	0	1
Bladder carcinoma	31	0	0
Stomach carcinoma	29	0	0
Lymphoma	26	0	0
Colon carcinoma	22	2	0
Myeloma	18	0	0
Thyroid carcinoma	13	0	0
Miscellaneous	9	0	0
Total	361	3	1

Table 3. Distribution of positive results in patients with benign conditions (group C)

Diagnosis	No. of patients	Positive scintigrams	
		MDP	HDP
Back pain	94	0	0
Arthritis/synovitis	41	0	1
Trauma/fracture	26	0	0
Soft tissue swelling	20	0	0
Osteoporosis	7	0	0
Paget's disease	6	0	0
Hypercalcaemia	5	0	0
Painful prostesis	5	0	0
Miscellanous	3	0	0
Total	207	0	1

Bone scintigrams were performed with either ^{99m}Tc-MDP or ^{99m}Tc-HDP as described earlier [13] but exclusively with ^{99m}Tc-MDP for the last 16 months of the study. In some cases extra views (left lateral and left anterior oblique) were taken. When myocardial uptake was seen, a quality check on the labelled radiopharmaceutical and a review of other bone scintigrams performed using the same vial were always carried out.

The intensity of myocardial uptake was graded on a scale of 0 to 4+ where: 0 = no uptake, 1+ = equivocal uptake, 2+ = definite uptake but less than the sternum, 3+ = definite uptake equal to the sternum and 4+ = definite uptake greater than the sternum [14]. Grades of uptake were agreed upon by consensus amongst three interpreters.

Cases that showed myocardial uptake of grade 1+ were not included in this study. Those that showed grade 2+ and over were regarded as positive and investigated further to exclude possible cardiac or non-cardiac aetiology by checking the clinical history, reviewing relevant investigations (chest radiograph, blood picture, electrolytes and renal function), medications and therapy received. Electrocardiograms were carried out on patients with grade 3+ or 4+ myocardial uptake on the same day as the scintigram.

Results

A total of 965 scintigrams (MDP: 754, HDP: 211) of 812 patients (males=559, females =253; age range 50–91 years, average age 69.2 years) were reviewed. Myocardial

Table 4. Details of cases with positive myocardial uptake. Only grades 2+ and over were considered for statistical analysis

No.	Patient	Age (sex)	Diagnosis	Uptake grade		Comment
				MDP	HDP	
1	W.R.	89 (M)	Prostatic carcinoma	2+ to 3+	4+	Uneven (MDP), diffuse (HDP)
2	R.B.	82 (M)	Prostatic carcinoma	3+	N	Uneven
3	P.J.	88 (M)	Prostatic carcinoma	N	3+	Diffuse
4	S.H.	87 (M)	Prostatic carcinoma	N	2+	Diffuse
5	G.W.	87 (M)	Prostatic carcinoma	2+	N	Diffuse
6	J.H.	87 (M)	Prostatic carcinoma	2+	N	Diffuse
7	R.T.	82 (M)	Prostatic carcinoma	2+	N	Diffuse
8	R.J.	80 (M)	Prostatic carcinoma	2+	N	Diffuse
9	Y.C.	80 (M)	Prostatic carcinoma	2+	N	Diffuse
10	I.J.	78 (M)	Prostatic carcinoma	2+	N	Diffuse
11	G.T.	72 (M)	Prostatic carcinoma	2+	N	Diffuse
12	S.L.	74 (M)	Prostatic carcinoma	2+	N	Diffuse
13	G.S.	79 (M)	Prostatic carcinoma	1+	2+	Diffuse
14	T.E.	80 (F)	Ca. breast	2+	N	Diffuse
15	D.M.	80 (M)	Ca. colon	2+	N	Diffuse
16	O.T.	81 (M)	Ca. colon	2+	N	Diffuse
17	A.R.	81 (M)	Ca. lung	N	2+	Diffuse
18	D.E.	61 (M)	Wrist pain	N	2+	Diffuse

N, Not performed

Table 5. Distribution of positive results amongst different subgroups

Subgroup/category	No. of patients		Mean age (years)	Total scintigrams	Positive		Total (%)
	Males	Females			MDP	HDP	
A1: prostatic carcinoma >80	71	–	84	80	7	3	10/80 (12.5)
A2: prostatic carcinoma <80	173	–	70.4	242	3	1	4/242 (1.7)
B1: other malignancies >80	64	57	83.1	155	3	1	4/155 (2.6)
B2: other malignancies <80	135	105	58.7	272	–	–	0/272 (0)
C1: benign disorders >80	40	21	80.8	63	–	–	0/63 (0)
C2: benign disorders <80	76	70	59.7	153	–	1	1/153 (0.6)
Total	559	253	69.2	965	13	6	19/965 (2%)

uptake of grade 2+ and over was detected in 19 bone scintigrams (Table 4) in 18 patients (2% of total patients, 17 males, one female), of which 13 were carried out with ^{99m}Tc-MDP and six with ^{99m}Tc-HDP. Most male patients with increased myocardial uptake were elderly (average age 80.5 years), with a high incidence of prostatic carcinoma (13/17 males). The only female who showed uptake was 80 years old and had breast carcinoma. There was only one patient (male aged 61 years) with non-malignant wrist pain. The myocardial uptake was diffuse in all six ^{99m}Tc-HDP and in 11 of the 13 ^{99m}Tc-MDP scintigrams, but uneven in 2 of the 13 ^{99m}Tc-MDP scintigrams. When patients were imaged with both agents, grades of uptake were always higher with ^{99m}Tc-HDP. The original patients' groups were divided into the following subgroups for easy reference and statistical analysis (Table 5):

Group A1, consisting of 80 scintigrams in 71 male patients aged over 80 years (age range 80–89, average age 84 years) with prostatic carcinoma. Results showed ten positive scans (12.5%) in nine patients (seven MDP and three HDP). One patient (no. 1) showed a diffuse grade 4+ left ventricular myocardial uptake with ^{99m}Tc-HDP (Fig. 1) but an uneven uptake of grade 2+ (left ventricle) and grade 3+ (right ventricle) upon repeat scintigraphy with ^{99m}Tc-MDP 2 years later (Fig. 2).

Group A2, consisting of 242 scintigrams in 173 male patients aged under 80 years (age range 55–79, average age 70.4 years) with prostatic carcinoma. This group had four positive scintigrams (1.7%) in four patients (three MDP, one HDP).

Group B1, consisting of 155 scans in 121 patients aged over 80 years (males=64, females=57; age range 80–91 years, average age 83.1 years) with various malignant conditions but excluding prostatic carcinoma (Table 2). Results showed four positive scintigrams (2.6%) in three male and one female patients. Three of these were carried

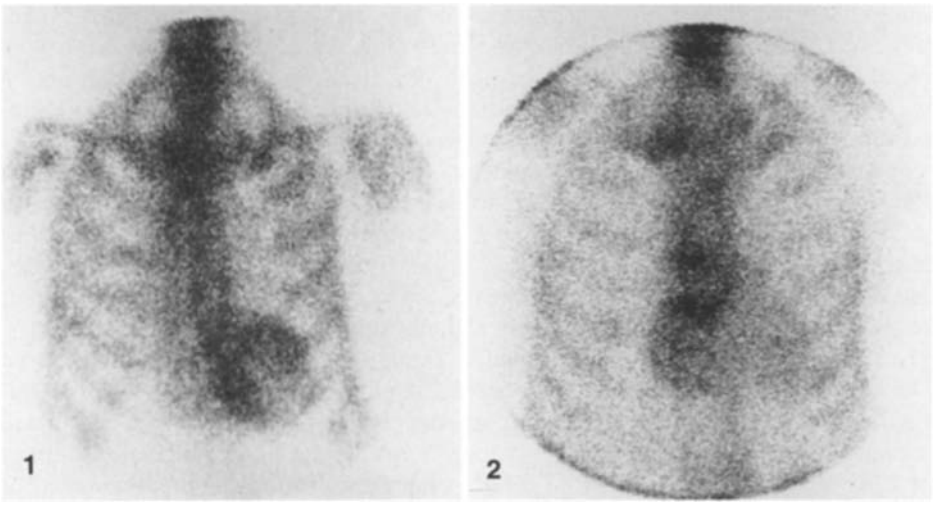

Fig. 1. Diffuse grade 4+ left ventricular myocardial uptake of ^{99m}Tc-HDP in a patient with prostatic carcinoma

Fig. 2. Same patient as in Fig. 1 showing uneven myocardial uptake of ^{99m}Tc-MDP (grade 2+ in the left ventricle and grade 3+ in the right ventricle) 2 years later (note shine through of spinal metastasis)

Table 6. Chi-squared analysis of different groups and subgroups

Group	*P* value
A and B	<0.01
A and C	<0.01
B and C	NS
A1 and A2	<0.001
B1 and B2	<0.01
A1 and B1	<0.01
A1 and C1	<0.01
C1 and C2	NS

NS, Not significant

out with ^{99m}Tc-MDP (two colon carcinoma, one breast carcinoma) and one with ^{99m}Tc-HDP (lung carcinoma).

Group B2, consisting of 272 scans of 240 patients aged under 80 years (males=135, females=105; age range 50–79, average age 58.7 years) with various malignant conditions but excluding prostatic carcinoma. None showed myocardial uptake.

Group C1, consisting of 63 scans of 61 patients aged over 80 years (males=40, females=21; age range 80–88 years, average age 80.8 years) suffering from a variety of benign diseases (Table 3), including two cases of hypercalcaemia. None showed uptake in the myocardium.

Group C2, consisting of 153 scans of 146 patients aged below 80 years (males=76, females=70; age range 50–79 years, average age 59.7 years) suffering from a variety of benign diseases (Table 3), including three cases of hypercalcaemia. Myocardial uptake of ^{99m}Tc-HDP was detected in one scintigram (0.6%) of a 61-year-old male patient with painful wrists and normal calcium level.

Review of clinical history and radiological, biochemical and haematological tests, done at the time of the scintigram for all 18 patients with positive scintigrams, failed to reveal any disorder known to be associated with myocardial uptake and showed that the patients were asymptomatic of cardiac disease up to the time of completion of this study.

At the time of acquisition, all electrocardiograms done for grades 3+ and 4+ were normal and the patients were not receiving any relevant medication or chemotherapy. Regular quality checks on labelled radiopharmaceuticals ensured an acceptable limit of free pertechnetate which was confirmed by normal scintigrams obtained on the same day from the same vial.

Statistical analysis

Chi-squared analysis (Table 6) showed a significant difference in myocardial uptake between patients with prostatic carcinoma and those with other malignant disorders (groups A and B, $P<0.01$) or with benign disorders (groups A and C, $P<0.01$), but no significant difference between groups B and C. There was also a significant difference between the following subgroups:

1. Patients with prostatic carcinoma who were >80 years old compared with those <80 years old (A1 and A2, $P<0.001$).
2. Patients with prostatic carcinoma who were >80 years old compared with those of the same age group but with other malignancies (A1 and B1, $P<0.01$).
3. Patients with prostatic carcinoma who were >80 years old compared with those of the same age group but with benign disorders (A1 and C1, $P<0.01$).
4. Patients with malignant disorders other than prostatic carcinoma who were >80 years old compared with those <80 years old (B1 and B2, $P<0.01$).

There was no significant difference between patients with benign musculoskeletal disorders who were >80 years old compared with those <80 years old (C1 and C2).

Discussion

The mechanism of localization of radiophosphate compounds is thought to involve rapid chemisorption onto

the shells of hydoxyapatite crystals and gradual incorporation into the crystals [15] of newly formed bone. Soft tissue uptake has been detected in a variety of malignant, inflammatory and metabolic disorders [5, 8, 11]. This effect is thought to be due to either increased blood flow or augmented local calcium ion concentration [16], which may also explain the myocardial uptake observed in damaged myocardial tissue [1–3, 6, 17]. Non-cardiac causes of myocardial uptake as in renal failure, amyloidosis and hyperparathyroidism are also documented and are attributed to hypercalcaemia and altered plasma binding [4, 9–11, 16, 18].

Myocardial uptake of ^{99m}Tc-PYP or ^{99m}Tc-HDP (but not ^{99m}Tc-MDP) has been noted in apparently healthy people with no evidence of cardiac or non-cardiac disorders [2, 3]. In a recent report [12] HDP myocardial uptake (with discordant MDP uptake) was detected mainly in elderly males with prostatic carcinoma. Unlike previous reports, we have documented myocardial uptake of ^{99m}Tc-MDP in patients who, at the time of scintigraphy, were free of cardiac or non-cardiac conditions that might have accounted for such uptake. The higher detection rate with ^{99m}Tc-MDP reflects the higher number of studies done with this radiopharmaceutical.

Our results showed a significant difference between myocardial uptake in patients with prostatic carcinoma particularly in those >80 years, compared to patients with other benign or malignant disorders. The importance of the age factor is demonstrated by the significant difference in uptake between older and younger sufferers from prostatic carcinoma. A less significant difference was found between older and younger patients with other malignancies but none in those suffering from benign disorders.

It is of note that the uptake of ^{99m}Tc-HDP in our patients was always more diffuse and of higher grade than that of ^{99m}Tc-MDP.

The explanation of this "benign" myocardial uptake remains difficult. Mild asymptomatic atherosclerosis is thought to be the most plausible explanation for increased uptake in elderly patients, particularly of the male sex [12], but our results suggest that this in itself is not enough to be considered as a causal factor except in association with prostatic carcinoma.

Prasquire and colleagues [3] found that 84% of patients with myocardial uptake demonstrated a linear uptake in the femoral vasculature, suggesting reduced radiopharmaceutical clearance and a blood pool effect. They did not separate cardiac from non-cardiac cases, classify types of malignancies or indicate the degree of hypercalcaemia, which is though by others to be the reason for femoral vascular uptake [4]. The concept of vascular activity being the cause of apparent myocardial uptake is unlikely to be correct because the uptake of thallium-201 and ^{99m}Tc-methoxyisobutylisonitrile is identical to that of ^{99m}Tc-MDP or ^{99m}Tc-HDP [4, 12], indicating uptake in the myocardium rather than in the ventricular cavity.

The association between soft tissue uptake of ^{99m}Tc-labelled phosphates and hypercalcaemia has been well documented [4, 5, 9–11, 18] but the high concentration needed to form colloid complexes as suggested by Palmer et al. [16] was not evident in our cases. All five cases of hypercalcaemia in our series showed normal uptake. It is interesting to note that MDP preparations are known to form a number of complexes depending on the types of stabilizer used in the formulation of MDP kits [19, 20]. These complexes are known to have varying bone: soft tissue affinity and may play a part in soft tissue uptake.

A possible explanation for the higher incidence of myocardial uptake in elderly males with prostatic carcinoma is the presence of a prostatic carcinoma-related metabolite which may interact and change the stability of ^{99m}Tc-MDP complexes, leading to predominance of complexes with lower bone: soft tissue affinity. The presence of mild atherosclerotic heart disease may localise this uptake in the myocardium.

Specific and individual factors interfering with bone: soft tissue affinity of ^{99m}Tc-HDP and ^{99m}Tc-PYP complexes may explain similar uptake in both young and elderly patients.

To conclude: We have documented benign myocardial uptake of ^{99m}Tc-MDP during routine bone scintigraphy. The uptake of both ^{99m}Tc-MDP and ^{99m}Tc-HDP was seen in 2% of sequential bone scintigrams carried out in our institution for malignant and non-malignant disorders. The series demonstrated an association with prostatic carcinoma (4.3% of all cases) particularly in those aged over 80 years (12.5%). The findings indicate that uptake of ^{99m}Tc-MDP or ^{99m}Tc-HDP in the myocardium of elderly male patients with prostatic carcinoma is not uncommon and probably of little relevance in the absence of cardiac symptoms.

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