2 Patient Preparation for FDG PET with an Emphasis on Soft Tissue Sarcoma and Melanoma: What Matters (and What Doesn't)

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Biological Background and Mechanism of F-18 FDG PET/CT

The purpose of functional imaging is to assess certain systems or functions of the body in the most unaltered state as possible. As such, in the evaluation of malignancy or potential malignancy with PET/CT, patient preparation is extremely important when assessing metabolic status with fluorine-18 fluorodeoxy-glucose (F-18 FDG or FDG). For many malignant cells, although not all and not all to the same degree, there is a higher level of metabolic activity compared to the normal surrounding tissue. This increase in metabolic activity increases the need for glucose. This was first studied by Warburg, who examined carbohydrate metabolism in rapidly growing dedifferentiated tumors and demonstrated that there was an increase in aerobic glycolysis and a decrease in cellular respiration. In his study, he used the example of normal liver cells compared to a hepatoma and proposed that a neoplastic change occurred when there was damage to the cellular respiration process, causing the cell to respond with an increase in its aerobic glycolysis to maintain normal ATP production (Fig. 2.1). This concept has since been named the Warburg effect [1, 2]. With an increase in metabolic demand for rapid growth, the tumor cells adapt to increase the efficiency of the metabolic pathway. These adaptations include an increase in the number of glucose membrane transporters (GLUTs), increased activity of hexokinase II (HX II), and a decreased level of glucose-6-phosphatase (G-6-P). These adaptations facilitate tumor growth by (a) increasing the amount of glucose entering into the cell through GLUT, (b) increasing the rate of phosphorylation by HX II to have glucose in the cell available for metabolism, and (c) decreasing the rate of dephosphorylating due to very low level of G-6-P that results in a decrease in the rate, if not the cessation, of the diffusion of G-6-P out of the cell (Fig. 2.2a and b).

The ability of PET/CT to evaluate the status of the metabolic activity of a cell is due to the use of the glucose analog fluorine-18 fluorodeoxy-glucose (FDG). F-18 FDG is taken into cells and phosphorylated by the same mechanism as natural glucose. To extract glucose from the blood circulation, cells use three independent mechanisms which include (1) diffusion; (2) protein-mediated, bidirectional, facilitated diffusion; and (3) active, protein-mediated transport [3]. The cell uses predominantly two families of glucose transporters: the GLUTs, which are the major glucose facilitators, and to a lesser degree sodium-driven glucose symporters (SGLT) to

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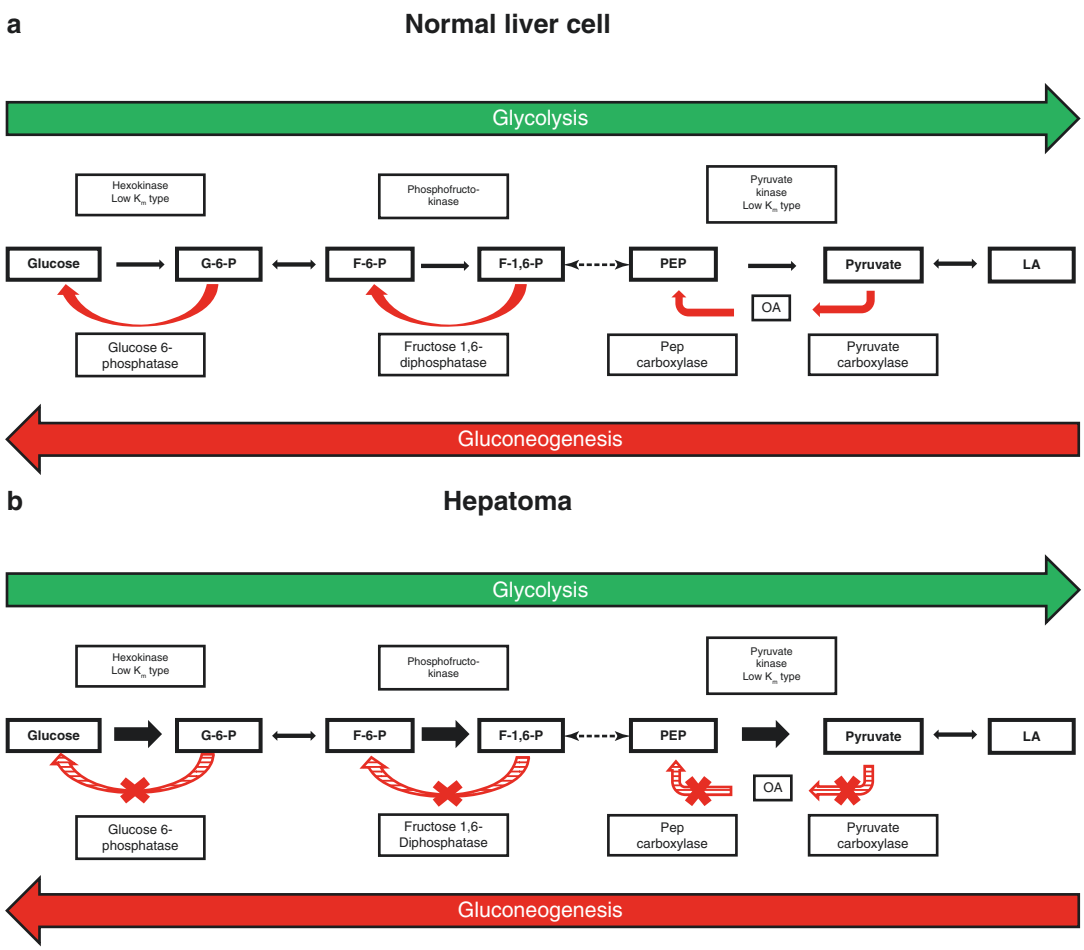


Fig. 2.1 Illustration of carbohydrate metabolism in a normal liver cell (**a**) compared to that of a hepatoma (**b**). Abbreviations: G-6-P glucose-6-phosphate, F-6-P fructose-6-phosphate, F-1,6-P fructose-1,6-phosphate, PEP phosphoenolpyruvic acid, OA oxaloacetate, and LA lactic acid

actively transport glucose into the cells [4]. The major glucose transporter family, the GLUTs, are comprised of 14 isoforms, although GULT-1 to GLUT-7 and GLUT-10 to GLUT-12 are the major transporters responsible for the active transport of F-18 FDG into the cells [4, 5]. Once F-18 FDG enters the cell, it is immediately phosphorylated by the hexokinase isozymes (HX I to IV). The phosphorylation creates F-18 FDG-6-phosphate (F-18 FDG-6-P), which is unable to diffuse out of the cell and awaits the next step in the glycolysis pathway. In tumor cells the GLUT-1 and HX II subtypes are the most important. However, unlike natural d-glucose, once F-18 FDG is phosphorylated into F-18 FDG-6-P, it is unable to continue through the pathway. F-18 FDG-6-P is not a substrate in the glycolysis pathway – this is because the next step in the pathway requires an oxygen atom at the C-2 position, which is missing in F-18 FDG-6-P [5]. Inside the cell there is an alternative pathway to glycolysis where the G-6-P/F-18 FDG-6-P can diffuse out of the cell. As mentioned previously, this pathway uses the enzyme glucose-6-phosphatase (G-6-P), which causes dephosphorylation of glucose-6-phosphate/F-18 FDG-6-P, allowing diffusion of glucose/F-18 FDG out of the cell. Certain cells in the body have an increased level of this enzyme naturally (i.e., liver and bowel), and thus there can be a lower concentration of F-18 FDG in

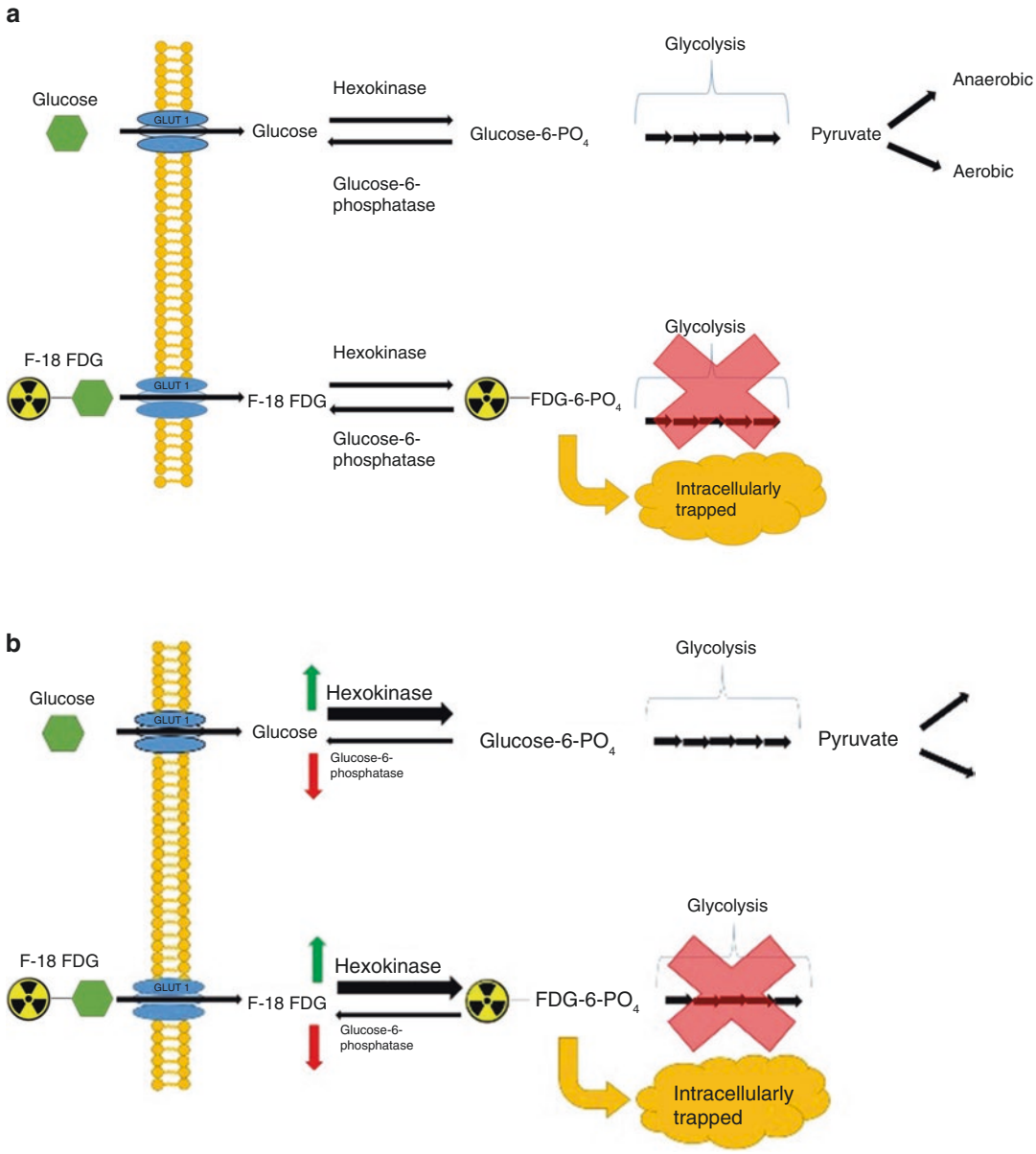


Fig. 2.2 (**a**) Normal cell and (**b**) cancer cell. Normal D-glucose and F-18 fluorodeoxy-glucose (F-18 FDG) import and trapping in normal and malignant cells

these cells. Other tissues in the body have a lower level of this enzyme (i.e., the brain and heart), and so there is higher concentration of F-18 FDG in these tissues [5]. Like the brain and heart, there are decreased levels of G-6-P in most malignant cells, which decreases the diffusion of F-18 FDG out of the cell and increases the intracellular concentration.

Following intravenous injection of F-18 FDG, the molecule is rapidly distributed throughout the body. The background activity, from circulating F-18 FDG, decreases as cellular uptake and excretion occurs. The main route of excretion of F-18 FDG is through the kidneys. Approximately 75% of the injected dose of F-18 FDG is still in circulation throughout the body 2 h after injection

where it undergoes beta+ radioactive decay, with a physical half-life of almost 110 min [6]. Beta+ decay occurs in proton-rich elements that have a minimum excess energy of 1.011 MeV, which convert a proton into a neutron and a positively charged electron. The positively charged electron is ejected and collides with a negatively charged electron to produce two 511 keV gamma photons, which are emitted at an angle of approximately 180 degree and are detected by the detectors assembled in a ring in the PET scanner. This beta+ decay by the fluorine-18 element to an oxygen-18 element transforms the molecule from a fluorine-18 glucose-6-phosphate to oxygen-18 glucose-6-phosphate. This new molecule is now able to be metabolized through glycolysis like an ordinary molecule of glucose to produce non-radioactive end-products [7, 8]. The retained F-18 FDG is cleared from non-cardiac tissues within 3–24 h post injection, while clearance from cardiac tissue may take up to 96 h [9].

The main excretion pathway of F-18 FDG is through the renal system and, to a much less extent, the bowel. Within approximately 33 min after injection, 3.9% of the injected activity is cleared by the kidneys and within 2 h 20.6% is cleared [9]. These account for the biological half-life, approximately 16 min, which is much shorter than the physical half-life of 110 min. The significantly shorter biological half-life goes along with the structural difference between F-18 FDG and natural glucose. This structural difference is the reason why F-18 FDG is not reabsorbed by the proximal tubules to be retained by the kidneys, in contrast to natural glucose [10]. The retention of natural glucose by the kidneys is a normal mechanism to keep a baseline concentration of glucose in the circulating blood and low levels of glucose in the urine. There is also a small amount of F-18 in the urine that is no longer attached to the FDG [6].

The distribution of F-18 FDG is grossly reflective of the glucose distribution and metabolism in the various organs and systems of the body. One organ that normally shows a significantly high concentration of F-18 FDG is the brain, largely because it is an obligate glucose user. The urinary system is another organ system (kidneys, ureters, bladder, and sometimes the urethra) that shows increased FDG presence, primarily due to the renal system being the main route of clearance. In the liver there is moderate and occasionally heterogeneous uptake – this is due to the high level of glucose-6-phosphatase, which allows F-18 FDG to diffuse out of the tissue (Fig. 2.3). Other organ systems show variable uptake activity, such as the heart, gastrointestinal tract, salivary glands, and testes (Fig. 2.4). The uterus can show increased uptake in the endometrium, which can be normal in age-appropriate patients due to the phase of the ovulatory and menstrual cycles. Diffuse low uptake throughout the bone marrow is common and expected. Bone marrow uptake can be increased when it is in a reactive state, such as in anemia or reacting to chemotherapy treatment. The percentage of the injected dose of F-18 FDG to these organ systems is approximately as follows: urine 20–40%, brain 7%, liver 4.5%, heart 3.3%, bone marrow 1.7%, kidneys 1.3%, and lungs 0.9% [11, 12].

Patient Preparation

There are many factors that can affect F-18 FDG distribution, uptake, and clearance from the body. These factors include, but are not limited to, diet, medications, hydration, physical activity, and uptake time. When developing a protocol for conducting PET, PET/CT, or PET/MR studies with FDG, these factors, alone or in combination, will affect the performance of FDG. There are multiple societies that have developed guidelines for performing PET, PET/CT, and PET/MRIs, which include the Society of Nuclear Medicine and Molecular Imaging (SNMMI), the European Association of Nuclear Medicine (EANM), the American College of Radiology (ACR), the National Cancer Institute (NCI), and the Netherlands Society of Nuclear Medicine. The guidelines from these societies attempt to set

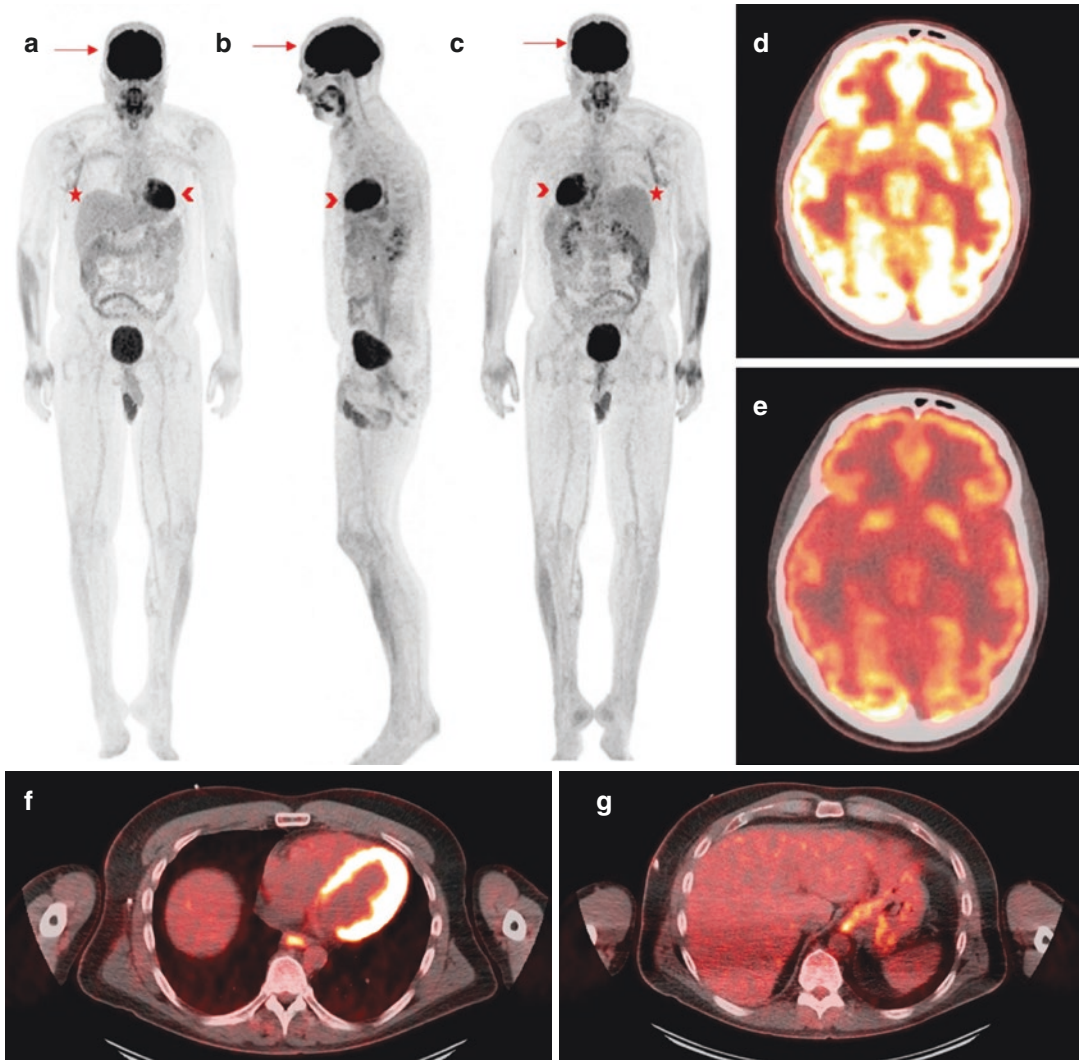


Fig. 2.3 Example of a normal F-18 FDG PET/CT showing a normal biodistribution of F-18 FDG. (**a**–**c**) MIP images in anterior, left lateral, and posterior views showing normal intense uptake in the brain (arrow) and heart (arrowhead). Heterogeneous FDG uptake in the liver and spleen (star). There is also normal increased activity in the kidneys and bladder due to normal excretion. (**d**–**e**) Intense activity in the brain at a normal intensity setting and a decrease in the intensity level showing normal increased activity in the gray matter. (**f**) Intense FDG activity in the myocardium of the right and left ventricle which can be variable. (**g**) Normal heterogeneous FDG activity in the liver and the spleen along with increased FDG uptake in the stomach possibly due to inflammation

standards for performing FDG PET studies and include patient preparation and image acquisition parameters, to produce good-quality images [13].

Dietary The use of FDG in the evaluation of metabolic activity of malignancy or suspected malignancy can be complicated by the diet of the patient. The effects of diet on the scan involve several factors: type of food ingested, timing of the meal, total glucose released (ingested along with endogenously released), and serum insulin (endogenous and administered) levels.

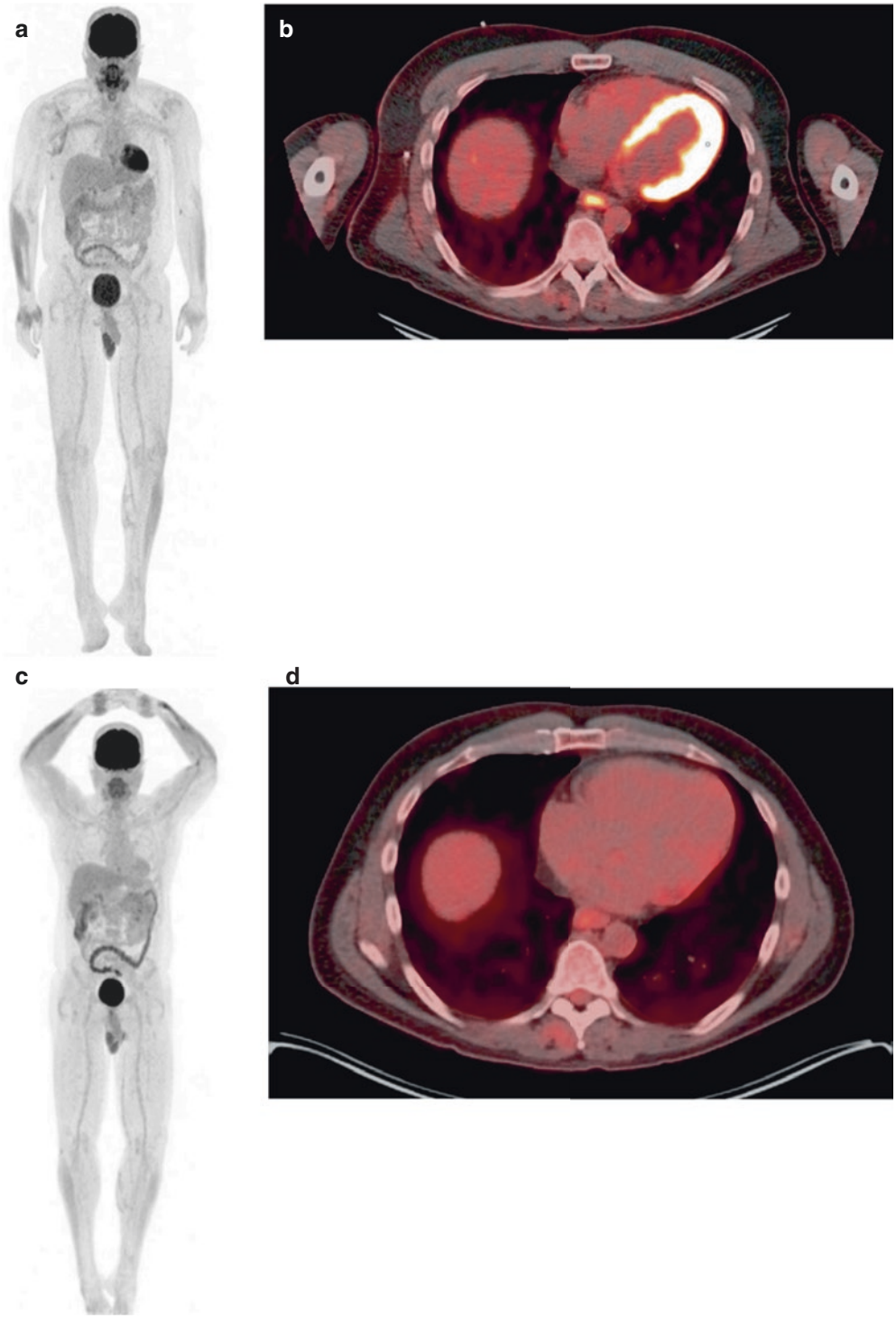


Fig. 2.4 Example of normal variable F-18 FDG uptake in the myocardium of the previous patient from two different F-18 FDG PET-CTs 1 year apart. (**a**) Anterior MIP image and (**b**) axial fused image illustrating the intense uptake in the myocardium. (**c**) Anterior MIP image and (**d**) axial fused image of the same patient 1 year later showing minimal F-18 FDG uptake in the myocardium

Fasting The ingestion of food is known to increase total blood glucose level, followed by an increase in serum insulin levels. These increases alter the distribution of normal glucose and its analog FDG by (1) causing competition between glucose and FDG for uptake by normal and malignant cells and (2) shunting delivery of FDG from malignant cells towards tissues such as fat, skeletal, and cardiac muscle by increasing the expression of insulin-dependent GLUT4 transporters in those organs. The blood glucose increases, not only from the release of glucose from the food ingested but also from the ongoing endogenous release, by gluconeogenesis and glycogenolysis via the liver and adipose tissue. The endogenous release of glucose is normally suppressed in non-diabetic patients by insulin, but in type 2 diabetic patients, this suppression can be impaired resulting in an excessive release of glucose into the circulation [14]. The first 90–120 min postprandial period shows the greatest increase in blood glucose levels, followed by a steady drop in blood glucose levels, and a subsequent increase and then drop in serum insulin over a 6 h period [14, 15] (Figs. 2.5 and 2.6).

All of the protocols from the major recognized societies require some period of fasting, ranging from 4 to 6 h prior to injection of the F-18-FDG, in order to minimize the blood levels of glucose, which competes with the injected FDG [13]. In addition to keeping the blood glucose levels at a basal state, this period of fasting will also keep the endogenous insulin levels to a basal level to prevent insulin-mediated altered biodistribution. This fasting includes tube feeding, intravenous fluids containing dextrose, and parenteral nutrients. Patients are allowed water with no added sugar or carbohydrates. The fasting recommendations also include refraining from chewing gum and ingesting candy, including breath mints [13].

Glucose When discussing preparations prior to a PET/CT, the pre-injection blood glucose level is one, if not the major, focus. This focus comes from multiple early studies like those by Wahl et al. and Lindholm et al., which showed a decrease in the FDG uptake in glucose-dependent tissues and tumor tissues with concurrent increase in the FDG uptake in skeletal muscle [13, 16–21] (Fig. 2.7). The focus of pre-injection blood glucose was so strongly accepted from these studies that the SNMMI and other societies recommend measuring blood glucose prior to FDG PET. The recommended blood glucose level cutoff for performing a scan ranges from 120 to 200 mg/dL. Some authorities, such as the NCI, separate the cutoff levels based on non-diabetic versus diabetic status – with the cutoff of 120 mg/dL (6.7 mmol/L) and 150–200 mg/dL (8.3–11.1 mmol/L), for non-diabetic and diabetic patients, respectively. In instances where blood glucose levels are greater than the cutoff for diabetic patients, some of the societies state that

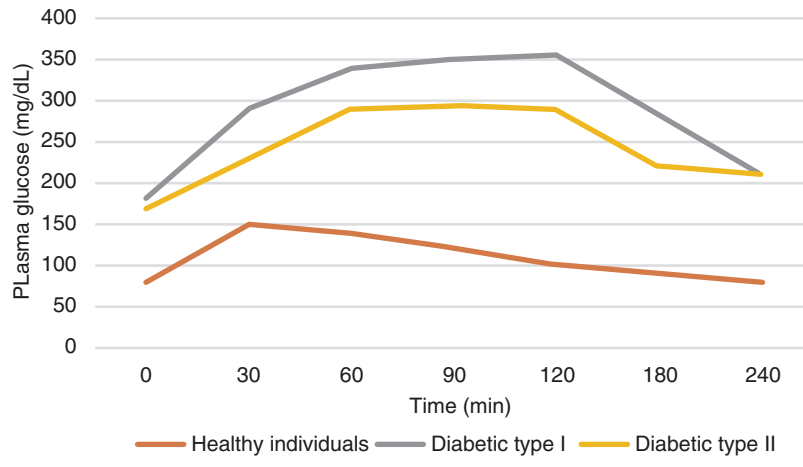


Fig. 2.5 A comparrison of the postprandial glucose response in healthy, diabetic type I, and diabetic type II individuals. Reproduced with permission from Bantle et al. [1], Copyright Massachusetts Medical Society

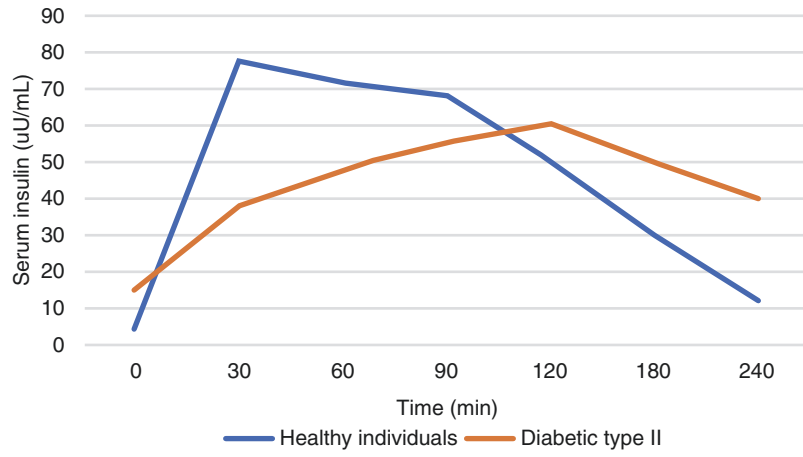


Fig. 2.6 A comparrison of the postprandial insulin response in healthy and diabetic type II individuals. Reproduced with permission from Bantle et al. [1], Copyright Massachusetts Medical Society

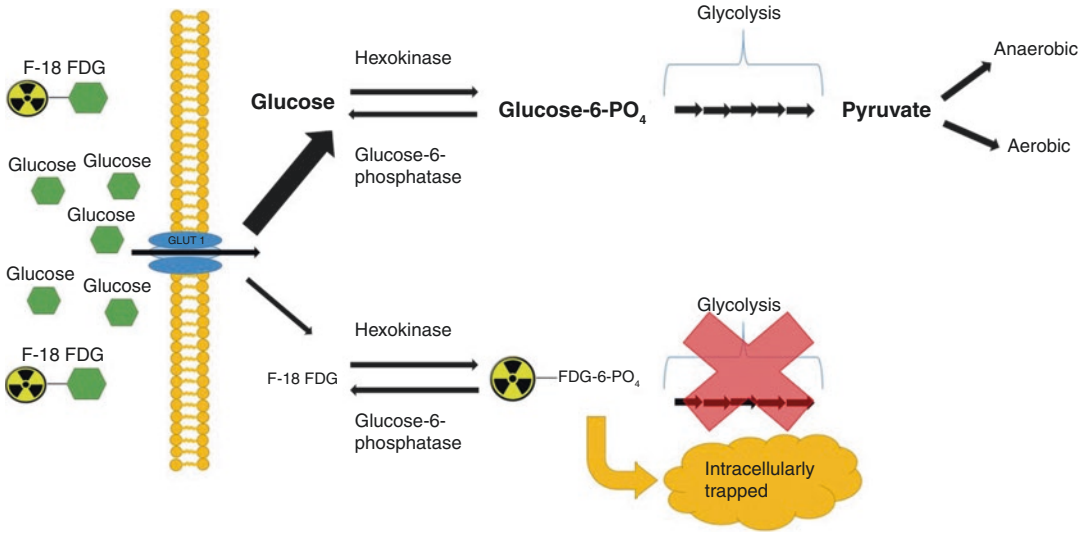


Fig. 2.7 Normal D-glucose and F-18 fluorodeoxy-glucose (F-18 FDG) import and trapping in a hyperglycemic state

administration of insulin can be considered. For example, the SNMMI recommends the administration of insulin but also recommends that the injection of FDG be delayed, with the duration of the delay depending on the type of insulin and the route used for administration. The EANM suggests that, if insulin is given, the delay for FDG injection should be more than 4 h, no matter the type or route of insulin given. Contrastingly, the NCI suggests that when blood glucose levels are more than 200 mg/dL (11.1 mmol/L), the study should be rescheduled, and insulin should not be given to adjust the blood glucose level [13].

Despite these recommendations, most newer studies would suggest that there is essentially no evidence that a higher glucose level, as a single factor, negatively impacts the readout of FDG PET scan. There is in fact some data indicating that this is probably not the case [22, 23]. It should be noted that the limited available original data examining the effect of glucose on tumor uptake, which are cited in the current societal recommendations mentioned above, were obtained in non-diabetic patients with normal glucose levels [18, 24]. In reality, these data indicate the effect of high insulin, and not high glucose, on FDG

uptake in malignant tumors, a situation that does not apply to diabetic patients who lack insulin.

Timing is also a critical issue in the decision of whether the advantages of attempting to lower blood glucose prior to conducting a PET scan outweigh the disadvantages. In our institution, we obtain blood glucose prior to FDG injection in every patient. However, based on more recent literature and our experience of performing several thousand FDG PET annually, we usually go ahead with scanning the patient and account for the high blood glucose and the negative effect that it might have on the PET scan at the time of readout. This approach is due to the fact that the results of FDG PET are very often needed within a short time period in order to render a diagnosis or decide on treatment. This time period is usually shorter than the time that would be needed to obtain better blood glucose control. It should be kept in mind that if someone is under active medical care, as is the case in cancer patients, and still has a high blood glucose level, the attempts to gain better blood glucose control have probably been exhausted. As such, it is highly unlikely that delaying the PET scan will lead to a lower or normal glucose level within a timeframe that would allow for the PET scan to still be obtained and have an impact on patient's management. As is often the case in the practice of medicine, the correct course of action is a weighing of cost and benefit to the patient.

This is not to say that a patient's blood glucose should be completely discounted when conducting PET scans. There are factors that we are mindful of and to take into consideration when a patient presents for FDG PET:

1. The tumor type and its FDG avidity. Sarcomas are generally less and heterogeneously FDG avid, while melanomas are invariably intense on FDG PET. As such, melanomas are much less likely to be affected by high glucose level than sarcomas.
2. The expected location of potential findings. For instance, the PET signal from a tumor deep in the pelvis or retroperitoneum is much more likely to be attenuated than the signal from a tumor in the chest.
3. Body habitus. In a larger patient, PET signal is more attenuated than in a smaller patient.

We take into account the abovementioned factors when reading FDG PET in a diabetic patient with blood glucose higher than 200 mg/dL. Besides reading the scan under the abovementioned considerations, we adopted the following maneuvers for image acquisition in these patients:

1. Longer uptake time. We wait 90 or 120 min after FDG injection instead of the standard 60 min. The longer uptake time leads to increased tumor uptake and decreased background activity, allowing for better visualization of the tumor.
2. Longer acquisition time for the entire PET or certain bed positions, i.e., areas where abnormal findings are expected and/or are more prone to attenuation, such as the pelvis. Also, some institutions give patients water to drink to increase the washout of radiotracer and decrease background PET signal. With this practice of acquiring and interpreting FDG PET, if we still feel that we may be missing important findings – for instance, based on the overall poor quality of images or recent CT or MR findings that we cannot convincingly confirm as positive or negative on FDG PET – we offer the referring physician to repeat the scan at no cost after reducing the blood glucose level.

In our experience the quality of FDG PET images is sometimes actually much more severely affected in non-diabetic patients. This practically happens when they undergo PET as inpatient. This is due to the fact that they receive intravenous glucose infusion along with insulin, which leads to shifting of FDG away from tumor tissue and towards muscle and fat. The resulting decreased FDG availability for uptake in tumor and increased background signal in muscle and fat decreases the diagnostic value of the scan. Of course, these patients have a normal glucose level when arriving in PET suite. This normal glucose level is due to their non-diabetic state. This scenario, although uncommon, also indicates that

measuring blood glucose prior to FDG PET has limited utility and may actually be misleading by diverting the attention away from other factors that have an influence on FDG distribution and FDG PET image quality (Fig. 2.8).

On a similar note, the value of measuring blood glucose prior to FDG PET in non-diabetic patients should be questioned. Our group studied a cohort of 117 patients with 574 scans: 91 non-diabetic patients with 429 scans and 26 diabetic patients with 145 scans. The goal was to determine the frequency of blood glucose level higher than 150 mg/dL at the time of FDG PET scan in non-diabetic patients. The cutoff of 150 mg/dL was selected based on the SNMMI guideline, recommending measuring blood glucose prior to

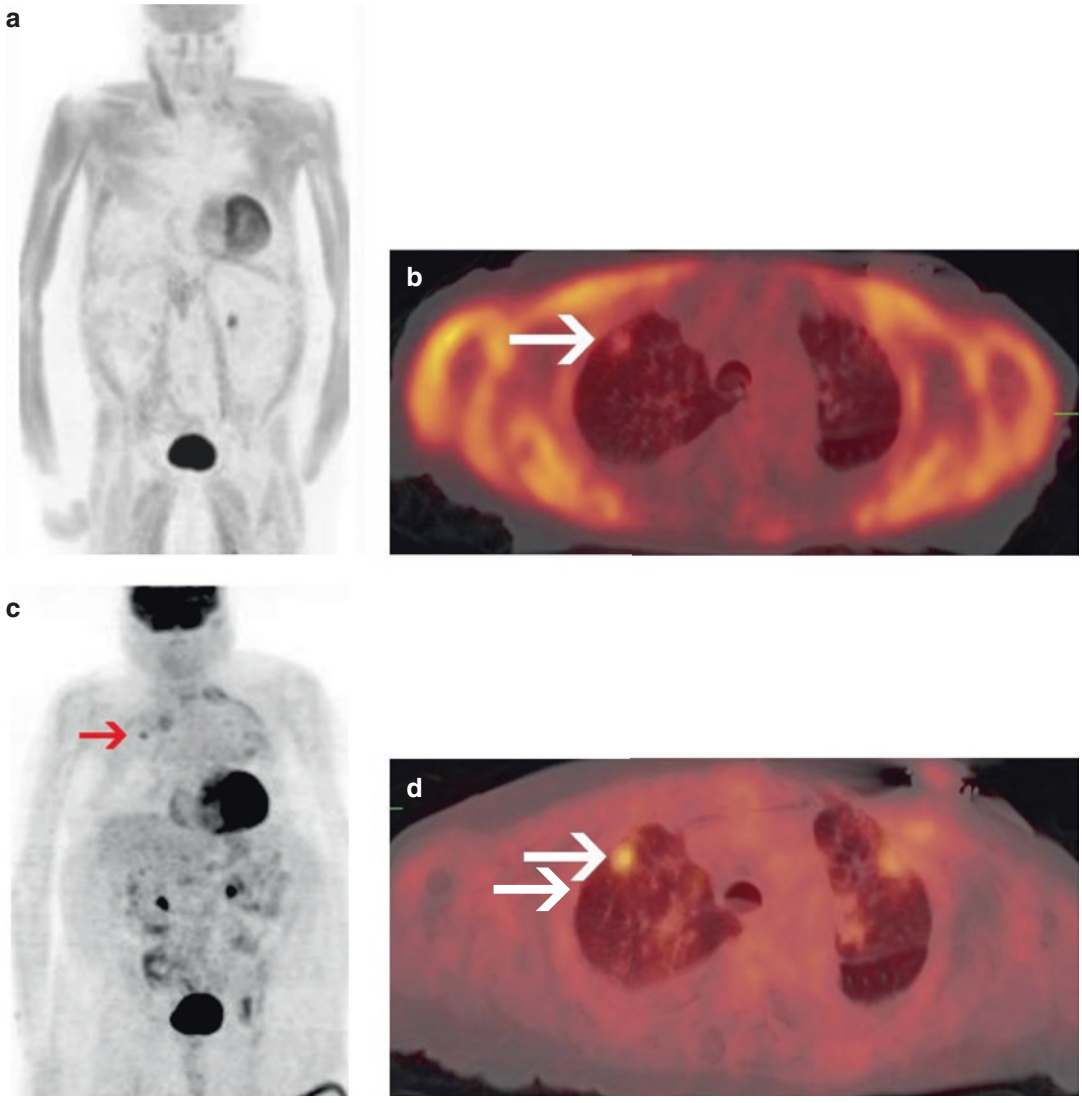


Fig. 2.8 Example of 2 FDG PET/CTs of a non-diabetic patient with normal glucose. (**a**) Anterior MIP images showing an altered biodistribution after 6 h of fasting but with IV glucose stopped shortly before imaging. Glucose was 127 mg/dL at the time. (**b**) Axial fused images showing high fat and muscle uptake with low lesion (white arrow) uptake. (**c**) Anterior MIP images of a next day repeat PET/CT after 6 h of fasting and without IV glucose, showing normal biodistribution and right lung lesion (red arrow). Glucose was 108 mg/dL at the time. (**d**) Axial fused images showing low soft tissue uptake and increased lesion (white arrow) uptake

FDG PET in every patient and not performing FDG PET if blood glucose is higher than 150–200 mg/dL. In our study, blood glucose level ranged from 44 to 259 mg/dL: 44 to 144 mg/dL in non-diabetic patients and 73 to 259 mg/dL in diabetic patients. There was no non-diabetic patient with a glucose level higher than 150 mg/dL at the time of any scan. Only one scan was performed with a blood glucose of 144 mg/dL in a non-diabetic. All other scans were performed in non-diabetic patients with a glucose level less than 140 mg/dL. Our data indicated that blood glucose level measurement prior to FDG PET could potentially be omitted in non-diabetic patients without missing any patient with blood glucose of higher than 150 mg/dL [25].

Blood Glucose Level Effects on Soft Tissue Sarcoma Evaluation Due to the generally low level and heterogeneous uptake and high recurrence and metastatic rate of the STSs, it is important to perform FDG PET with the least effect of high glucose or high insulin on FDG uptake as outlined above. Remember that the evaluation of STSs with PET/CT is twofold: (1) the identification of the most metabolically active site for biopsy and (2) the identification of local/regional or distant metastases. The presence of high blood glucose potentially decreases the FDG uptake in metabolically active regions and increases the overall background activity of the images. These alterations in the FDG distribution would potentially decrease the FDG uptake – specifically of those tumor types that are low-grade, resulting in a decrease in the sensitivity to localize the best biopsy site or identify local, regional, or distant metastases. Therefore, a "sensitive read" vs "conventional read" may be needed in order to not miss important findings – i.e., taking into account the fact that the FDG uptake in metabolically active tissue is lower even when glucose and insulin levels are normal.

Blood Glucose Level Effects on Melanoma Evaluation Melanoma is one of the most FDG-avid malignancies. The effects of a high blood glucose level would potentially have little effect on the sensitivity and accuracy of PET/CT evaluation due to this intense FDG avidity. Recall that the role of PET/CT in the evaluation for melanoma is reserved for those patients that have been categorized as stage III or IV, assessing for local, regional, or distant metastatic disease and disease burden. Nevertheless, a high blood glucose level would potentially decrease the sensitivity and accuracy of FDG PET in detecting smaller metastases potentially below the resolution of PET, which may be undetectable even in a low blood glucose state due to partial volume effect. There is also the potential of a decrease in sensitivity for the identification of residual disease post-resection as well as specificity for the identification of absence of residual disease and presence of post-resection change. Regardless, it is still important to minimize the alteration of biodistribution caused by a high blood glucose and continue to follow the proposed guidelines.

Insulin Although the focus of the competitive effects of serum glucose on the biodistribution of FDG is important, insulin plays just as important of a role. Glucose enters cells through three independent mechanisms, with the use of GLUTs as the major point of entry as described earlier. Insulin has the ability to alter the serum levels and biodistribution of both glucose and FDG, via a direct effect on the concentration of the insulin-dependent GLUT4 at the surface of the cell. When insulin levels are low, GLUT4 stays within the cytoplasmic vesicles where they are inactive. As the level of insulin rises and insulin binds to its receptors on the cells, the vesicles bind with the plasma membrane. Once the vesicles bind, the GLUT4 transporters are inserted into the plasma membrane, allowing for the cell to more efficiently take up glucose. As the level of insulin decreases, the GLUT4 transporters are sequestered back into the cytoplasmic vesicles. These transporters and this process occur in the skeletal and myocardial muscle, as well as adipose tissue [26]. Throughout the remaining tissues, other GLUTs are constantly present that are not insulin dependent. For example, the liver and brain use GLUT1 and GLUT3, which do not require insulin to be inserted to import glucose into the cell (Fig. 2.9). Also, GLUTs expressed

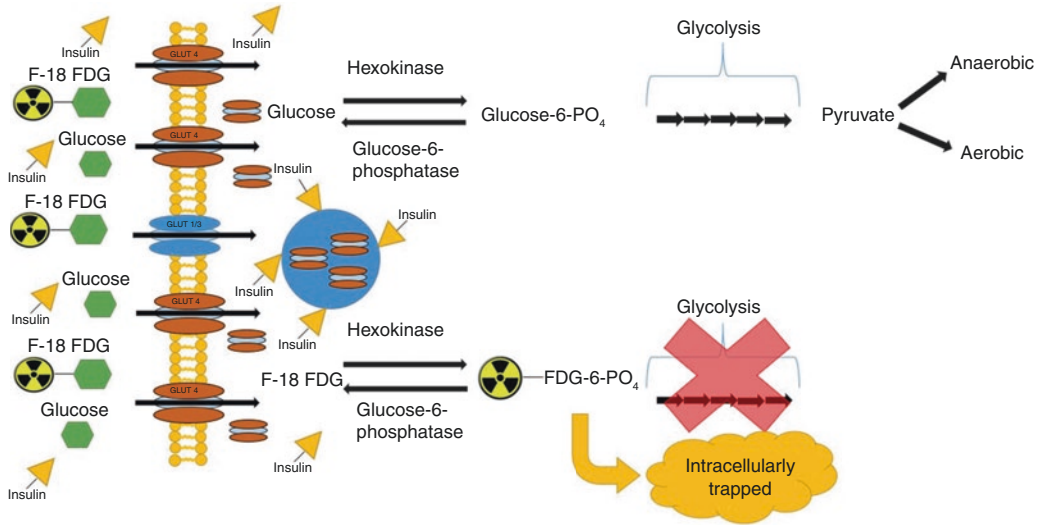


Fig. 2.9 Normal D-glucose and F-18 fluorodeoxy-glucose (F-18 FDG) import and trapping in a hyperinsulinemia

in cancer cells, mainly GLUT1 and GLUT3, are insulin independent.

An additional mechanism of insulin that alters the serum glucose level and biodistribution is its effect on the liver and its production of glycogen. Of the absorbed glucose, a large portion is quickly taken up by the hepatocytes and converted to glycogen. Insulin stimulates the production of glycogen in multiple steps. First, insulin activates hexokinase, which phosphorylates and traps glucose into the cell. With the activation of hexokinase, there is inhibition of glucose-6-phosphatase – this decreases the amount of glucose that diffuses from the cell. It has been shown by Iozzo et al. that in a hyperinsulinemic state, there is enhanced hepatic glucose influx and phosphorylation of FDG. This effect by insulin is similar in insulin-sensitive and insulin-resistant individuals. This same study also showed that even though there was an overall enhancement of phosphorylation, there was a lower ratio of phosphorylation to dephosphorylation in the low insulin-sensitive group compared to the normal insulin- and high insulin-sensitive group. This resulted in a decrease in the trapping of FDG in individuals resistant to insulin [27]. Further into the production of glycogen, which FDG does not enter, insulin activates multiple enzymes such as phosphofructokinase and glycogen synthase to produce glycogen (Fig. 2.10).

When imaging diabetic patients who use insulin, consideration needs to be given to when the patient normally takes his or her medication in the context of determining the timing of the FDG injection and imaging. At our institution, we typically coordinate the scheduling of the diabetic patients to minimize any possible interference with blood glucose and insulin level and quality of PET images. Diabetic patients are either (1) scheduled for early morning, around 8 am, and instructed to eat and take their insulin and other diabetic medications the evening before, around 10 pm, or (2) scheduled for an early afternoon slot, around 1 pm, with food and insulin and medication taken early in the morning, around 6 am. In any case, we are watchful of the blood glucose level of the diabetic patients not only to obtain high-quality PET images but also out of concern for the safety of the patient. The instruction to take diabetic medications and food at certain times and arrive on time for PET has to be communicated to the patient very clearly and may necessitate the help of the referring physician or physician familiar with patient's diabetes

treatment. We also instruct the diabetes patients to bring food and their medications with them to the PET appointment. They very often eat and take their medication before leaving our PET facility.

Increased Serum Insulin Levels with Soft Tissue Sarcoma Evaluation More pronounced compared to the effects of a high blood glucose state, an increase in serum insulin levels could potentially decrease FDG uptake in STSs. The altered biodistribution in a high insulin state results from the shunting of glucose and FDG to insulin-dependent GLUT4s. The shunting of glucose and FDG is directed towards tissues like skeletal muscle, myocardial muscle, and adipose tissue and could potentially decrease the sensitivity in identification of the most metabolically active region of the primary tumor and/or local, regional, or distant metastatic disease. In a group of tumors that already have a mild and heterogeneous uptake pattern, it is important to minimize the potential impact of postprandial high insulin levels on biodistribution by adhering to the proposed fasting time.

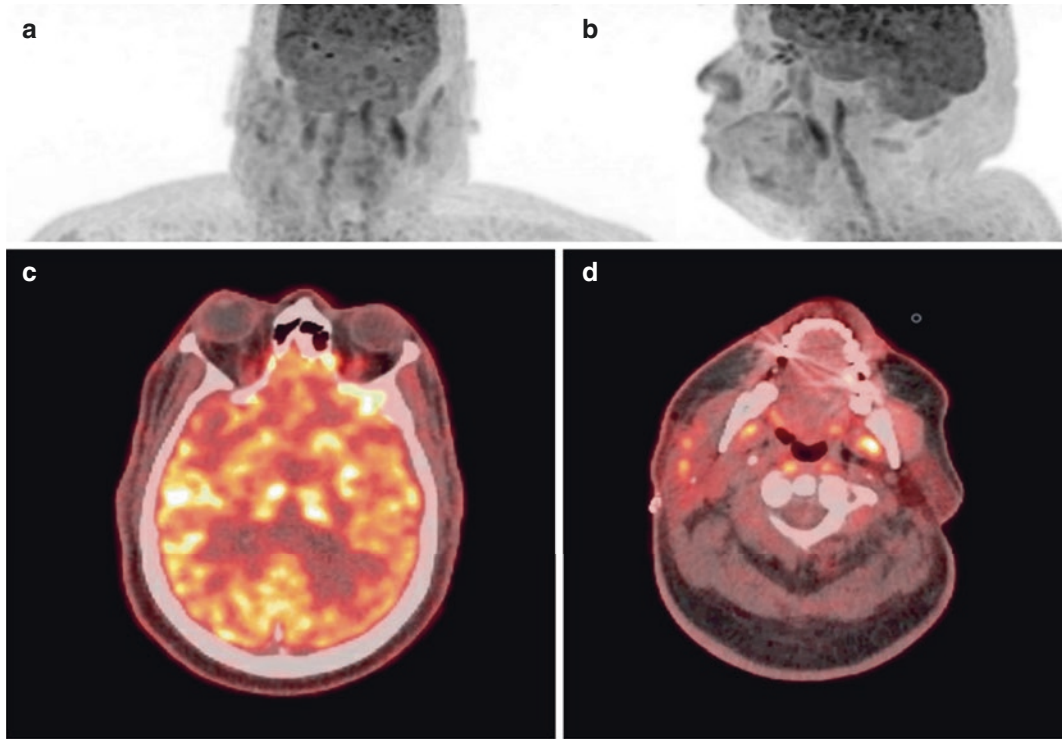


Fig. 2.10 A 69-year-old diabetic male with a right-sided parotid tumor and F-18 FDG PET/CT with altered biodistribution due to administered insulin prior to imaging. (**a**, **b**) Anterior and left lateral MIP images of the head and neck and whole body illustrating decreased uptake in the brain. (**c**) Axial fused PET/CT image illustrating overall decreased FDG uptake throughout the brain. (**d**) Axial fused PET/CT image showing mild increase in F-18 FDG uptake in the right parotid gland relative to the surrounding tissue most consistent with residual tumor. (**e**, **f**) Anterior and left lateral MIP images of the body showing increased shunting of F-18 FDG to the soft tissue and myocardium along with decreased FDG uptake in the liver and spleen. (**g**) Axial fused PET/CT image showing increased shunting of F-18 FDG to the myocardium. (**h**) Axial fused PET/CT image showing overall decrease in F-18 FDG uptake in the liver and spleen but with increased uptake in the crural muscles. (**i**) Axial fused PET/CT image showing increased uptake in the gluteal muscles bilaterally illustrating shunting of FDG to insulin-dependent tissue

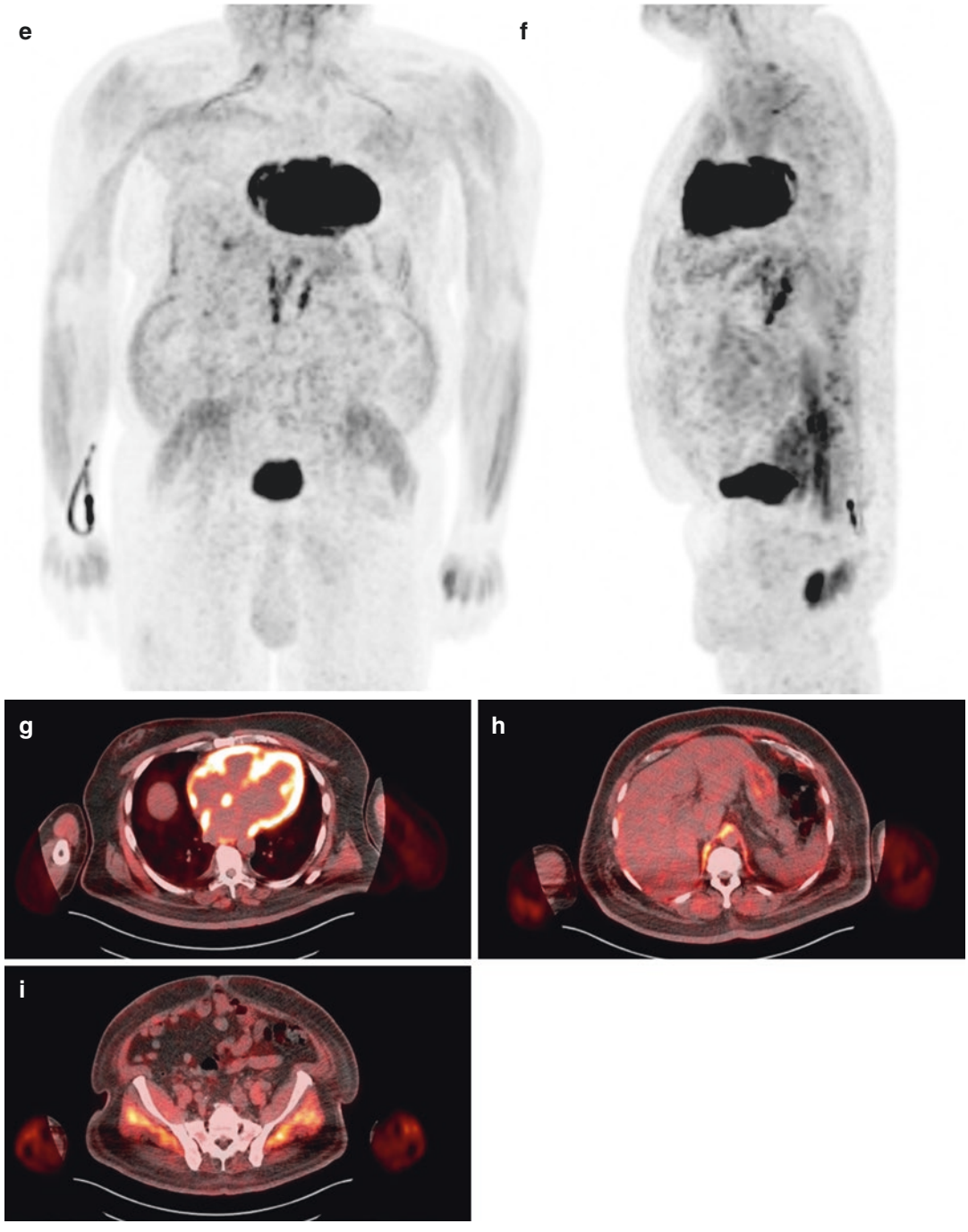


Fig. 2.10 (continued)

Increased Serum Insulin Levels with Melanoma Evaluation Although more pronounced compared to the effect of high blood glucose levels, the effects of a high insulin state on the sensitivity for the detection of metastatic melanoma may still be minimal. The high metabolic rate of melanoma would potentially still create a high target-to-background ratio, allowing for acceptable sensitivity rates. There is however a chance that there would be a decrease in sensitivity of metastatic disease potentially below the resolution threshold of PET and/or recurrent/residual disease due to the shunting of FDG into non-glucose-dependent tissue. These smaller metastases and/or recurrent/residual disease may not be detectable even under normal insulin levels, but efforts to keep insulin levels acceptable should be made to produce the best-quality images possible (Fig. 2.11).

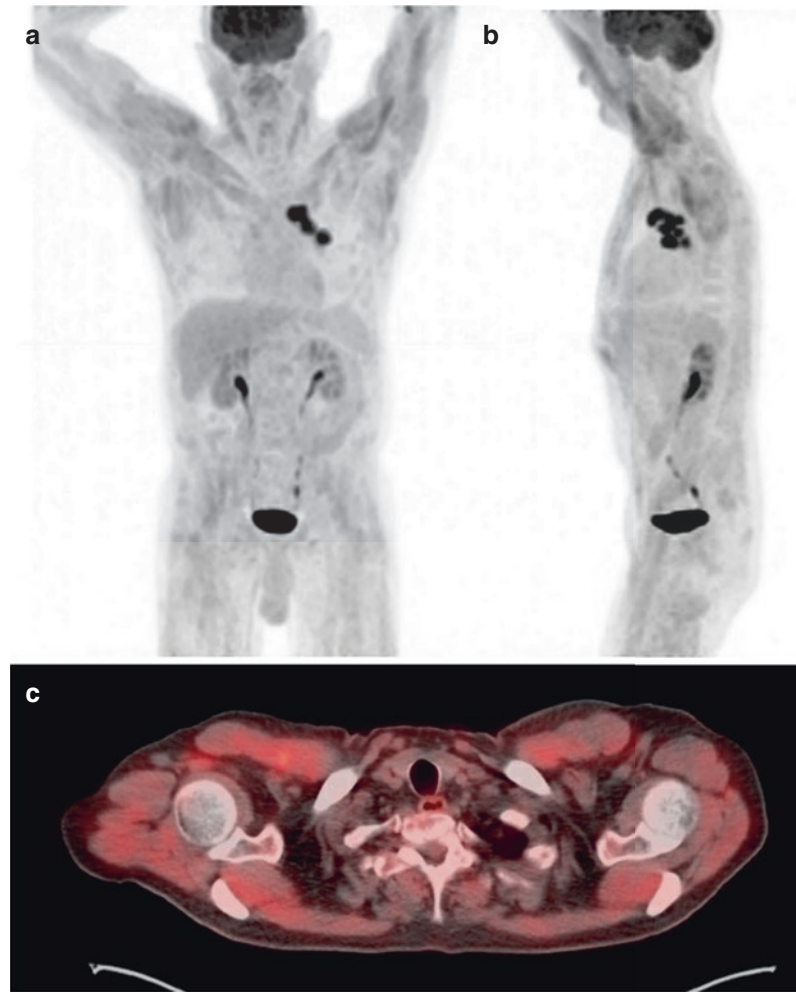
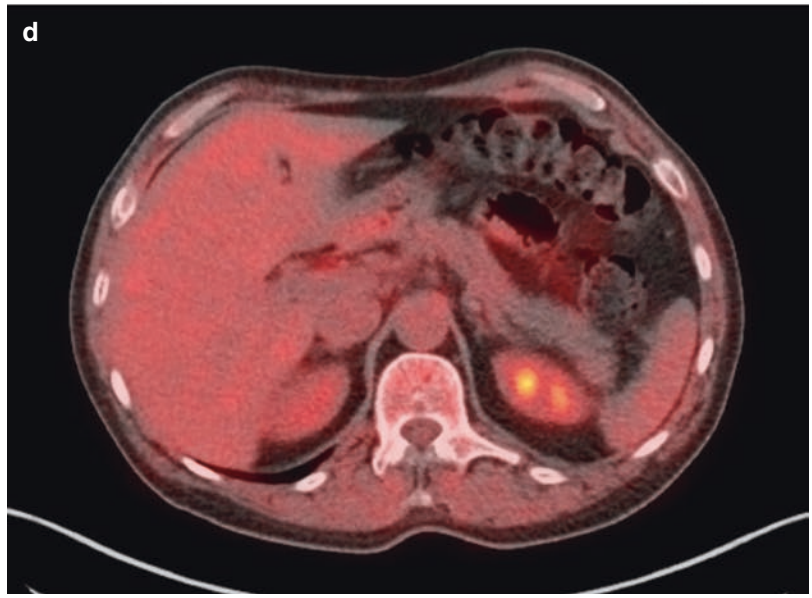


Fig. 2.11 PET image illustrating postprandial imaging. (**a**, **b**) Anterior and left lateral MIP images showing diffuse increase in F-18 FDG throughout the soft tissue and musculature. (**c**) Axial fused image of the upper thorax/upper extremities showing the increased F-18 FDG uptake in the musculature without anatomical abnormalities. (**d**) Axial fused image of the abdomen illustrating F-18 FDG uptake in the paraspinal muscle equal to that in the liver and spleen

Fig. 2.11 (continued)



Other factors that indirectly through an increase in insulin can influence the distribution of FDG away from tumor and to the muscles and fat include long-standing eating habits and physical activity.

Additional Dietary Recommendations Many groups, societies, and institutions recommend an altered diet prior to FDG PET. The recommended altered diet consists of a high-protein, low-carbohydrate diet for 24 h prior to scanning. The reduction in carbohydrates is intended to decrease the blood glucose, and resulting insulin levels, which may still exist after normalization of blood glucose levels. Another dietary recommended protocol is a high-fat, high-protein, and low-carbohydrate diet. This diet is routinely used when assessing the FDG uptake in the heart for a myocardial sarcoidosis patient being evaluated for inflammation and active sarcoidosis of the myocardium. In this setting, the assumption is that the resulting low insulin decreases the FDG uptake in normal myocardium; hence, inflamed myocardium can be better visualized. A high-fat, high-protein, and low-carbohydrate diet for 72 h has been shown to successfully suppress the normal physiologic uptake of FDG in the heart [28]. It has been proposed that this same diet could be used for oncological studies in lieu of fasting only. However, one mouse model study showed that there was no difference in tumor FDG uptake with a 72 h high-fat diet compared to overnight fasting alone [29]. We do not restrict the diet of our patients for oncology FDG PET since we overall have not observed any notable interference. Restricting diet is also a matter of practicability and patient compliance. Our overarching approach has been to limit the patients' instructions to a necessary minimum in order to achieve a good image quality across the board in a busy academic PET facility.

An alteration in the types of foods consumed is not the only dietary recommendation. It is also recommended that the patient abstain from the ingestion of caffeine and nicotine for at least 12 h prior to the study. It has been shown that caffeine is an alkaloid that increases the activity of the sympathetic nervous system, which results in an increase in thermogenesis. Nicotine is another alkaloid that increases norepinephrine turnover and thermogenesis. The effects of both caffeine and nicotine are more prominent in the brown

adipose tissue. Consequently, the use of nicotine has shown a decrease in the FDG uptake in the stomach and muscle [30]. But again, also here we do not put any restriction on the patients prior to their FDG PET scan.

When evaluating such malignancies such as STSs or malignant melanoma with FDG PET/CT, an altered diet, such as the high-protein, low-carbohydrate or high-fat, high-protein, low-carbohydrate diet used in cardiac imaging, is not needed. The potential added control from the implementation of these diets is not as beneficial as the patient adhering to fasting overnight or at least for 4–6 h prior to imaging. The abstinence from caffeine and nicotine is another suggestion that could be beneficial but is not required. In the time prior to injection, keeping the patient warm will help to decrease the physiologic uptake of FDG by the brown fat more significantly than the abstinence of caffeine and nicotine.

Physical Activity An increase in activity prior to the injection and during the uptake time can cause an increase in the uptake of FDG into the musculature (Fig. 2.12). The avoidance of a wide range of strenuous activities is recommended for a period of at least 6 h (more commonly 24 h) prior to the study, including but not limited to exercising (running, biking, weightlifting, etc.), house/yard work, and sexual activity. Some societies also recommend the avoidance of chewing gum, not only during the uptake period but also 24 h prior to injection. The abstinence from chewing gum decreases uptake in the masseter muscles, which is particularly helpful when evaluating patients with head and neck cancer [13]. But again, also here, as a matter of practicability, we do not put any restriction on the patients prior to their FDG PET scan.

The increased uptake in the skeletal muscle has the potential to decrease the available circulating FDG; mask smaller, more discreet lesions; and

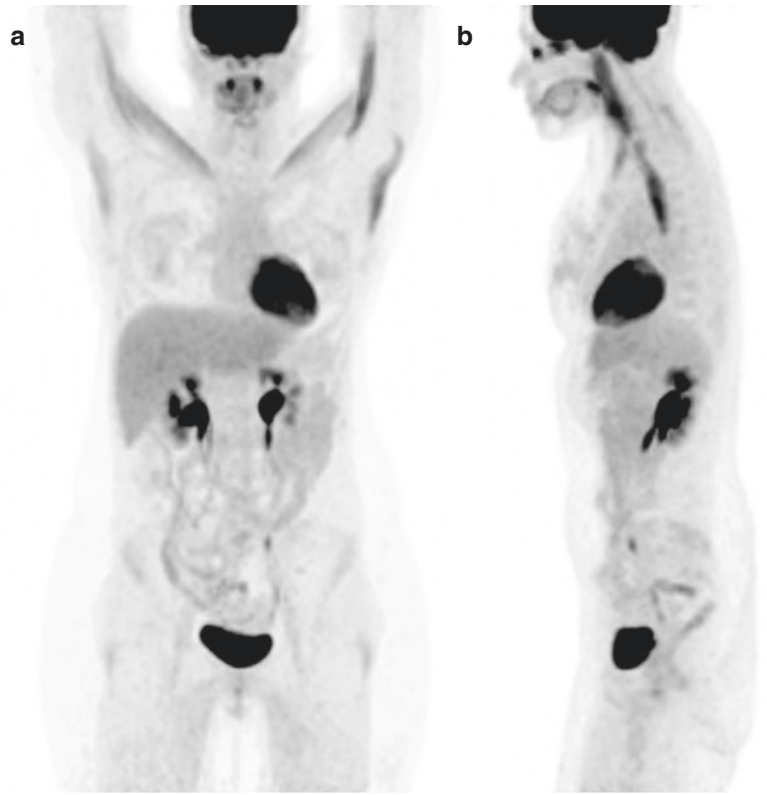
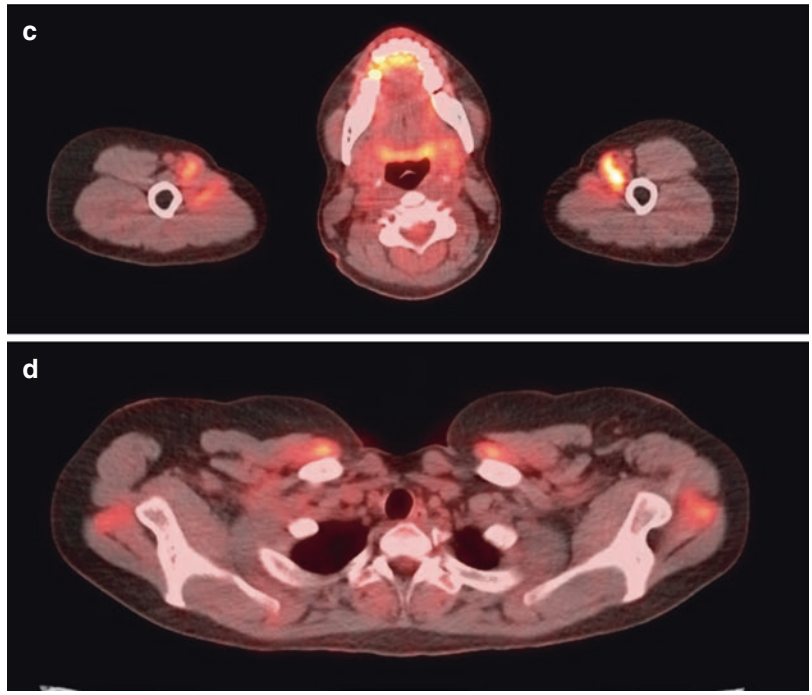


Fig. 2.12 An example of a PET image illustrating muscular uptake post-exercise. (**a**, **b**) Anterior and left lateral MIP images showing increased F-18 FDG in the bilateral upper extremities and central and lateral chest areas. (**c**, **d**) Axial fused image showing increased F-18 FDG in the bilateral biceps, pectoralis, and latissimus muscles

Fig. 2.12 (continued)



decrease the target-to-background ratio. These potential alterations are less likely to negatively affect the identification of sites of metastatic melanoma due to the high target-to-background ratio uptake. In the case of STSs, however, these alterations in distribution may decrease any subtle focal increases in low-grade tumors, thus decreasing the sensitivity required to successfully locate the most aggressive site for biopsy. There also may be blurring of the tumor edge if there is surrounding skeletal muscle with increased uptake.

Uptake Time When using FDG PET/CT, there are recommended preprocedural processes to attempt to capture the body in a basal metabolic state. Prior to the FDG injection, optimally, particularly pediatric patients should be kept in a warm room for approximately 30–60 min [31]. The patient is kept warm to try and minimize normal brown fat uptake (Fig. 2.13). After FDG injection, the patient is kept in a quiet and warm room and asked not to talk excessively, in order to try to minimize resulting increased uptake in the tongue and vocal cords (Fig. 2.14). Reading or watching TV should not create any significant muscle uptake and is permissible at our institution. In some patients, when claustrophobia is a concern, sedatives can be administered during this time. The administration of beta-blockers or benzodiazepines can also be used for prevention of normal brown fat uptake, though effectiveness varies and is mostly not needed in the area of PET/CT, since the fused images are helpful in distinguishing brown fat uptake from pathology [31].

Once the dose is injected, there is a period of time that is needed for circulation, uptake, and clearance of the tracer. Multiple studies have been conducted to evaluate for the optimal time for scanning post radiotracer administration, which is important not only for the visual quality but even more for the quantitative measurements such as SUVs. The original studies, investigating the optimal uptake time, were performed using homogenous brain tissue in order to calculate the time of the plateau phase of uptake, which was found to be 45–60 min.

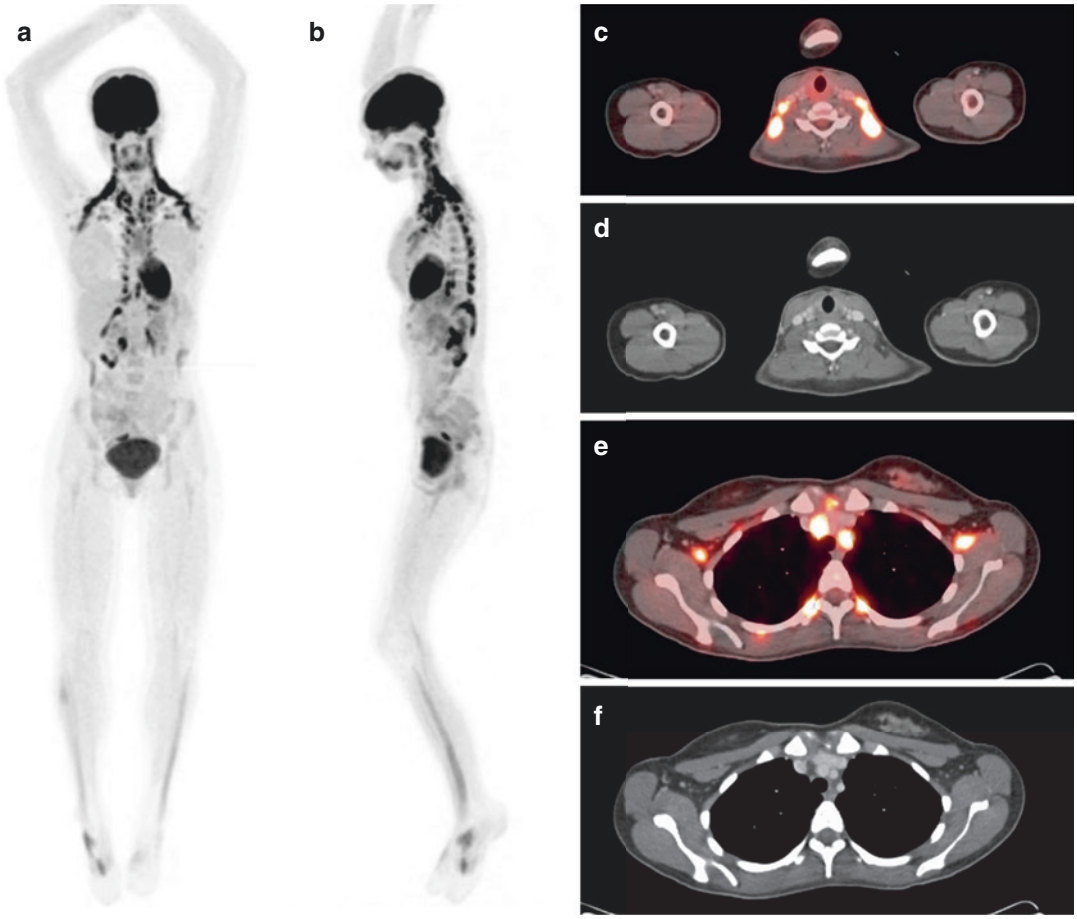


Fig. 2.13 Example of a F-18 FDG PET/CT illustrating physiologic increase in uptake in brown fat. (**a**, **b**) Anterior and left lateral MIP image showing symmetrical increased uptake in the bilateral cervical and paraspinal regions. (**c**, **d**) Axial fused and low-dose non-contrast CT showing increased F-FDG uptake in the bilateral cervical fat planes. (**e**, **f**) Axial fused and low-dose non-contrast CT showing increased F-18 FDG in the mediastinum, bilateral axial, and paraspinal fat spaces

Multiple studies since have looked at the many factors affecting the uptake of FDG including multi-compartment/rate constant equations, heterogeneous tissues, tumor/normal tissue uptake ratios, biological constructs of specific tumors, and multiple biological rates. The biological rates included uptake, phosphorylation, dephosphorylation, and clearance rates. These later studies concluded that the uptake time of 45–60 min underestimates the calculated SUVmax values and showed that, for many tumors, the FDG uptake did not plateau until several hours after injection. Additional studies investigated other factors such as treatment changes and specific tumor types. An example of such a study that investigated the plateau time of malignant tissue was by Hamberg et al.; this study showed that with stage III lung cancer, the average time to plateau was 298 min (before treatment) and 154 min (posttreatment) [17, 18]. A study conducted by Lodge et al. looked at the uptake peak time in malignant soft tissue masses versus benign lesions, specifically high-grade sarcomas. In this study, 29 patients with soft tissue masses (12 malignant and 8 benign) were evaluated. It was found that peak FDG uptake was at approximately 4 h post-injection in malignant tumors, whereas benign tumors peaked around 30 min.

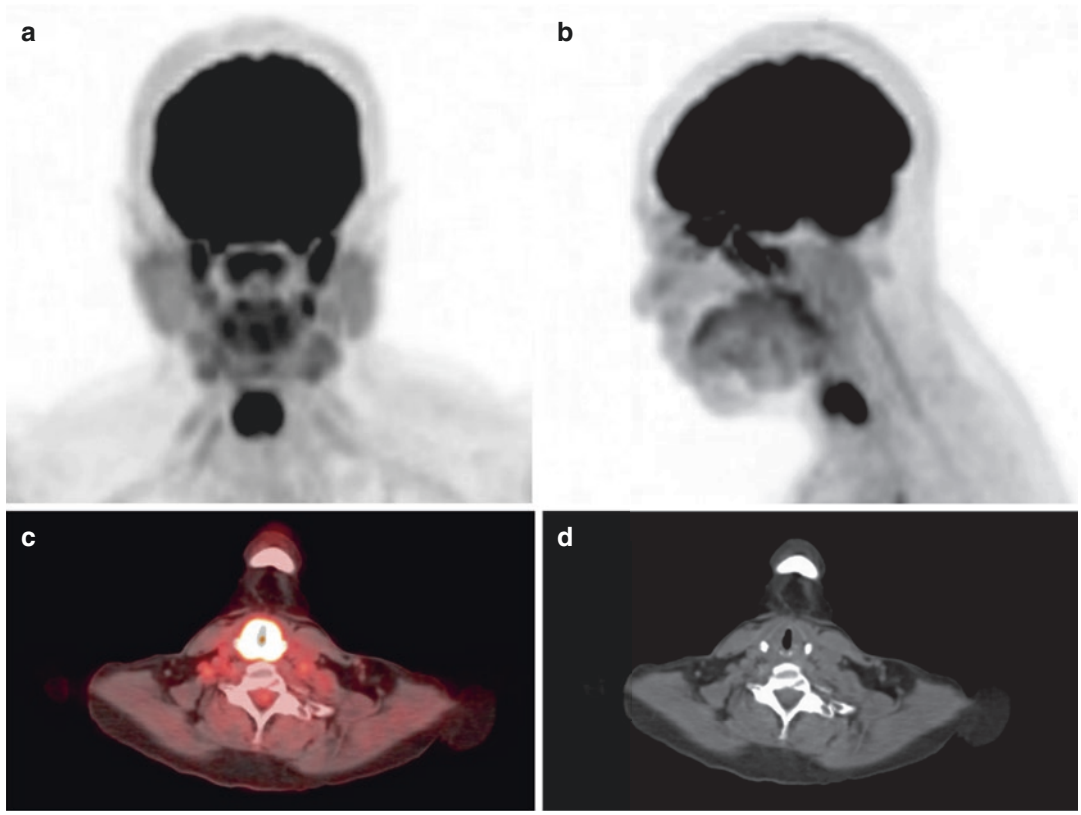


Fig. 2.14 Example of normal physiologic uptake in the vocal cords due to patient talking during the uptake time. (**a**, **b**) MIP images showing the intense uptake in the anterior lower neck. (**c**, **d**) Axial fused F-18 FDG PET/CT and low-dose non-contrast CT localizing the increased uptake in the vocal cord without anatomical abnormality

The 4 h SUV measurement was found to have a sensitivity and specificity of 100% and 76%, respectively [32]. In clinical practice, an uptake time of 4 h is impractical to efficiently keep up with patient throughput. A study by Al-Faham et al. studied the optimal uptake time for evaluating liver lesions in which they found that an uptake time of approximately 90 min significantly improves target-to-background ratio above that of an uptake time of 60 min [33].

In our practice of performing several thousand oncology FDG PET scans annually for almost 20 years, the uptake time of 60 min has worked out very well. An increased uptake time to 90 or 120 min could be considered in patient with blood glucose levels of higher than 200 mg/dL in an attempt to increase tumor and decrease background signal. This would be particularly important in sarcoma patients with high blood glucose levels. Other than that, the goal should be to keep the uptake time as close as possible to 60 min. This is important for intra-patient and inter-patient comparison of the findings.

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