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***Radiopharmaceuticals and Dialysis***

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# **RADIOPHARMACEUTICALS AND DIALYSIS**

## **STATEMENT OF OBJECTIVES**

The purpose of this lesson is to increase the reader's knowledge and understanding of the effects of dialysis on radiopharmaceutical biodistribution and of purposeful uses of radiopharmaceuticals in patients undergoing dialysis.

***Upon completion of this lesson, the reader should be able to:***

1. describe the basic process of dialysis, both hemodialysis and peritoneal dialysis.
2. describe reported alterations in radiopharmaceutical biodistribution associated with dialysis or complications thereof.
3. describe reported uses of radiopharmaceuticals to purposefully evaluate complications of dialysis.
4. discuss radiopharmaceutical therapy in dialysis patients, in terms of both patient management and radiation safety.
5. describe reported uses of radiopharmaceuticals to evaluate certain functional aspects of dialysis equipment.

## **COURSE OUTLINE**

### **I. INTRODUCTION**

### **II. DESCRIPTION OF DIALYSIS**

### **III. ALTERATIONS IN RADIO-PHARMACEUTICAL BIODISTRIBUTION**

### **IV. USE OF RADIOPHARMACEUTICALS TO EVALUATE COMPLICATIONS OF DIALYSIS**

### **V. RADIOPHARMACEUTICAL THERAPY IN DIALYSIS PATIENTS**

### **VI. USE OF RADIOPHARMACEUTICALS TO EVALUATE DIALYZER FUNCTION**

### **VII. REFERENCES**

### **VIII. QUESTIONS**

# RADIOPHARMACEUTICALS AND DIALYSIS

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## INTRODUCTION

Nuclear pharmacists and other nuclear medicine staff are occasionally confronted with situations involving nuclear medicine procedures in dialysis patients. For example, questions may arise regarding dialysis-related alterations in radiopharmaceutical biodistribution, either prospectively or in retrospective trouble-shooting of atypical images. On the other hand, suggestions can be offered regarding nuclear medicine procedures that may be valuable in the evaluation of certain complications of dialysis. Also, consultation can be provided in cases involving the desire to treat a dialysis patient with a therapeutic radiopharmaceutical.

Unfortunately, there exists a paucity of readily available information regarding

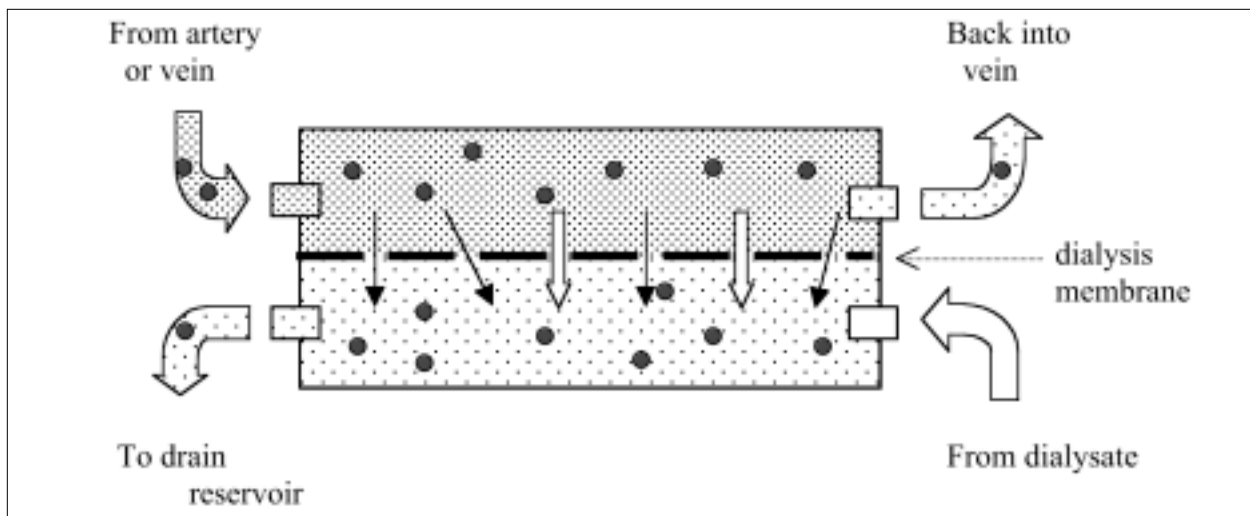
radiopharmaceuticals and dialysis. Such information is rarely mentioned in standard textbooks and radiopharmaceutical references--for example, a classic review article on alterations in radiopharmaceutical biodistribution includes only two paragraphs on the subject,<sup>1</sup> and a similar chapter in a prominent book includes only three paragraphs.<sup>2</sup> Information scattered throughout the primary literature consists almost entirely of anecdotal descriptions, abstracts, and isolated case reports; only a few small studies involving the evaluation of certain complications have been published. Therefore, to address this information gap to the extent possible, the purpose of this lesson is to summarize and review available information on the various topics involved with radiopharmaceuticals and dialysis.

## DESCRIPTION OF DIALYSIS

The term *dialysis* derives from the Greek *dia* (meaning through or across) and *lyein* (meaning dissolve or loosen). Hence, dialysis can be defined as the separation of substances in solution by means of their unequal diffusion through semipermeable membranes. In the healthcare setting, dialysis is a general term used to describe some type of

**Figure 1. Simplified schematic diagram of a hemodialyzer.**

Small solutes (·) diffuse through pores in the dialysis membrane dependent on a concentration gradient (arrows). Fluid and larger molecules (●) pass through membrane pores dependent on a pressure gradient (block arrows).



renal replacement therapy in patients with insufficient renal function or renal failure. Although dialysis can be used as an acute therapy (e.g., in patients with acute renal failure), it is most commonly used as a chronic therapy (e.g., in patients with end-stage renal disease). Although the goal of dialysis is to remove metabolic waste products from the blood, many drugs are also subject to removal by dialysis.

### Hemodialysis

The conventional approach is hemodialysis--withdrawing blood from an artery or vein, passing it through a dialyzer, and infusing it back into a vein. Within the dialyzer, a semi-permeable membrane separates the blood compartment from the dialysate compartment. During transit through the dialyzer, certain molecules in the blood can pass through the membrane and be eliminated in the dialysate solution (see Figure 1). Movement of small solute molecules across the membrane is primarily by the process of diffusion, with net movement from an area of high concentration (i.e., the blood) to an area of low concentration (i.e., the dialysate). Diffusion is dependent on a concentration gradient, so blood and dialysate generally

flow in opposite directions to better maintain concentration gradients and thereby maximize diffusive transfer.

Fluid removal occurs primarily by the process of convection, i.e., movement along a pressure gradient. Some solutes and larger molecules are removed by being dragged along with the solvent (see Figure 1). This process does not require a concentration gradient. However, convective transport is dependent on a pressure gradient, so the dialysate compartment is typically maintained at a lower atmospheric pressure relative to the blood compartment. The term "ultrafiltration" is often used in association with high-permeability membranes that maximize convective transport.

Dialyzers have evolved over the years to increase the available surface area of the membranes. Twin-coil and parallel-plate designs have now been superseded by hollow fiber technology. In current designs, blood flows through the hollow fibers, in bundles of thousands, while dialysate circulates around them. This allows for a large surface area and high transfer rates, while keeping the physical dimensions to a reasonable size.

Dialysis membranes may be manufac-

**Table 1. Characteristics of Common Dialysis Membranes**

(adapted from references 4 and 5)

Type	Material	Flux	Biocompatibility
cellulose	cuprammonium [Cupraphane]	low	low
substituted cellulose	cellulose acetate	low	intermediate
	cellulose diacetate	high	intermediate
	cellulose triacetate	high	intermediate
cellulosynthetic	cellulose with tertiary amino substitutions [Hemophan]	low	high
synthetic	polyacrylonitrile (PAN)	high	high
	PAN-methylallyl sulfonate	high	high
	polyamide	high	high
	polycarbonate	low	high
	polymethylmethacrylate (PMMA)	high or low	high
	polysulfone (PS)	high or low	high

tured from many different materials. Traditional, or conventional, membranes are based on cellulose. For the commonly used Cuprophane membrane, the cellulose is regenerated using a cupric ammonium process. Because unsubstituted cellulose has a large number of free hydroxyl groups that can activate the complement system as blood flows along its surface, substituted cellulose and synthetically-modified cellulose products have been developed which are more biocompatible. Non-cellulose synthetic membranes have also been developed which have high-flux capabilities and are biocompatible. Table 1 summarizes characteristics of several common dialysis membranes.

The term "high efficiency" refers to dialyzers that are capable of high urea clearance. Traditional cellulosic membranes, which have only a modest urea clearance, can be made into high-efficiency dialyzers by increasing the surface area.

The term "high flux" refers to dialyzers whose membranes possess large pore sizes and thus have high ultrafiltration characteristics. The high-permeability membranes used in this type of dialyzer allow greater convective clearance of larger molecules. Although cellulosic membranes can be manufactured with large pore sizes, most high-flux dialyzers rely on synthetic membranes (see Table 1).

Many factors influence the dialyzability of molecules.<sup>3-5</sup> First are the physiochemical characteristics of the substance. Molecular weight is a very important factor; generally, any substance with a molecular weight of < 1000 daltons will diffuse much more easily than those with molecular weights > 1000 daltons. Larger molecules, up to about 10,000 daltons, are not readily removed by diffusion, but may undergo convective removal in high-flux dialyzers. Also important is the solubility of the substance; because the dialysate is aqueous, highly water soluble substances will be removed to a greater extent than will be lipid-soluble substances.

A second group of factors is the biological handling of the substance. Generally,

dialysis is potentially useful for those substances normally excreted by the kidney but is ineffective for substances excreted by non-renal routes (e.g., hepatobiliary). In order to be available for diffusion across the dialysis membrane, substances must be free in plasma; conversely, substances that are highly protein bound are not readily dialyzed. Also, because diffusion is dependent on a concentration gradient, substances that have a small volume of distribution (i.e., are more concentrated in the blood) are better dialyzed than are substances that have a large volume of distribution (i.e., are distributed throughout tissues).

A third group of factors is the functionality of the dialysis membrane. Numerous membranes are available, each with unique characteristics including pore size, ultrafiltration coefficient, surface area, and material composition. Pore size dictates the molecular weight of substances that can pass through the membrane; membranes with a larger pore size allow better dialysis of larger molecules. The ultrafiltration coefficient is the amount of ultrafiltrate that can be produced at a given transmembrane pressure; membranes with a higher ultrafiltrate coefficient have the potential to remove more substance through the process of convection. Surface area determines the opportunity for substance exposure to the membrane; the greater the surface area, the greater the potential for diffusion across it and hence the greater efficiency. Membranes are created from different types of materials based on cellulosic and synthetic polymers (see Table 1). Because different membranes have different water- and solute-removing characteristics, making broad generalizations about membranes is difficult. Detailed specifications of commonly used dialyzers are available in standard texts.<sup>4,5</sup>

The final factor is the operation of the dialyzer. Dialysate and blood flow through the unit in opposite directions. The faster the blood flow, the more rapidly the substance is exposed to the dialysis membrane. Once the substance passes through the membrane, it accumulates in the dialysate and thereby



decreases the concentration gradient. Removal of the accumulated substance from the dialyzer is necessary to maintain an adequate concentration gradient for further dialysis. Hence, increasing the dialysate flow rate will increase the rate of removal and thus will better maintain a high concentration gradient and maximize the dialytic efficiency. For larger molecules removed by convection, increasing the transmembrane pressure (i.e., increasing the pressure differential between the blood and the dialysate) will increase clearance by ultrafiltration.

Given the large diversity in dialysis membranes and dialyzer operation, caution should be used in applying drug removal data from one hemodialysis technique to another.

### **Peritoneal Dialysis**

A reasonable option for many patients needing chronic dialysis is peritoneal dialysis. In contrast to hemodialysis which uses artificial membranes *in vitro*, peritoneal dialysis uses an *in vivo* biological membrane – the peritoneal membrane. Simply, dialysate fluid is periodically placed into the peritoneal cavity where it accumulates substances that transfer into it by passing through the peritoneal membrane. Peritoneal dialysis involves a combination of diffusive and convective transport for solute removal. Diffusion occurs along a concentration gradient, similar to that occurring in hemodialysis. Convection with fluid removal occurs because of an osmotic pressure gradient, which is created by using hyper-osmotic dextrose dialysate, analogous to the hydrostatic pressure gradient in hemodialysis.

Peritoneal dialysis is inherently an intermittent batch process. Dialysate is instilled into the peritoneal cavity, dwells there for some period of time during which solute and fluid transfer occurs, and then is drained. Initially after instillation of the dialysate into the peritoneal cavity, high concentration and pressure gradients allow maximal diffusion and convection. However, as these gradients diminish over time, the rates of diffusion and

ultrafiltration correspondingly diminish. Therefore the dialysate must be periodically changed, which may be performed either an intermittent basis or continuously.

Intermittent peritoneal dialysis (IPD) generally consists of dialysate changes 3-4 times per week for 10-14 hours per session. Because of its low efficiency and inconvenience, IPD is now rarely used. Nocturnal intermittent peritoneal dialysis (NIPD), a more effective and convenient variant of IPD, typically consists of 8-10 hours of therapy every night, and involves the use of a cycler device to perform 4-5 dialysate changes per nightly session. Continuous ambulatory peritoneal dialysis (CAPD), as the name implies, is performed continuously 24 hours per day, seven days a week. CAPD typically involves 4-5 dialysate changes each day. Because a cycler machine is not needed, this method is preferred by many active patients. A hybrid of NIPD and CAPD is continuous cycling peritoneal dialysis (CCPD). CCPD consists of 4-6 cycler-controlled dialysate changes during the night and then allows a dialysate batch to dwell in the peritoneal cavity throughout the day. This method provides good performance with less interruption of the patient's day-time schedule.

Advantages of peritoneal dialysis over hemodialysis include eliminating the chance of acquiring blood-borne viral infections from other patients (e.g., from re-use of contaminated dialysis equipment), elimination of the need to have an arterial-venous access, elimination of the need to spend many hours per week at a dialysis center, and lower cost.<sup>6</sup> Peritoneal dialysis patients are allowed to ambulate freely and carry out normal activities in between fluid exchanges, which can easily be performed by the patients themselves at home.

In peritoneal dialysis, substances are removed by diffusion and by convection. Many of the physicochemical (e.g., molecular weight) and biological characteristics (e.g., normal route of excretion, protein binding, volume of distribution) that influence the hemodialyzability of substances, as

described above, similarly influence peritoneal dialyzability. Additional factors influencing peritoneal dialysis include the exchange volume, the frequency of exchanges, and the presence of peritonitis.<sup>3-5</sup> Larger exchange volumes will provide greater initial concentration gradients and allow more total accumulation of waste substances before equilibrium is reached. Each exchange of dialysate provides a renewed concentration gradient, so more frequent exchanges result in greater substance removal. The presence of peritonitis (i.e., inflammation of the peritoneal membrane) may provide increased "pore size" and allow greater accumulation of substances with larger molecular weights.

Given the large diversity in peritoneal dialysis methods and protocols, caution should be used in applying drug removal data from one peritoneal dialysis technique to another.

### **ALTERATIONS IN RADIOPHARMACEUTICAL BIODISTRIBUTION**

Many radiopharmaceuticals are eliminated, in significant fraction, by the kidneys. In renal failure, abrogation of this elimination pathway results in altered biodistribution such as prolonged blood pool activity and possible enhanced clearance through hepatobiliary tract. In addition, the biodistribution of some radiopharmaceuticals may be altered by the development of conditions secondary to renal failure. In some cases, dialysis performed shortly after radiopharmaceutical administration may effectively substitute for kidney elimination and thus allow the imaging procedure to proceed relatively unaffected.

#### **Bone Agents**

Approximately half of the injected dose of Tc-99m bone agents is normally excreted in the urine in the first several hours after administration. In patients with renal insufficiency, decreased clearance of the radiopharmaceutical results in prolonged blood pool activity and higher than normal soft-tissue activity. However, increased blood lev-

els in these patients do not lead to higher uptake of the radiopharmaceutical in the bone. Hence, in patients with renal failure (and without metabolic bone disease), bone-to-soft tissue ratios are substantially lower than normal. In these patients, hemodialysis performed from 15 minutes to 5 hours after injection of the radiopharmaceutical can successfully decrease blood pool and soft tissue activity to nearly normal levels.<sup>7,8</sup>

Diffuse abdominal uptake of Tc-99m bone agent was reported in a patient undergoing CAPD.<sup>9</sup> Tc-99m medronate (MDP) is able to diffuse through semi-permeable membranes, so localization in the peritoneal cavity occurred as a result of diffusion from the blood into the dialysate solution along a concentration gradient.

The selective adsorption of Tc-99m diphosphonates to newly mineralizing bone suggests that overall skeletal uptake will be related to the general metabolic state of the skeleton, as influenced by parathyroid hormone (PTH), vitamin D, calcium, and phosphorous availability. For conditions associated with increased bone turnover, and thus increased bone formation, increased uptake and whole-body retention of Tc-99m diphosphonates will result. Hence, bone scintigraphy in dialysis patients with metabolic bone disease (e.g., osteitis fibrosa) typically exhibit generalized increased uptake in the skeleton.<sup>8</sup> This increased bone metabolism, and corresponding increased radiopharmaceutical uptake, in renal failure is largely related to secondary hyperparathyroidism.

Dialysis patients frequently have elevated blood levels of calcium and phosphorous. When the  $\text{Ca} \times \text{PO}_4$  solubility product is exceeded, extra-osseous precipitation can occur. This is referred to as calcinosis or metastatic calcification. Similar to uptake on bone, Tc-99m diphosphonates can localize at these sites. The threshold for this phenomenon in dialysis patients is a  $\text{Ca} \times \text{PO}_4$  product of about 60, where the concentration of each substance is in units of mg/dl.<sup>10</sup> Solubility is also affected by regional pH, so calcification tends to occur initially in tissues that are relatively alkaline, namely lungs

(because of expiration of carbon dioxide), gastric mucosa (because of secretion of hydrochloric acid), kidneys (because of excretion of hydrogen ion), and left ventricle (because of low carbon dioxide content).<sup>10</sup>

Increased uptake on skeletal scintigraphy due to calcification is most often seen in lungs, but may also be observed in stomach, heart, kidneys, and joints.<sup>8,10-19</sup> Calcifications can occur in other soft tissues, including major blood vessels, and can be similarly observed with bone scintigraphy.<sup>13,20</sup> Calcifications of coronary arteries and cardiac valves, while common in patients with end-stage renal disease, are rarely visualized with bone scintigraphy due to their small size, but may be detected with electron beam computed tomography.<sup>21,22</sup> Uptake of Tc-99m bone agent in a calcified dialysis access graft has also been reported.<sup>23</sup> A word of caution however: stomach uptake is not always related to gastric calcification. In one report, visualization of stomach (with or without thyroid visualization) in several hemodialysis patients was related to uptake of free pertechnetate liberated from radiochemical interaction of Tc-99m bone agents with dialysate solution constituents (i.e., calcium and magnesium) in a closed-circuit hemodialysis device that used recirculating dialysate.<sup>24</sup>

Another condition associated with hemodialysis is amyloidosis (i.e., a condition associated with deposition of  $\beta_2$  microglobulin in joint spaces). Increased uptake of Tc-99m bone agents has been observed in amyloid deposits, especially in periarticular areas.<sup>8,25</sup>

High blood levels of aluminum are occasionally encountered in dialysis patients secondary to use of aluminum hydroxide as a phosphate binding agent. Hyperaluminemia can cause aluminum-related bone disease, which manifests as a generalized decrease in skeletal uptake on bone scintigraphy. This decreased uptake may be related to aluminum directly suppressing the parathyroid glands' secretion of parathyroid hormone and/or directly inhibiting bone mineralization.<sup>8</sup>

The radiation dose received by patients with impaired renal function is expected to be somewhat higher because of prolonged retention in blood pool and soft tissues and/or increased skeletal uptake due to metabolic bone disease. Under these conditions, the effective dose equivalent is slightly increased from 4.4 mSv/550 MBq (440 mrem/14.86 mCi) to 4.5 mSv/550MBq (450 mrem/14.86 mCi).<sup>8</sup>

### **Brain Agents**

Unusual brain images in two patients on chronic hemodialysis have been reported.<sup>26</sup> In each patient, prominent and dilated appearance of cranial sinuses on the 3-4 hour delayed images suggests excessive blood pool activity. In one patient, this altered biodistribution was possibly caused by hemodialysis-related elevated blood levels of tin that resulted in *in vivo* radiolabeling of red blood cells with Tc-99m sodium pertechnetate. In the other patient, the authors speculate that chemical alteration of Tc-99m pentetate (DTPA) or mechanical damage to the red cells may have played a role.

Localization of Tc-99m pertechnetate in the choroid plexus has been observed in numerous hemodialysis patients, in spite of pre-medication with potassium perchlorate or iodide.<sup>27</sup> Persistent localization in the salivary and thyroid glands of these same patients suggest that some alteration in anion handling occurs in renal failure. The fact that visualization of choroid plexus was not seen when Tc-99m DTPA was used further supports the hypothesis of altered anion handling in renal failure patients.

### **Myocardial Perfusion Agents**

The mainstay myocardial perfusion agents, Tl-201 thallous chloride (Tl-201), Tc-99m sestamibi, and Tc-99m tetrofosmin, are also used in the evaluation of parathyroid glands. Increased uptake of these agents in parathyroid glands is seen in dialysis patients who have developed secondary hyperparathyroidism. The purposeful use of this procedure to detect and evaluate this complication is discussed later in this lesson.

Visualization of bone structure with Tc-99m sestamibi was observed in one patient on hemodialysis.<sup>28</sup> The cause of this abnormal uptake was not related to increased bone turnover or to marrow hyperplasia, as indicated by normal bone and marrow scintigrams. Perhaps delayed clearance due to renal failure played a role in this case.

Tl-201 has also been reported to accumulate in articular and periarticular sites of active amyloidosis.<sup>25</sup> This localization may be related to a local inflammatory process.

### **Renal Agents**

In many centers, imaging with Tc-99m renal agents is performed early after renal transplantation to monitor function and provide information about post-operative complications. In patients undergoing renal transplantation directly from CAPD maintenance, loculated collections of residual dialysate solution may remain in the abdomen for up to a week. These fluid collections may produce photon-deficient lesions on Tc-99m DTPA renal transplant scintigrams performed soon after transplantation.<sup>29</sup> Such photon-deficient areas could be misinterpreted as hematoma, urinoma, lymphocele, etc. In these situations, an ultrasound procedure should be performed for clarification.

### **Gallium-67 Citrate**

Early after injection, gallium-67 citrate (Ga-67) undergoes significant bowel and urinary elimination. However, because Ga-67 is highly protein-bound to plasma transferrin, dialysis may be much less effective in reducing plasma levels of Ga-67 than it is in reducing plasma levels of radiopharmaceuticals that are not highly bound to plasma proteins.

In a study of 3 patients, Levine et al.<sup>30</sup> determined that peritoneal dialysis removed 2-5% of administered Ga-67 in the first 24 hours. This compares to normal urinary excretion of 12-26% in the first 24 hours. The concentration of Ga-67 in the dialysate was proportional to that in the plasma, with a plasma:dialysate ratio of approximately

50:1. Although peritoneal dialysis was only modestly effective for removing Ga-67, imaging at 24 hours revealed normal biodistribution. The authors concluded that peritoneal dialysis is not a contraindication to radiogallium scintigraphy.

A case report involving another CAPD patient found similar results.<sup>31</sup> Following Ga-67 injection, two successive 12-hour periods of peritoneal dialysis removed only 0.57% and 0.66% of the administered activity, respectively. Plasma clearance of Ga-67 was determined to be 0.7 ml/min. Although peritoneal dialysis removed a negligible fraction of Ga-67, images obtained up to 144 hours after injection showed normal biodistribution with the exception of mild diffuse lung accumulation and some uptake at the site of the dialysis catheter.

Studies of the effect of hemodialysis on Ga-67 removal also found similar results.<sup>32</sup> In eight patients undergoing hemodialysis with a standard membrane, 0.5%-8% of the injected Ga-67 was removed. In one patient undergoing ultrafiltration, Ga-67 removal was 0.5%. Images of all patients at 24 hours showed good quality with no alterations attributable to dialysis. Moreover, the time of injection prior to dialysis, ranging from 10 minutes to 4 hours, had no effect on the quality of the images.

Diffuse pulmonary uptake of Ga-67 has been noted in some dialysis patients.<sup>16</sup> In the absence of other causative factors (e.g., pulmonary inflammation, infection, malignancy, or pulmonary-toxic medications), this uptake appears to be related to uremic pulmonary calcification (calcinosis), similar to that observed with Tc-99m bone agents.

Another case report of altered Ga-67 biodistribution in a hemodialysis patient involved the additional factors of aluminum toxicity and desferoxamine treatment.<sup>33</sup> The image of this patient obtained at 48 hours showed diffuse whole body activity with minimal localization in any organ. The mechanism for this altered biodistribution is not confirmed, but it is known that high levels of aluminum can displace gallium from transferrin binding sites and that desferox-

**Table 2. Reported Alterations in Radiopharmaceutical Biodistribution Caused by Chronic Renal Failure/Dialysis.**

(see text for further descriptions and reference citations)

Radiopharmaceutical	Alteration	Mechanism
Tc-99m bone agents	↑ soft tissue activity	↓ renal clearance
	diffuse abdominal uptake	diffusion into CAPD dialysate solution
	↑ bone uptake	↑ bone metabolism due to secondary hyperparathyroidism
	↑ uptake in lungs, stomach, kidneys, heart, and joints	calcinosis
	↑ uptake in joints	amyloidosis
	↓ bone uptake	aluminum-related bone disease
Tc-99m pertechnetate	↑ blood pool activity	radiolabeled red cells due to ↑ blood levels of Sn
	↑ uptake in choroid plexus, thyroid, and salivary glands	altered anion handling by tissues
Tc-99m DTPA	↑ blood pool activity	↓ renal clearance; mechanical damage to red blood cells (?)
	"cold spots" in abdomen	collections of CAPD dialysate fluid
Tc-99m sestamibi	↑ uptake in parathyroid nodules	parathyroid hyperplasia
	↑ uptake in bone	↓ renal clearance
Tc-99m tetrofosmin	↑ uptake in parathyroid nodules	parathyroid hyperplasia
Tl-201	↑ uptake in parathyroid nodules	parathyroid hyperplasia
	↑ uptake in joints	amyloidosis
Ga-67 citrate	↑ blood pool activity	↓ renal clearance
	↑ uptake in lungs	calcinosis
	diffuse whole body activity	binding to desferoxamine
	↑ uptake in joints	amyloidosis
I-131 sodium iodide	↑ blood pool activity	↓ renal clearance
	↑ thyroid uptake	prolonged plasma concentrations provide increased availability of I-131 for thyroid uptake
I-131 MIBG	↑ soft tissue activity	↓ renal clearance
	↑ adrenal uptake	prolonged plasma concentrations provide increased availability of I-131 MIBG for adrenal uptake
In-111 or Tc-99m leukocytes	↑ lung uptake	leukocyte aggregation related to activation of the complement cascade by the dialysis membrane

amine avidly binds gallium.

Ga-67 has also been reported to accumulate in articular and periarticular sites of active amyloidosis.<sup>25</sup> This localization may be related to a local inflammatory process.

### **Radioiodine**

It is difficult to determine thyroid function in patients with severe renal disease because the usual radioactive iodine techniques depend on normal excretion of iodide. Low renal clearance of iodine results in elevated and prolonged plasma concentrations which promotes increased radioactive iodine uptake in the thyroid, at least until saturation of the trapping mechanism occurs. Hence, a thyroid radioactive iodine uptake value in the normal range may not rule out hypothyroidism.<sup>34</sup>

The ability of hemodialysis to remove radioiodine was studied in seven patients.<sup>34</sup> Dialysis performed one hour after oral administration of I-131 sodium iodide was capable of removing approximately 82% of radioactivity present in the blood.

In a more detailed study involving 13 patients, hemodialysis was performed 2-6 days following administration of I-131 sodium iodide.<sup>35</sup> The amount of "available" iodine (i.e., iodine not already taken up into the thyroid gland) removed by dialysis ranged from 3% to 77%, with a mean of 45%. The percent removed was directly related to the plasma concentration of radioiodine, i.e., it correlated with the concentration gradient between plasma and dialysate. During the dialysis procedure, the clearance of radioiodide was  $154 \pm 18$  mL/min, which is approximately six-fold greater than the renal clearance in control subjects of  $26.2 \pm 7.4$  mL/min.

### **I-131 MIBG**

I-131 iobenguane (MIBG) is primarily excreted unchanged through the kidneys. Hence, impaired renal function would be expected to alter its biodistribution and kinetics. This hypothesis was confirmed in one anephric patient on hemodialysis.<sup>36</sup> Imaging of this patient showed higher back-

ground activity and more prominent adrenal uptake compared to patients with normal renal function. This probably resulted from sustained, high blood activity that forced more of the agent to the tissues. Dialysis proved to be ineffective, with negligible or only slight decrement of blood activity following two hemodialysis sessions. The distribution of radioactivity between plasma and red cells demonstrated an unusually high plasma concentration in the anephric patient (89% vs. 15% in controls). As a result of altered kinetics and clearance in renal failure, the radiation dose to blood in this anephric patient was approximately 30 times greater than in patients with normal renal function.

### **In-111 Leukocytes**

Hemodialysis can lead to complement activation with subsequent leukocyte aggregation in the pulmonary capillaries. Increased localization of In-111 leukocytes may be observed in the lungs of dialysis patients, and should not necessarily be interpreted as infection.<sup>37</sup>

### **Summary of Reported Alterations**

Alterations in the biodistribution of radiopharmaceuticals may be caused by a variety of factors associated with chronic renal failure or dialysis, including decreased renal excretion, electrolyte abnormalities, hormonal modulation, and inflammatory processes. Reported alterations are summarized in Table 2.

## **USE OF RADIOPHARMACEUTICALS TO EVALUATE COMPLICATIONS OF CHRONIC RENAL FAILURE AND DIALYSIS**

Several metabolic conditions are associated with chronic renal failure and dialysis, including disorders of the skeleton, joints, and parathyroid glands. Non-metabolic complications, such as peritoneal leaks during peritoneal dialysis, can also occur. Although these complications are frequently diagnosed and monitored by physical assess-

ment and lab testing, nuclear medicine imaging can play an important role in many patients.

### **Metabolic Bone Diseases**

Renal osteodystrophy describes the spectrum of disorders of mineral and skeletal metabolism associated with chronic renal failure. The mechanisms involved in the development of osteodystrophy are complex and include numerous factors which interact to variable degrees to result in variable manifestation of disease.

Osteitis fibrosa, the most common bone disorder in end-stage renal disease, involves increased bone turnover (resorption and formation) and is associated with variable degrees of marrow fibrosis. As functional renal mass is lost, the renal conversion of Vitamin D to its active metabolites decreases, which leads to reduced intestinal absorption of calcium, which leads to hypocalcemia. Failing kidneys also inadequately excrete phosphate, thus leading to hyperphosphatemia which further aggravates hypocalcemia. Hypocalcemia is the most powerful stimulus for secretion of parathyroid hormone, which attempts to normalize calcium and phosphate concentrations by increasing tubular reabsorption of calcium and excretion of phosphate. Laboratory studies suggest that elevated serum phosphorus can also stimulate parathyroid hormone synthesis and release, independent of serum calcium concentrations.<sup>38</sup> Parathyroid hormone stimulates bone resorption and formation, and prolonged elevation of parathyroid hormone levels leads to a variable degree of marrow fibrosis and subperiosteal neo-ostosis (new bone formation).<sup>8</sup>

Osteomalacia is characterized by a delay in matrix mineralization, resulting in the accumulation of osteoid tissue. Commonly co-existing with osteitis fibrosa, osteomalacia is also associated with deficiency of Vitamin D active metabolites. Another factor associated with osteomalacia is high concentrations of aluminum, mainly due to aluminum-contaminated dialysis solutions<sup>8</sup> and the use of aluminum hydroxide as a phos-

phate binder.

Adynamic bone disease is also related to aluminum overload, which interferes with osteoblast function. Hence, this leads to formation of defective bone, which is more susceptible to fracture.<sup>8</sup>

Common features of bone scintigraphy in the evaluation of metabolic bone disease, especially in patients with secondary hyperparathyroidism, include diffuse increased activity in the axial skeleton, long bones, sternum, skull, jaw, and wrists, beading of the costochondral junctions, and faint or absent kidney uptake.<sup>8,20,39-41</sup> If bone disease is aluminum-related or is purely osteomalacic, however, bone scintigraphy shows decreased skeletal uptake and high soft tissue activity.<sup>8,41</sup> Skeletal fractures related to osteomalacia or adynamic bone disease are readily detected by bone scans as focal lesions.<sup>8</sup>

A simple method to evaluate diffuse increased skeletal activity in patients with metabolic bone disease is with target-to-non-target (i.e., bone-to-soft tissue) ratios on delayed images.<sup>39,42-44</sup> For example, one study reported mean 4-hour bone-to-soft tissue ratios of  $4.05 \pm 0.69$  and  $6.29 \pm 1.6$  in normal controls and in patients with renal osteodystrophy, respectively.<sup>44</sup> Additionally, elevated bone-to-soft tissue ratios may favorably decrease in response to medical (e.g., oral calcium and Vitamin D) or surgical (e.g., parathyroidectomy) treatment.<sup>41-42</sup> In some cases, however, the magnitude of diffuse increased skeletal uptake in metabolic bone disease may be difficult to discern, especially in patients with mild disease or who exhibit less substantial changes during serial monitoring. Simple bone-to-soft tissue ratios are of limited utility in these situations because of the variability in soft tissue concentrations. Hence, semi-quantitative techniques for evaluating skeletal uptake have been developed.<sup>7,40,45-47</sup> The semi-quantitative analyses may also be helpful in evaluating response to oral calcium and Vitamin D therapy.<sup>46</sup> A quantitative method has also been described which relies on determination of 24-hour whole body retention of Tc-99m

diphosphonate.<sup>44</sup>

### Calcinosis

Crystal deposition in soft tissues can occur in patients with renal bone disease. Elevations in the Ca X P product, predominantly due to increased phosphorous concentration, is a common cause of extra-osseous calcifications in patients on chronic hemodialysis; at autopsy, pulmonary calcifications were observed in 60-75% of adult patients, renal calcifications in 53-92%, gastric calcifications in 53-60%, and cardiac calcifications in 53-58%.<sup>8</sup> Depending on size and chemical composition, these calcifications are readily detected on bone scintigraphy (see Figure 2). In dialysis patients with hyperphosphatemia and hypermagnesemia, formation of amorphous Ca/Mg/P complexes may result in calcifications in visceral organs. However, poor localization of Tc-99m diphosphonates in crystals high in Mg and pyrophosphate content leads to a fairly low overall sensitivity of bone scintigraphy for visceral calcinosis.<sup>8</sup>

Deposition in joints of hydroxyapatite, alone or in combination with calcium pyrophosphate dihydrate crystals, can cause

significant articular disease, especially in shoulders, hips, knees, and wrists.<sup>8,11</sup> Elevations in the Ca X P product in patients on peritoneal dialysis or hemodialysis may be related to the development of articular calcifications.<sup>11</sup> Increased joint uptake of Tc-99m bone agents is non-specific, however, so correlation with other tests is necessary for a specific diagnosis.

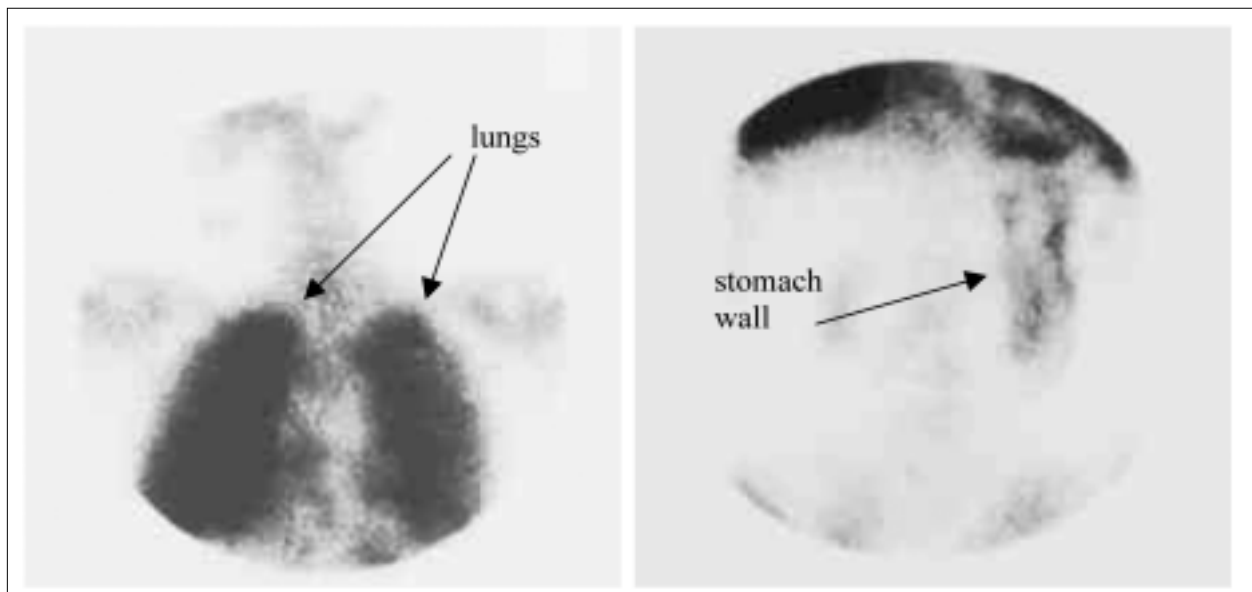
Pulmonary calcification in hemodialysis patients is associated with impaired lung diffusion capacity. In one rare case, diffuse calcification of alveolar capillary walls led to acute respiratory failure and death of a hemodialysis patient.<sup>19</sup> Tc-99m diphosphonate imaging for detection of pulmonary calcinosis may be useful in the evaluation of hemodialysis patients who have unexplained dyspnea.<sup>12,19</sup>

Cardiac calcification in hemodialysis patients poses a serious risk for life-threatening thromboembolic complications. Tc-99m diphosphonate imaging for detection of cardiac calcinosis may be useful in the evaluation of hemodialysis patients who have cardiac complications, and in the monitoring of treatment modifications in these patients.<sup>18</sup>

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### Figure 2. Calcinosis.

Chest and abdomen images from a Tc-99m medronate bone scan demonstrate localization in lungs and stomach wall due to calcification in these organs.





## **Amyloidosis**

Deposition of amyloid in various areas of the body may result in a number of different clinical syndromes such as carpal tunnel syndrome, cystic bone lesions, and arthritis in various joints. Amyloid (specifically  $\beta_2$ -microglobulin amyloid) deposits appear to be related to duration of dialysis, and are seldom seen with hemodialysis therapy of less than 5 years.<sup>8</sup> The development of amyloidosis rises to about 50% after 15 years and essentially 100% after 20 years of dialysis. The optimal treatment of amyloidosis is renal transplantation.<sup>48</sup> Unfortunately, most patients with amyloidosis are not suitable candidates for transplantation. For these patients, palliative treatment may include analgesics, corticosteroids, or surgery.<sup>48</sup> Switching from conventional cellulose membranes to high-flux biocompatible membranes may also provide subjective improvement.<sup>48</sup>

Amyloid preferentially deposits in collagen-rich osteo-articular tissue. Accordingly, bone scintigraphy frequently demonstrates increased uptake in articular and/or periarticular areas, such as wrists, hips, knees, and ankles.<sup>8,25,49,50</sup> Although bone imaging cannot make a definite diagnosis of amyloidosis, it is particularly useful as a diagnostic adjunct, especially in those patients unable or unwilling to undergo biopsy.<sup>50</sup> Moreover, bone imaging is useful in determining appropriate site(s) for biopsy.<sup>25</sup> However, bone imaging is not able to differentiate active from inactive amyloidosis, and hence is not useful for monitoring response to therapy.<sup>25</sup>

In a study of 8 patients demonstrating increased periarticular uptake on bone scintigraphy associated with dialysis-related amyloidosis, Tl-201 and Ga-67 citrate imaging showed analogous increased periarticular uptake in 6 of these patients.<sup>25</sup> Repeat imaging performed after 3 months of therapy showed marked reductions in periarticular uptake of Ga-67 citrate and nearly complete resolution of Tl-201 uptake. Hence, Tl-201 and Ga-67 citrate appear to be able to differentiate active from inactive amyloidosis, and thus may be useful for monitoring response

to therapy.

Theoretically, radiolabeled amyloid should be able to provide improved sensitivity and specificity for detecting abnormal amyloid deposition. Successful visualization of amyloid deposits in wrists, shoulders, hips, and knee joints of hemodialysis patients has been reported using I-131  $\beta_2$ -microglobulin.<sup>49</sup> One limitation of this agent, however, is that it cannot be used in individuals with any intact renal function since  $\beta_2$ -microglobulin is promptly excreted; hence, it cannot be used to monitor amyloidosis after renal transplantation. A similar agent, I-123 radiolabeled serum amyloid protein (SAP), has also shown extremely promising results in visualizing amyloid deposits, especially in wrists, knees, and spleen.<sup>51</sup> Localization in affected shoulders and hips has been more difficult, however, because of blood pool background, tissue attenuation, and anatomical constraints. I-123 SAP has also demonstrated utility in monitoring regression of amyloid deposits in long-term dialysis patients following renal transplantation.<sup>51</sup> [Note: neither I-131  $\beta_2$ -microglobulin nor I-123 SAP is commercially available in the United States.]

## **Secondary Hyperparathyroidism**

Parathyroid hormone secretion is stimulated in patients receiving dialysis in response to hypocalcemia and hyperphosphatemia. Secondary hyperparathyroidism can be satisfactorily treated or prevented in most dialysis patients, but in a few patients it escapes medical control. Progressive, severe hyperparathyroidism probably occurs because of a shift in parathyroid tissue growth pattern, switching from polyclonal to monoclonal or oligoclonal proliferation.<sup>52</sup> In advanced stages, this tumor-like clonal growth results in a change from diffuse to nodular tissue hyperplasia. Treatment in these situations is surgical.

Although parathyroid scintigraphy is of proven utility in the pre-operative localization of parathyroid glands or adenomas in primary hyperparathyroidism, its usefulness in managing secondary hyperparathyroidism

pre-operatively is still controversial. The sensitivity for identifying hyperplastic glands is only about 50-70%.<sup>52-54</sup> However, for those hyperplastic glands that are identified, the specificity is nearly 100%.<sup>52</sup> Also, parathyroid scintigraphy may be very helpful in detecting ectopic parathyroid glands.<sup>52,53,55</sup> Parathyroid scintigraphy is superior to magnetic resonance imaging and to ultrasonography in the localization of hyperplastic parathyroid glands and ectopic parathyroid glands in hemodialysis patients with secondary hyperparathyroidism.<sup>53</sup>

In the continued management of patients with persistent or recurrent hyperparathyroidism post-parathyroidectomy, parathyroid scintigraphy is the method of choice to localize parathyroid glands missed by surgery.<sup>55</sup>

Parathyroid scintigraphy has traditionally been performed using Tl-201 with thyroid (i.e., I-123 or Tc-99m pertechnetate) subtraction.<sup>56</sup> Nowadays, most centers use Tc-99m sestamibi for parathyroid scintigraphy. Imaging is usually performed very soon after injection, which shows uptake in both thyroid and hyperplastic parathyroid glands, and again after 90-120 minutes to assess dif-

ferential washout.<sup>52,53,55</sup> Hyperplastic parathyroid glands generally exhibit a much slower rate of washout than does thyroid tissue, so these foci tend to stand out on delayed images (see Figure 3). In some patients, the anatomic location of these glands may be better delineated using SPECT (see Figure 4). It is postulated that addition of I-123 subtraction may further improve sensitivity.<sup>52</sup> Tc-99m tetrofosmin may also be used for early localization of hyperplastic parathyroid glands,<sup>54</sup> but does not provide washout information like Tc-99m sestamibi does.

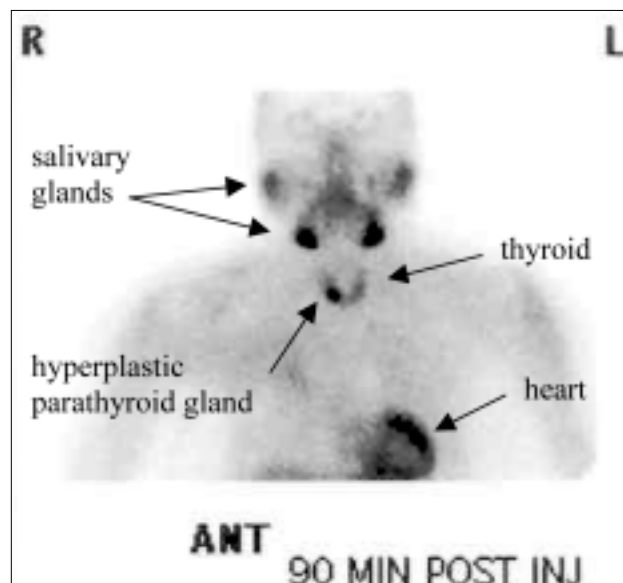
### Hypothyroidism

Many patients on chronic hemodialysis develop symptoms of hypothyroidism.<sup>34</sup> The cause of this is poorly understood, and is probably multi-factorial. The thyroid gland itself appears to maintain its functionality, as demonstrated by normal pertechnetate scans and normal increased I-131 uptake in response to TSH stimulation.<sup>34</sup> Thus other factors, affecting thyroid function either directly or indirectly, appear to be responsible. Available evidence suggests that the predominant mechanism may be direct effects by uremic toxins on the pituitary gland resulting in decreased release of TSH. Other potential mechanisms include direct effects by uremic toxins on the thyroid gland, interference of thyroid function by malnutrition, and elevation of inorganic iodide levels in plasma.<sup>34,57</sup>

Unfortunately, determination of thyroid radioactive iodine uptake in these patients is of little value in establishing the degree of hypothyroidism. For example, an abnormally low rate of thyroid uptake may be counterbalanced by the elevated and prolonged plasma concentration of radioiodine which may produce a final radioactive iodine uptake in the normal range.<sup>34</sup>

The decreased clearance of iodine, especially in combination with a high dietary intake of iodine, can result in a marked elevation in serum iodine levels in hemodialysis or CAPD patients.<sup>58</sup> Another cause of elevated serum iodine levels in dialysis patients

**Figure 3. Parathyroid Hyperplasia.** Planar image at 90 minutes shows greater retention of Tc-99m sestamibi in a hyperplastic parathyroid gland than in thyroid tissue.



may be absorption of iodine from topical or intraperitoneal povidone-iodine antiseptics, especially in CAPD patients.<sup>59</sup> In rare cases, this iodine excess can induce hypothyroidism. Such patients exhibit elevated TSH levels, enlarged thyroid glands, preserved radioactive iodine uptake values, and positive perchlorate discharge tests, all indicating an organification defect in the thyroid due to the Wolff-Chaikoff effect (i.e., iodine-induced inhibition of organification).<sup>58</sup> Correction of organification failure and restoration of euthyroidism may be achieved with a restricted iodine diet and avoidance of povidone-iodine products.

### Peritoneal Leaks

Peritoneal dialysis can induce leakage from the peritoneum into other cavities and spaces. The mechanism is not entirely clear, but may be related to pressure-enhanced transit of fluid through lymphatic channels, pressure-enhanced flow through microscopic or macroscopic defects in membranes, or pressure-induced opening of hernias.<sup>60-62</sup> In addition to the dialysate fluid itself, the

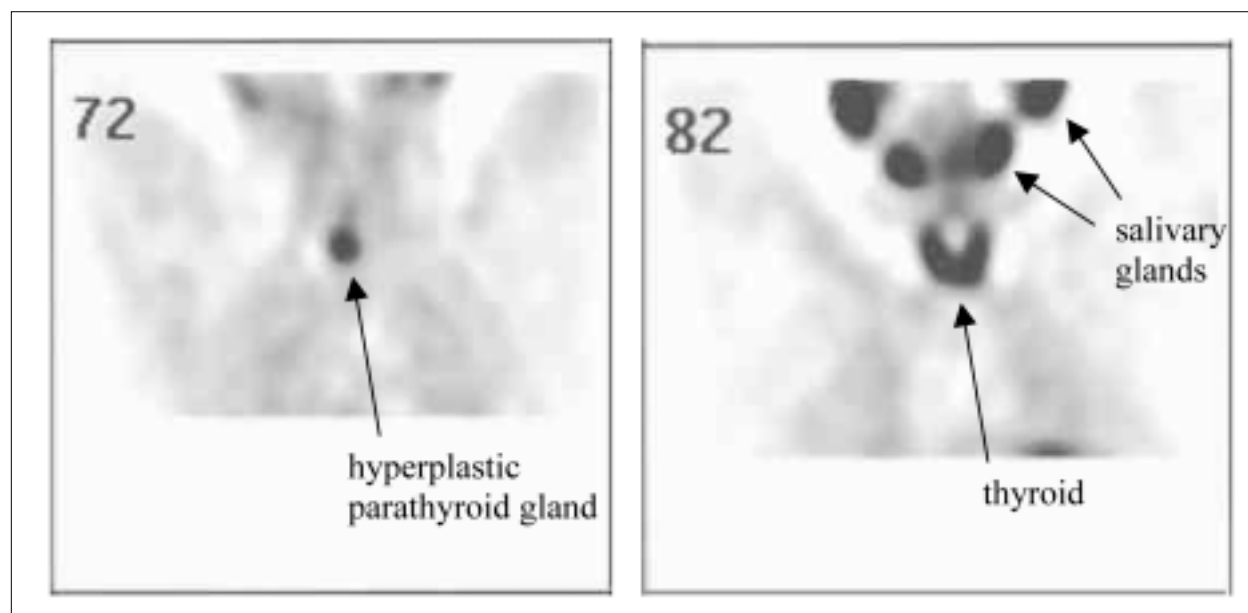
hypertonicity of the dialysate may draw local fluid into the cavity, thus adding to the volume and pressure. Chronic inflammation may also play a role in the leakage. Treatment of CAPD-induced leakage from the peritoneum is generally limited to either modification of CAPD therapy (e.g., smaller dialysate volume, intermittent therapy with rest periods in between, or switch to hemodialysis) or surgical interventions,<sup>6,62-67</sup> although intra-cavitary administration of sclerosing agents has been used successfully in some cases.<sup>62,68,69</sup>

Peritoneal leaks often develop in CAPD patients who have pre-existing structural defects. Prospective peritoneal scintigraphy prior to initiating CAPD is of limited prognostic value, however, because many pre-existing asymptomatic structural defects do not develop into symptomatic peritoneal leaks, and many peritoneal leaks develop *de novo* in the absence of identifiable pre-existing defects.<sup>70</sup>

Hydrothorax refers to the accumulation of fluid in the pleural cavity. In some cases, it may result in serious problems such as

### Figure 4. Parathyroid Hyperplasia.

SPECT imaging shows uptake of Tc-99m sestamibi in a hyperplastic parathyroid gland on a coronal slice (72). This slice is relatively deep in the body, demonstrating that the hyperplastic parathyroid gland is posterior to the thyroid gland which is seen in a more anterior slice (82).



dyspnea or respiratory distress. Dialysis-related hydrothorax may be unilateral or bilateral, but most commonly occurs on the right side.<sup>62,66</sup> It occurs more commonly in females than in males.<sup>66</sup> Hydrothorax may develop at almost any time during CAPD therapy, from one day to 8 years,<sup>62</sup> with about 40% occurring within the first 2 weeks.<sup>66</sup> The overall incidence of hydrothorax in CAPD patients is in the range of about 1.6% to 10%.<sup>62</sup>

The diagnosis of CAPD-related hydrothorax can usually be established with standard tests such as chest x-ray and pleurocentesis that demonstrates high glucose, low protein, and low lactate dehydrogenase content.<sup>68</sup> However, differential diagnosis is sometimes difficult, especially in the presence of other conditions such as congestive heart failure, hypoalbuminemia, malignant pleural effusion, or diabetes. In these situations, imaging of Tc-99m macroaggregated albumin (MAA) or Tc-99m colloid injected

into the peritoneal cavity can be valuable for detection of peritoneal-pleural communication<sup>60,62,66-74</sup> (see Figure 5).

Hernias are a relatively common complication of CAPD. The sustained elevation of intra-abdominal pressure during CAPD predisposes these patients to developing structural defects in the peritoneum and abdominal wall. The incidence of hernias in this population is in the range of about 5-24%. Identification and surgical correction of hernias are important because of their potential for life-threatening complications such as strangulation or incarceration. Hernias of various types (i.e., inguinal, umbilical/periumbilical, and ventral) can be readily detected following administration of Tc-99m DTPA or Tc-99m sulfur colloid into the peritoneal contents.<sup>6,64,67,70,75,76</sup>

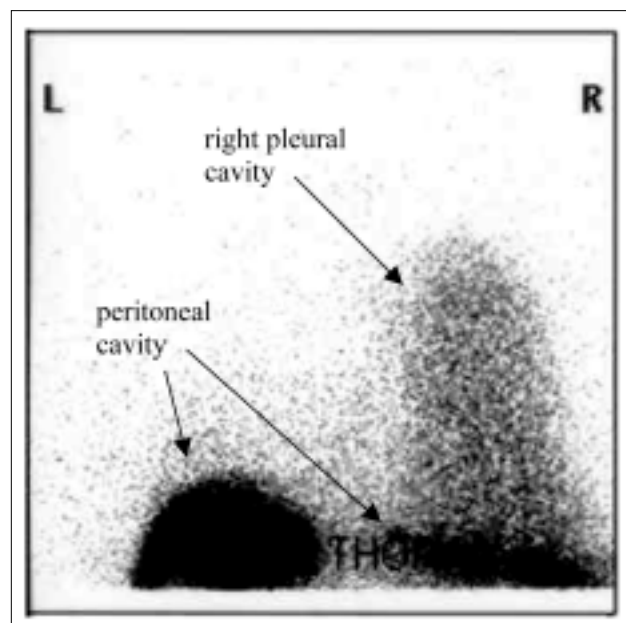
Scrotal edema can develop in some men following initiation of CAPD. This is apparently caused by opening of an inguinal hernia due to increased intra-abdominal pressure and flow of dialysis fluid from the peritoneal cavity through a patent processus vaginalis into the scrotum. The processus vaginalis is a downward fingerlike projection of the peritoneal cavity that develops during the second trimester of fetal life. It extends through the inguinal ring to allow the hormonally-stimulated descent of the testes into scrotum. Normally, almost all of this channel closes and a fibrous band retains the testicle at the distal end. However, in up to 15-37% of males, the processus vaginalis fails to obliterate and complete or partial patency persists.<sup>77</sup> Peritoneal-scrotal communication can be readily visualized following administration of Tc-99m MAA, Tc-99m DTPA, or Tc-99m sulfur colloid into the peritoneal contents.<sup>60,63,64,67,70,75-82</sup>

Pericatheter leaks of dialysis fluid at the site where the dialysis catheter passes through the abdominal wall can cause soft-tissue edema of the abdominal wall, flanks, buttocks, and external genitalia. These leaks can be readily visualized following administration of Tc-99m colloid into the peritoneal contents.<sup>6,60,65,67,70,75</sup> Corrective action for pericatheter leaks generally consists of either

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**Figure 5. Peritoneal-Pleural Communication.**

Following injection into the peritoneal cavity, Tc-99m sulfur colloid is observed in the right pleural cavity, indicating the existence of a peritoneal-pleural communication.



revision of catheter placement or insertion of a new catheter.

Several technical factors have been cited as important aspects in performing peritoneal scintigraphy in order to provide optimal diagnosis of peritoneal leaks.<sup>6,64,67,75,82</sup> Obviously, correct camera positioning over the area of suspected leakage and clinical correlation at the time of imaging is a prerequisite for a diagnostically accurate procedure. A non-absorbable radiopharmaceutical is preferred in order to prevent transfer across the normal, intact peritoneal membrane. The radiopharmaceutical should be mixed with or administered into the usual volume of dialysate solution used by the patient (e.g., typically 2 L), because lesser volumes may not increase intra-abdominal pressure sufficiently to demonstrate some dialysis-related leaks. Imaging soon after instillation is important to confirm uniform distribution within the peritoneal space, but delayed imaging is also important because some leaks may not become apparent for several hours. In some cases, leaks may be enhanced by patient activities, such as positional changes vis-à-vis gravity (e.g., standing vs. supine), movement (e.g., twisting, rolling, ambulation), or increased intra-abdominal pressure (e.g., Valsalva's maneuver). Lastly, some small leaks may only be demonstrated following drainage of the radiopharmaceutical/dialysate to remove background intraperitoneal activity. Tc-99m sulfur colloid is the radiopharmaceutical of choice because it is non-absorbable and shows little retention in the peritoneal space following drainage. Tc-99m MAA, while also non-absorbable, may be inferior for detection of certain leaks because it is less likely to flow through very small structural defects and it demonstrates substantial retention in the peritoneal cavity following drainage.<sup>60,75</sup>

### **Catheter-Related Infections**

Infection of vascular access sites is a significant complication in patients on hemodialysis. Bacteremia frequently follows vascular access infection, which occasionally can lead

to localized infection elsewhere in the body.<sup>83</sup> Risk factors for vascular access infection include excessive catheter manipulation, length of catheter placement, number of dialysis sessions, and diabetes. *Staphylococcus aureus* is the most common cause of vascular access infections in dialysis patients.

In rare cases, vascular access infections can lead to osteomyelitis. Clavicle, thoracic spine, ribs, tibia, and toes are usual sites of infection. Sternal osteomyelitis is rare. In-111 leukocyte imaging, with or without Tc-99m diphosphonate bone imaging, or Ga-67 imaging may be useful in establishing a diagnosis of osteomyelitis.<sup>84</sup> These imaging procedures can also be useful in monitoring response to antibiotic therapy.<sup>84</sup>

### **Abscess**

Minimal kidney function/urinary output in dialysis patients is associated with the development of urinary tract infections, especially in patients with polycystic kidney disease. In spite of antibiotic treatment, many of these infections go on to result in perinephric abscesses. Such perinephric abscesses can be readily identified with Ga-67 citrate scintigraphy.<sup>85</sup>

### **Pneumonitis**

Pulmonary edema in the absence of fluid overload or cardiac failure is a recognized complication of chronic renal failure. One contributing factor may be reduced plasma osmotic pressure, especially in patients with hypoalbuminemia resulting from malnutrition, proteinuria, or peritoneal losses while on CAPD. Another contributing factor may be increased permeability of the alveolar membrane resulting from endothelial damage caused by complement activation, neutrophil sequestration, or superoxide release associated with interactions with hemodialysis membranes. Limited information has been published, however, on the possible changes in pulmonary clearance of inhaled Tc-99m DTPA aerosol in dialysis patients.<sup>86</sup>

This information is important because some dialysis patients concurrently have AIDS, and thus are at risk of developing

*Pneumocystis carinii* pneumonia (PCP). The pulmonary clearance of inhaled Tc-99m DTPA aerosol in patients without renal disease has been shown to be markedly increased in patients with PCP. A recent study investigated the pulmonary clearance of inhaled Tc-99m DTPA aerosol in dialysis patients.<sup>86</sup> The results showed that Tc-99m DTPA clearance in both hemodialysis patients and CAPD patients, when controlled for smoking, were not significantly different from normal subjects. Therefore, pulmonary clearance of Tc-99m DTPA can be useful in the evaluation of suspected PCP in AIDS patients who are also on dialysis.

Another study evaluated alveolar permeability and lung ventilation in hemodialysis patients using Tc-99m DTPA aerosol.<sup>87</sup> The pulmonary clearance rate was slightly but significantly faster in hemodialysis patients than in normal control subjects. Visual assessment of the radioaerosol inhalation images revealed that nearly two-thirds of the hemodialysis patients showed ventilation abnormalities consisting of excess accumulation in the central portions of the lungs and/or hypoventilation of the basilar regions. The significance of these findings are unknown, but Tc-99m DTPA aerosol inhalation lung scans may be useful in the evaluation of lung ventilation and alveolar permeability in hemodialysis patients.

Alveolar permeability before and during hemodialysis was studied in a small group of patients using pulmonary clearance of Tc-99m DTPA aerosol.<sup>88</sup> Tc-99m DTPA aerosol clearance was significantly faster in non-smoking, chronic renal failure patients than in control subjects, indicating excessive alveolar permeability in the renal failure patients prior to hemodialysis. Following 4-5 hours of hemodialysis, however, Tc-99m DTPA aerosol clearance significantly slowed, indicating partial normalization of alveolar permeability. The mechanism for this improvement in alveolar permeability associated with hemodialysis is not known.

Tc-99m DTPA aerosol clearance was also used by another group to study alveolar permeability in hemodialysis patients.<sup>89</sup>

Using one particular hemodialysis membrane and dialysate solution, pulmonary clearance of Tc-99m DTPA aerosol did not significantly change before and after dialysis. This lack of effect, in contrast to that reported above, may have been related to use of one particular dialysis membrane and dialysate solution which was more biocompatible.

### **Pulmonary Embolism**

Approximately 50% of patients receiving hemodialysis have an arteriovenous polytetraethylene (PTFE) graft for vascular access. The rate of graft occlusion in these patients is about 25-45% per year. Thus clotted hemodialysis access grafts are a major source of morbidity and hospitalization of this group. Traditionally, surgery was the standard treatment for clotted access grafts. Recently, however, percutaneous thrombolysis has become widely accepted. This procedure is performed by administering a lytic agent (e.g., urokinase [historically] or alteplase) or a pulsed spray of heparinized saline, followed by angioplasty of the stenosed vein.<sup>90-92</sup>

A potential complication of these thrombolysis procedures is the production of pulmonary emboli. Perfusion imaging using Tc-99m MAA, with or without ventilation imaging (e.g., Xe-133), can readily detect significant pulmonary emboli in these patients.<sup>90-92</sup>

### **Dementia**

Some dialysis patients develop progressive mental deterioration, including diminished alertness, attention, and concentration; disturbances in memory, conceptualization, and speech; and dementia. Potential causes that have been suggested include inadequate dialysis (i.e., the presence of uremic toxins), recurrent hypotension or hypoglycemia, recurrent osmotic injury, electrolyte disturbances (e.g., hypercalcemia), depletion of water-soluble vitamins and metabolites, accumulation of heavy metals and aluminum, and accumulation of plasticizers.<sup>93</sup> Use of aluminum-free dialysate and reducing

other sources of aluminum has markedly reduced, but not eliminated, impairments in cognitive function.<sup>94</sup>

Traditional brain scans using Tc-99m pertechnetate in hemodialysis patients have been normal.<sup>93</sup> On the other hand, nuclear cisternography studies in these patients have demonstrated marked deviations in cerebrospinal fluid (CSF) flow and slow rates of clearance from the CSF.<sup>93</sup> Altered anion handling by the choroid plexus in hemodialysis patients, as demonstrated with Tc-99m pertechnetate imaging, may also be involved as it relates to secretion of CSF.<sup>27</sup> It remains unclear, however, whether these defects in CSF dynamics is the cause or an accompaniment of dialysis dementia.

SPECT brain imaging using Tc-99m exametazime (HMPAO) has demonstrated an abnormal distribution of cerebral perfusion in chronic hemodialysis patients.<sup>94</sup> Although hemisphere-to-cerebellar uptake ratios were normal, there was significant relative hypoperfusion in the frontal cortex and thalamus, while perfusion of the occipital cortex was well preserved. This perfusion pattern is distinctly different from that seen in patients with Alzheimer's disease. Because regional perfusion abnormalities did not correlate with cognitive test scores, however, the potential role of SPECT brain scans in dialysis patients remains unclear.<sup>95</sup>

PET studies using O-15 water and O-15 O<sub>2</sub> have been performed in hemodialysis patients to investigate the possible correlation of anemia with cerebral blood flow and oxygen metabolism.<sup>88</sup> Cerebral blood flow and oxygen extraction efficiency were higher in anemic hemodialysis patients compared to control subjects, apparently as an attempt to compensate for the decreased oxygen delivery in anemic hypoxia. Following treatment of anemia with recombinant human erythropoietin, cerebral blood flow and oxygen extraction efficiency decreased toward normal values as a direct function of hematocrit. Cerebral oxygen metabolism, however, was abnormally low in the anemic state and showed no improvement following treatment of anemia. Therefore it appears

that suppressed brain metabolism in hemodialysis patients is not related to anemia *per se*, but is probably due to vascular injuries or other chemical metabolic abnormalities related to chronic uremia.

### **Albumin Catabolism**

Hypoalbuminemia often occurs in patients with chronic renal failure, possibly because of restricted protein diets. This condition is generally corrected with maintenance hemodialysis. If desired in selected patients, albumin catabolism can be determined using radioiodinated human serum albumin.<sup>96</sup>

### **Gastric Emptying**

Many patients receiving peritoneal dialysis, and a few receiving hemodialysis, exhibit symptoms of anorexia, nausea, and vomiting which, in addition to presenting increased stress for the patient, may also contribute to malnutrition. These symptoms may be related, at least in part, to decreased rates of gastric emptying. Using Tc-99m labeled food (e.g., scrambled egg meal), gastric emptying rates can be easily determined in these patients.<sup>97-99</sup>

Gastric emptying of solids has been reported to be prolonged in about one-half of CAPD patients.<sup>97</sup> Several of these patients also exhibited delayed gastric emptying of liquids, as demonstrated using In-111 DTPA. These delayed gastric emptying results were unrelated to the presence of diabetes mellitus. The cause of delayed gastric emptying in these patients is unknown, but may be related to autonomic dysfunction or a direct effect of uremic toxins on gastric smooth muscle.

Another potential cause of delayed gastric emptying in CAPD patients is increased intra-abdominal pressure. A recent study in peritoneal dialysis patients indicates that gastric emptying is normal when no dialysis fluid is in the abdomen (drained) but is significantly slower when 2 L of dialysis fluid is in the abdomen.<sup>99</sup> Furthermore, this effect tended to be more pronounced in patients with smaller body surface area. In patients

**Table 3. Reported Use of Radiopharmaceuticals to Evaluate Complications of Chronic Renal Failure/Dialysis.**

(see text for further descriptions and reference citations)

Complication	Radiopharmaceutical	Characteristic Feature(s)
metabolic bone disease associated with secondary hyperparathyroidism	Tc-99m bone agents	↑ skeletal uptake, ↓ kidney uptake
metabolic bone disease, aluminum-related	Tc-99m bone agents	↓ skeletal uptake, ↑ soft tissue activity
calcinosis	Tc-99m bone agents	↑ uptake at sites of calcification (e.g., lungs, stomach, heart, kidney, joints)
amyloidosis	Tc-99m bone agents, Tl-201, Ga-67 citrate, I-131 β <sub>2</sub> -microglobulin, I-123 serum amyloid protein (SAP)	↑ uptake in joints
secondary hyperparathyroidism	Tl-201, Tc-99m sestamibi, Tc-99m tetrofosmin	↑ uptake in parathyroid hyperplasia
hypothyroidism	I-131 sodium iodide	not useful because ↓ rate of thyroid uptake may be counter-balanced by ↑ plasma concentrations which may result in a normal uptake value
peritoneal leaks in CAPD patients	Tc-99m sulfur colloid, Tc-99m MAA, Tc-99m DTPA (administered into peritoneal cavity)	flow into communicating structures (e.g., pleural cavity, hernias, scrotum, catheter tunnel)
infection/abscess	In-111 leukocytes, Ga-67 citrate	↑ uptake at site of infection
pneumonitis/pulmonary edema	Tc-99m DTPA aerosol	↑ rate of pulmonary clearance due to ↑ capillary permeability
pulmonary embolism secondary to thrombolysis of clotted access graft	Tc-99m MAA	↓ uptake in affected lung region
dementia	I-131 radioiodinated serum albumin (intrathecal)	altered CSF flow and ↓ clearance from CSF; unclear whether this is a cause or an effect
	Tc-99m HMPAO	↓ uptake in frontal cortex and thalamus; however, these abnormalities do not correlate with cognitive test scores
	O-15 oxygen	↓ cerebral oxygen metabolism



**Table 3 Continued.**

Complication	Radiopharmaceutical	Characteristic Feature(s)
hypoalbuminemia associated with excessive albumin catabolism	I-131 radioiodinated serum albumin	↓ plasma half-life, ↑ urine excretion
delayed gastric emptying	Tc-99m sulfur colloid in cooked egg, Tc-99m DTPA	↓ rate of gastric emptying due to autonomic dysfunction or effects of uremic toxins
delayed gastric emptying in CAPD patients	Tc-99m sulfur colloid in cooked egg	↓ rate of gastric emptying due to increased intra-abdominal pressure related to dialysis fluid in peritoneal cavity
pericardial effusion	Tc-99m HSA	accumulation in pericardial sac
cardiac neuropathy	I-123 MIBG	heterogenous cardiac uptake, ↑ clearance from the heart, ↓ clearance from the lungs

who demonstrate slowed gastric emptying, use of smaller dialysis fluid volumes and/or nocturnal intermittent peritoneal dialysis should be considered.

Solid phase gastric emptying studies are useful not only in the evaluation of dialysis-related gastroparesis, but also in assessing response to therapy.<sup>98</sup> Improvements in gastric emptying in response to prokinetic drug therapy (e.g., metoclopramide or erythromycin) can be extremely useful to guide therapy. Successful treatment of gastroparesis in these patients has resulted in significant improvements in serum albumin levels, at least in patients with moderately severe hypoalbuminemia.

### Pericardial Effusion

Pericardial effusion has been reported as an infrequent complication in hemodialysis patients.<sup>100</sup> Excessive fluid accumulation in the pericardial sac may occur in patients with uremic pericarditis associated with inflammation and fibrin formation. Such effusion can be readily visualized following intravenous injection of Tc-99m human serum albumin (HSA).<sup>100</sup> [Note: because human serum albumin kits are no longer commercially available in the United States, this radiopharmaceutical would have to be

extemporaneously compounded.]

### Cardiac Neuropathy

Some patients with chronic renal failure develop cardiac complications such as myocardial hypertrophy or decreased left ventricular contractility. Using I-123 iobenguane (MIBG) imaging, a group of hemodialysis patients exhibited more heterogeneous myocardial distribution and significantly faster cardiac clearance of I-123 MIBG compared with control subjects.<sup>101</sup> Plasma levels of dopamine and norepinephrine were also higher in hemodialysis patients than in controls. These data suggest that chronic renal failure patients on hemodialysis develop cardiac sympathetic overactivity. In addition, abnormal clearance of I-123 MIBG from the lungs in these patients implies concurrent pulmonary sympathetic dysfunction and/or endothelial dysfunction. The impact of this information on patient management remains to be determined. [Note: I-123 MIBG is not commercially available in the United States.]

### Summary of Reported Uses to Evaluate Complications

Routine nuclear medicine procedures can play an important role in evaluating compli-

cations of chronic renal failure or dialysis, including metabolic disorders in organs such as the skeleton, joints, and parathyroid glands and non-metabolic problems such as peritoneal leaks. Reported uses of radiopharmaceuticals to evaluate complications are summarized in Table 3.

### **RADIOPHARMACEUTICAL THERAPY IN DIALYSIS PATIENTS**

Compared to diagnostic procedures, radiopharmaceutical therapies represent a very small, but expanding, fraction of nuclear medicine practice. Needless to say, the need to perform radiopharmaceutical therapy in a patient receiving dialysis is rare. However, the situation may arise, and may elicit concerns such as modification of treatment dose, increased radiation doses to normal tissues, and increased radiation exposure to medical staff and family members. As might be expected, published information on the subject is limited, and is primarily in the form of case reports.

#### **I -131**

An early report described I-131 ablation therapy in a dialysis patient following subtotal thyroidectomy.<sup>102</sup> Preliminary investigations using a tracer dose of I-131 showed that, in this patient, thyroid uptake increased from 6% at 24 hours to 10% at 48 hours, and that hemodialysis was able to remove approximately 90% of radioiodide in plasma. Calculations indicated that waiting to perform dialysis until 48 hours after radioiodine administration would result in a cumulated activity (i.e., mCi-hours) of about 4 times that for patients with normal renal function. Accordingly, the patient was treated with only one-fourth of the customary dosage of I-131.

The second report of I-131 ablation therapy in a hemodialysis patient revealed somewhat different findings.<sup>103</sup> Following subtotal thyroidectomy for thyroid papillary carcinoma, the patient was treated with a relatively low dose, 50 mCi, of I-131 based on the case report described above. Residual and progressive disease, indicated by persist-

ent focal uptake of diagnostic I-131 and persistently elevated thyroglobulin levels, was subsequently treated with 120 mCi I-131, and again with 150 mCi I-131, but without success. Review of these failed treatments suggested that inadequate radiation dose was delivered because of rapid plasma clearance of I-131 by dialysis. Consequently, a tracer dose of I-131 was administered to the patient and its clearance from blood by the dialysis unit was monitored (each dialysis removed about 72% of the I-131 in the blood). Based on new dosimetry calculations incorporating these clearance data, the patient was treated with a high dose, 250 mCi, of I-131 with hemodialysis performed at 48 hour intervals after I-131 administration. Finally, partial success was achieved for ablating the patient's residual and metastatic thyroid tumor.

These same authors also described some of the radiation safety aspects of I-131 treatment in the hemodialysis patient.<sup>103</sup> After removing disposable parts and flushing the machine, contamination of the dialysis equipment was minimal and was therefore used again the next day for other patients. As might be expected, moderate contamination was detected on the patient's pillow case and inside the toilet. The only significant contamination occurred during one dialysis session when the dialysis waste fluid was directed into an improperly drained sink.

The management of I-131 therapy for thyroid cancer in another dialysis patient was detailed in a recent report.<sup>104</sup> Diagnostic imaging and blood sampling following a tracer dose of I-131 showed that hemodialysis performed 67 hours after administration removed 67% of whole body activity (80% of blood pool activity), and that a second hemodialysis performed at 115 hours removed 59% of remaining whole body activity (65% of remaining blood pool activity). Calculations determined that 100 mCi could be administered to this patient, which would deliver approximately 16,000 rads to residual thyroid tissue and functioning metastases and approximately 68 rads to the whole body. The patient was treated with

100 mCi I-131 and dialysis was performed 41 hours and again at 89 hours. Survey meter measurements before and after the first dialysis showed a whole body reduction in radioactivity of 76%.

These authors also described radiation safety aspects involved in this particular treatment.<sup>104</sup> The patient's hospital room was prepared according to the institution's customary procedures for radioactivity contamination control. To avoid spills, the drain hose from the dialysis unit was connected to the toilet for drainage of effluent dialysis waste. A 10-cm thick mobile lead shield was positioned to provide radiation protection to dialysis operators, and direct patient contact was limited to a maximum of two hours for each nurse. Film badges worn by dialysis/nursing personnel demonstrated no significant exposures (i.e., all badges registered below 10 mrem). Thyroid surveys of nuclear medicine, dialysis, and health physics personnel indicated no detectable I-131 uptake. Radioactive contamination of the dialysis machine was insignificant, allowing the equipment to be safely used after routine flushing maintenance. Contamination of the patient's room was similar to that typically seen for other patients treated with I-131.

Another group also reported on iodine dialysance and radiation safety concerns in a case involving I-131 treatment in a patient on hemodialysis.<sup>105</sup> The dialytic efficiency for radioiodide removal from the body was found to be dependent on time (or really on the amount of radioiodine remaining in the body), with about 60-70% removal soon after administration but dropping to 10% or less at later times. Exposure rates and contamination levels from the dialysis machine were minimal following flushing, thus allowing the machine to be safely reused for other patients.

I-131 treatment of thyroid cancer in two dialysis patients is the subject of another report.<sup>106</sup> Iodine kinetics in thyroid, salivary gland, and blood were variable, suggesting the necessity for individualized measurements and dosimetry determinations. In one

patient, hemodialysis performed 3 days after I-131 administration showed reductions in whole body activity of 60% and in blood activity of 78%.<sup>107</sup> There was no significant contamination of dialysis equipment. The authors suggest that dialysis could be performed earlier to decrease the absorbed dose to extra-thyroidal tissues.

I-131 treatment in 3 dialysis patients, one with Graves' Disease and two with thyroid cancer, was recently described.<sup>108</sup> Removal of radioiodide from the body by hemofiltration was about 50% in the thyroid cancer patients and about 20% in the Graves' Disease patient. Whole body effective half-lives were prolonged 2- to 3-fold in the thyroid cancer patients compared to patients with normal renal function, and at least 4-fold in the Graves' Disease patient. Lower fractional removal by dialysis and prolonged body retention in Grave's Disease is due to the much higher thyroidal uptake of I-131.

Graves' Disease was successfully treated in another patient on hemodialysis.<sup>109</sup> Treatment with 12.5 mCi of I-131 resulted in frank hypothyroidism by 3 months, which was effectively treated with thyroid hormone replacement therapy. No problems were encountered during the treatment, and there was no detectable radioactive contamination of the hemodialysis tubing.

Peritoneal dialysis, rather than hemodialysis, may be performed in some patients. One group described I-131 ablation therapy in two CAPD patients following thyroidectomies for thyroid cancer.<sup>110,111</sup> Preliminary investigations using tracer doses of I-131 or I-123 showed slightly elevated thyroid remnant uptakes of 2.9% and 3.5% in these two patients (compared to an average of 0.14% in 6 patients with normal renal function) and markedly prolonged blood elimination half-lives of 81.1 hours and 52.8 hours (compared to an average of 10.2 hours in 8 patients with normal renal function), respectively. The 24-hour dialytic removal of radioiodide was 22.6% and 25.0% of the administered dose in the two CAPD patients (compared to an average 24-hour urinary excretion of 72.4% in 8 patients with normal renal function).

Because mean total body residence times were nearly 5-fold greater in CAPD patients than in patients with normal renal function, absorbed doses per mCi to red marrow and total body would be 4- to 5-fold greater in CAPD patients. Accordingly, only 26.6 mCi and 29.9 mCi of I-131 were administered to these two CAPD patients (compared to a customary dosage of 150 mCi in patients with normal renal function). After 7-8 years of follow-up, neither patient had clinical recurrence of thyroid cancer.

In summary, dialysis patients can be successfully treated with I-131 for hyperthyroidism or thyroid cancer. Because dialysis is less efficient at removing I-131, compared to normal renal function, blood and total body retention are prolonged in dialysis patients. Biological half-lives vary substantially between individuals and are further influenced by procedure-related factors such as type of dialysis (hemodialysis vs. peritoneal) and timing of dialysis. Therefore, preliminary investigations using a tracer dose of radioiodide should be performed in dialysis patients to determine individual kinetics and provide data for individualized dosimetry calculations. Radiation protection of dialysis and nursing personnel can be achieved with mobile shielding, time limitations for direct patient contact, and proper disposal of dialysis effluents. With proper handling and flushing, contamination of dialysis equipment can be held to acceptable levels.

### **Sm-153**

A recent report described bone pain palliation with Sm-153 leixidronam (EDTMP) in a dialysis patient.<sup>112</sup> Because 6-hour urinary excretion of Sm-153 EDTMP is normally about 35% of the injected dose, blood and whole body retention of Sm-153 EDTMP was expected to be prolonged in this patient. Therefore, the administered dose was reduced from the standard 1 mCi/kg to 0.75 mCi/kg. Hemodialysis was performed 44 hours post-administration. Counting of blood and dialysate samples indicated that the dialysate concentration of

Sm-153 was about 22% of the blood concentration. Disposable portions of the dialysis equipment showed slight contamination and were stored for decay.

### **USE OF RADIOPHARMACEUTICALS TO EVALUATE DIALYZER FUNCTION**

The unique properties of radiopharmaceuticals allow them to be used for other investigative purposes. Of relevance here are a few reports of using radiopharmaceuticals to study various aspects of dialyzer function.

Tc-99m DTPA has been investigated as to its utility for measuring the effectiveness of dialysis.<sup>113</sup> Clearances of both creatinine and Tc-99m DTPA were determined in eight patients undergoing hemodialysis therapy and in six patients undergoing peritoneal dialysis. In hemodialysis patients, Tc-99m DTPA clearance was significantly correlated with creatinine clearance but averaged only 38% of creatinine clearance. Although dialysance of Tc-99m DTPA increased linearly with increased rates of blood flow, this increase was markedly blunted compared to that observed with creatinine. The modest effect of blood flow rate on Tc-99m DTPA clearance is because the dialysance of larger molecules is primarily related to the membrane permeability and surface area, and is less dependent on blood flow. In the peritoneal dialysis patients, Tc-99m DTPA clearance was significantly correlated with creatinine clearance and averaged 65% of creatinine clearance. Higher clearance of Tc-99m DTPA, relative to creatinine, in peritoneal dialysis is due to the higher permeability of the peritoneum to larger molecules relative to that of standard hemodialysis membranes. Tc-99m DTPA is thus a good marker for studying the permeability of hemodialysis and peritoneal membranes for middle-sized molecules. Moreover, Tc-99m DTPA can be used to assess the efficacy of new dialyzers or dialysis protocol variables.

Tc-99m DTPA has also been used to

measure the effects of changes in dialysis parameters within a single hemodialysis session.<sup>114</sup> In a comparison of two different types of dialyzer units, no significant difference in clearance was seen. Similar to the results of the study reported in the previous paragraph, alterations in blood flow to the dialyzer resulted in small, but not statistically significant, changes in Tc-99m DTPA clearance. However, alterations in dialysate flow did result in significant changes in Tc-99m DTPA clearance.

Devices with large surface areas, such as dialyzers, have the potential to consume circulating platelets by platelet-thrombus formation, embolization, and platelet disintegration. Platelets radiolabeled with In-111 or Tc-99m have been used to quantitate the thrombogenicity of hemodialyzers.<sup>115</sup>

Transient leukopenia following initiation of hemodialysis is a common phenomenon. Animal studies have suggested that leukocytes are sequestered in the lungs rather than in the dialyzer. In order to study this effect in humans, imaging of autologous leukocytes labeled with Tc-99m HMPAO was performed following initiation of hemodialysis using three different dialysis membranes.<sup>116</sup> In comparison to normal Tc-99m leukocyte accumulation in lungs without hemodialysis, a marked spike in lung sequestration of Tc-99m leukocytes occurred 10-20 minutes after the start of hemodialysis. This abnormal spike in pulmonary sequestration of leukocytes is likely related to activation of complement cascade by the dialysis membrane. The magnitude of this spike in pulmonary sequestration of leukocytes is strongly dependant on the type of dialysis membrane used, ranging from marked to undetectable for different membrane types.

Related to leukocyte sequestration in lungs during hemodialysis, release of inflammatory mediators is thought to cause microcirculatory inflammation in the lungs. Changes in the alveolar-arterial oxygen gradient due to this leukocyte trapping and increased alveolar permeability may be responsible, at least in part, for hypoxemia seen in many hemodialysis patients.<sup>89</sup> Tc-

99m DTPA aerosol clearance is a useful tool for assessing alveolar inflammation. In a recent study utilizing one particular type of dialysis membrane and dialysate solution, there was no significant change in Tc-99m DTPA aerosol clearance before and after hemodialysis, indicating no measurable effect of hemodialysis on alveolar inflammation.<sup>89</sup> Thus, determination of Tc-99m DTPA clearance may be useful for assessing biocompatibility of various dialysis membranes and dialysate solutions.

Amyloidosis will invariably develop in anuric hemodialysis patients because dialysis cannot effectively remove  $\beta_2$ -microglobulin from the plasma. Nonetheless, some dialysis membranes and/or techniques, especially those utilizing highly permeable membranes, are better than others at clearing this protein and thus delaying the onset of clinical symptoms.<sup>4</sup> I-131  $\beta_2$ -microglobulin has been used to evaluate the effectiveness of various dialysis membranes and techniques for removal of  $\beta_2$ -microglobulin from the body.<sup>117</sup> Differences in the binding of  $\beta_2$ -microglobulin to various dialysis membranes has also been studied using I-131  $\beta_2$ -microglobulin.<sup>117</sup>

In the laboratory, Tc-99m MAA has been used as a nondiffusible marker molecule to investigate the ultrafiltration and pressure profiles in dialyzers with different hydraulic permeabilities.<sup>118</sup> Because this agent is too large to cross dialysis membranes, changes in its concentration occur in response to changes in blood water content. Imaging of the dialyzer unit during different experimental conditions showed changes in radioactive concentration along the length of the unit which provided information on water fluxes involving filtration and backfiltration.

## CONCLUSION

Dialysis, either hemodialysis or peritoneal dialysis, is a common therapy in patients with chronic renal failure. A variety of factors associated with chronic renal failure or dialysis can alter the biodistribution of many radiopharmaceuticals. On the other

hand, a variety of radiopharmaceuticals can be used in the evaluation of many metabolic and non-metabolic complications of chronic renal failure/dialysis, as well as in the evaluation of certain aspects of dialyzer function. Also, several dialysis-related factors may require modification or individualization of

radiopharmaceutical therapy regimens.

Hopefully the information reviewed and summarized in this lesson will assist the reader in his/her professional consultations with other healthcare staff and thereby enhance the care of patients undergoing dialysis.

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## QUESTIONS

- Dialysis refers to the separation of substances by:
  - Differential retention in a chromatographic column.
  - Specific binding to membrane-bound receptors.
  - Concentration-gradient dependent diffusion through a semi-permeable membrane.
  - Variable adsorption to an ion-exchange resin.
- Dialysis, in a healthcare setting, generally refers to supplementation or replacement of \_\_\_\_\_ function.
  - Gastrointestinal
  - Hepatic metabolism
  - Hepatobiliary
  - Renal
- Which of the following characteristics positively influences the ability of a particular molecule to be dialyzed?
  - Highly protein-bound
  - Highly soluble in water
  - Large molecular weight
  - Large volume of distribution
- Based on physiochemical characteristics and biological handling, which of the following would be expected to be most efficiently removed from the blood by hemodialysis?
  - Tc-99m gluceptate
  - Tc-99m mebrofenin
  - Tc-99m red blood cells
  - In-111 capromab pendetide
- In CAPD, movement of substances across the peritoneal membrane is by:
  - Active transport.
  - Convection along an osmotic pressure gradient.
  - Diffusion along a concentration gradient.
  - Both (b) and (c).
- Which of the following is NOT a common site of metastatic calcification in dialysis patients?
  - Heart
  - Liver
  - Lungs
  - Stomach
- Which of the following best describes the ability to remove Ga-67 citrate from plasma?
  - Normal kidneys > hemodialysis > CAPD
  - Hemodialysis > normal kidneys > CAPD
  - CAPD > hemodialysis > normal kidneys
  - All three methods are equally effective
- For which of the following is hemodialysis LEAST effective for removal from the blood?
  - Ga-67 citrate
  - Tc-99m bone agents
  - I-131 MIBG
  - I-131 sodium iodide
- In hemodialysis patients, In-111 leukocytes tend to exhibit increased localization in:
  - Liver.
  - Lungs.
  - Marrow.
  - Spleen.
- Skeletal scintigraphy generally demonstrates elevated bone-to-soft tissue ratios in dialysis patients with:
  - Aluminum-related bone disease.
  - Osteitis fibrosa accompanied by secondary hyperparathyroidism.
  - Hypothyroidism.
  - Osteomalacia.

11. Articular uptake of Tc-99m diphosphonates may be seen with each of the following, EXCEPT:
  - a. Amyloidosis.
  - b. Elevated Ca X P product.
  - c. Hydroxyapatite calcinosis.
  - d. Hypermagnesiemia.
12. Increased uptake in areas affected by amyloidosis has been reported with all of the following, EXCEPT:
  - a. Ga-67 citrate.
  - b. I-131  $\beta_2$  microglobulin.
  - c. Tc-99m DTPA
  - d. Tl-201 thallos chloride.
13. Parathyroid scintigraphy in dialysis patients may be useful in detecting each of the following, EXCEPT:
  - a. Diffuse hypofunction of the parathyroid glands.
  - b. Ectopic parathyroid tissue.
  - c. Nodular hyperplasia of parathyroid tissue.
  - d. Residual parathyroid tissue missed by surgery.
14. Which of the following is NOT a contributing factor for developing leakage of dialysate from the peritoneal cavity in patients undergoing CAPD?
  - a. Chronic inflammation of peritoneal membranes
  - b. Presence of pre-existing structural defects in the peritoneal membrane
  - c. Unnaturally high pressure in the peritoneal cavity
  - d. Use of hypotonic dialysis solutions
15. Peritoneal scintigraphy in CAPD patients can be used to detect each of the following, EXCEPT:
  - a. Hydrothorax.
  - b. Inguinal hernia.
  - c. Pericardial effusion.
  - d. Pericatheter leaks.
16. Technical factors recommended in performing peritoneal scintigraphy in CAPD patients include all of the following, EXCEPT:
  - a. Administration of radiopharmaceutical with or into the patient's regular dialysis volume.
  - b. Imaging at multiple times (e.g., soon after administration, after several hours delay, after dialysate drainage).
  - c. Maintaining the patient motionless in a supine position.
  - d. Use of a non-absorbable radiopharmaceutical.
17. Alveolar permeability in dialysis patients can be evaluated using:
  - a. Tc-99m DTPA aerosol.
  - b. Tc-99m MAA.
  - c. Tc-99m sulfur colloid.
  - d. Xe-133 gas.
18. A potential complication of thrombolytic treatment of a clotted hemodialysis access graft is:
  - a. Cardiac neuropathy.
  - b. Dementia.
  - c. Pericatheter leak.
  - d. Pulmonary embolism.
19. Potential factors involved in delayed gastric emptying in some peritoneal dialysis patients include each of the following, EXCEPT:
  - a. Autonomic dysfunction related to uremic toxins.
  - b. Direct effect of uremic toxins on gastric smooth muscle.
  - c. Large volumes of dialysis fluid in the abdomen.
  - d. Prophylactic treatment with erythromycin.



20. Hemodialysis performed soon after administration of I-131 sodium iodide for thyroid cancer treatment will generally remove about \_\_\_\_ of plasma activity.
- 10%-30%
  - 30%-50%
  - 50%-70%
  - 70%-90%
21. Peritoneal dialysis performed for 24 hours after administration of I-131 sodium iodide for thyroid cancer treatment will generally remove about \_\_\_\_ of body activity.
- 10%-30%
  - 30%-50%
  - 50%-70%
  - 70%-90%
22. Which of the following is recommended when treating a dialysis patient with I-131 sodium iodide?
- Preliminary determination of radioiodide kinetics and individualized dosimetry calculations
  - Treatment with the customary dosage of I-131
  - Treatment with 1/4 - 1/2 of the customary dosage of I-131 because prolonged blood pool activity produces increased thyroid uptake
  - Treatment with 2 – 3 times the customary dosage of I-131 because dialysis produces exceptionally rapid blood pool clearance
23. All of the following are recommended when treating a hemodialysis patient with I-131, EXCEPT:
- Limit time of direct patient contact.
  - Place mobile shielding between the patient and staff personnel.
  - Properly dispose of dialysis effluent.
  - Store dialysis machine for 10 half-lives before flushing.
24. Which of the following would be most useful for assessing the efficacy of new dialyzers or dialysis protocol variables?
- Tc-99m DTPA
  - Tc-99m MAA
  - Tc-99m sodium pertechnetate
  - Tc-99m sulfur colloid
25. Using various radiopharmaceuticals, functional differences in dialysis membranes have been evaluated with regard to each of the following, EXCEPT:
- Causing hypoalbuminemia.
  - Inducing pulmonary sequestration of leukocytes.
  - Removing  $\beta_2$ -microglobulin from the body.
  - Thrombogenicity.





