Continuing education

Update on the use of PET radiopharmaceuticals in inflammatory disease

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A B S T R A C T
The use of molecular imaging with PET/CT technology using different radiotracers, especially the 18F-FDG is currently spreading beyond the area of oncology, the most interest being placed on inflammatory and infectious diseases. This article presents a review of its contribution in different inflammatory conditions in the context of structural and conventional nuclear medicine imaging. Special emphasis is placed on the more significant diseases such as large-vessel vasculitis, sarcoidosis, rheumatoid arthritis and inflammatory bowel disease and the study of the atheroma plaque.

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Actualización del uso de radiotrazadores PET en patología inflamatoria

R E S U M E N
En la actualidad el uso de la imagen molecular con tecnología PET/TC con diferentes radiotrazadores, en especial la 18F-FDG, se está extendiendo más allá del ámbito de la oncología, siendo las enfermedades inflamatorias e infecciosas unas de las que más interés están despertando. En este artículo se hace una revisión de su aplicación y aportación en diferentes patologías inflamatorias en el contexto de las técnicas de imagen estructurales y de medicina nuclear convencional. Se hace especial énfasis en las de mayor entidad como son la vasculitis de grandes vasos, la sarcoidosis, la artritis reumatoide, la enfermedad inflamatoria intestinal y el estudio de la placa de ateroma.

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Introduction

In inflammation complex physiopathological defensive processes are produced in response to injury. This involves multiple factors including both cellular (macrophages, granulocytes, fibroblasts, platelets, and lymphocytes) and chemical mediators (cytokines, complement system, histamines, fibrinogen, and plasmin) and adhesion molecules which are associated with vasodilatation and an increase in vascular permeability which produces extravasation of proteins and cells in the area affected. The phases involved in the inflammatory process are the activation of the endothelium, migration of the leucocytes (which are recruited by the adhesion molecules of the endothelium) and resolution. Early diagnosis and localization are frequently essential for adequate therapeutic management of the patients.

Limitations of structural imaging techniques

Structural techniques provide excellent anatomical resolution, although presenting inconveniences and limitations inherent to them. Ultrasonography is operator-dependent, has difficulties for evaluating deep structures and has bad penetration in gas as well as in the intestine and in dense structures such as bone. The main disadvantage of computed tomography (CT) is the impossibility to use intravenous contrast in allergic patients or in those with renal function impairment. The limitations of magnetic resonance (MR) are derived from the presence of pacemakers and implants, a lower availability and higher cost, the long duration of the studies which produces artifacts by movement, frequent intolerance to the test and adverse reactions to gadolinium. However, their most important limitations are the lack of functional information (except in functional MR) and that they do not detect inflammation in the initial stages since only late anatomical changes are observed.

Conventional techniques in nuclear medicine

These techniques are easy and inexpensive, have been used for decades in inflammatory disease and have significantly contributed to the clinical and therapeutic management of patients. The principal indications are the detection and localization of inflammatory foci, the follow-up and evaluation of response to treatment and their great differential contribution to structural techniques in showing early functional changes.

A great variety of radiotracers have been used for the study of inflammatory disease. However, only a few are of generalized use in daily clinical practice. Among these are the phosphonates labeled with 99mTc for 3-phase bone scintigraphy, leucocytes labeled with 111In...
99mTc or 111In, 67Ga-citrate and nanocolloids labeled with 99mTc. The accumulation of these radiotracers in inflamed tissue is based on different mechanisms, but none of which are specific.

The angioscintigraphic and vascular phases of scintigraphy with 99mTc-phosphonates provide an image of hypervascularization and increased vascular permeability which is always associated with inflammatory reactions. The delayed phase provides specific images of the tracer molecule and reflects the activity of the osteoblasts as an active response of the bone to inflammation. The mechanism of the uptake of leukocytes labeled with 99mTc or 111In is its active migration to the sites of inflammation. The main disadvantages are related to the time-consumption of cellular labeling and the manipulation of the blood. In addition, it is not sensitive for the detection of diseases such as sarcoidosis in which the predominant cellular response is not neutrophilic. The numerous mechanisms involved in the uptake of 67Ga include the increase in blood flow and vascular permeability, the binding to transferrin and lactoferrin and the siderophores produced by bacteria and the direct uptake by leukocytes and bacteria. The main inconveniences are, from a biological point of view, the inherent lack of specificity, and from a physical point of view, the long period of semidisintegration, the high energy of the gamma radiation and the delay in diagnosis due to the need for late images. Other radiotracers such as the nanocolloids, ICG, albumin, antigranulocyte antibodies, interleukins or ciprofloxacin labeled with 111In, 99mTc or 121I have been incorporated in an attempt to improve the specificity, although their use has not become generalized.

The evolution of the conventional scintigraphic techniques has followed the technological progress both in instrumentation (from planar images to SPECT technique and posterior to co-registry with CT and the hybrid SPECT/CT equipment, which provide greater resolution and more precise anatomical localization) and in the software of image processing, reconstruction algorithms and quantification programs.

### From conventional scintigraphy to the PET technique

Similar to the case of conventional scintigraphy, advances in positron emission tomography (PET) have been produced in both the instrumentation and in the radiotracers. The instrumentation has evolved from the first PET equipment to co-registry and PET/CT up to the most modern PET/CT 4D with correction of respiratory and cardiac movements and PET/MR which provides greater definition of the soft tissue. Likewise, new software programs for image reconstruction and quantification have also been developed.

Although several PET radiotracers have been tested in inflammatory disease, including those initially developed for oncology and others specifically designed for inflammation and infection (Table 1), 18F-fluorodeoxyglucose (18F-FDG) is the most commonly used. The tumor cells show increased 18F-FDG uptake due to an elevated rate of glycolysis and overexpression of the number of glucose membrane transporters. However, this uptake is not tumor specific since it is present in inflammatory and infectious processes, being the main cause of false positive results in oncology, which, in turn, allows its use in these pathologies. Its accumulation in inflammatory tissue is also related to an increase in glucose metabolism in a process which is probably more complicated than in tumor cells. Numerous cytokines and growth factors act on the inflammatory cells (mainly macrophages and leukocytes) and transform them into activated cells. This process results in an increase in the expression and the affinity of the glucose transporters (mainly GLUT-1 and GLUT-3) and greater production of glycolytic enzymes such as hexokinase. It also results in an increase in the uptake of 18F-FDG which is dependent on the grade of cellular activation and is greater in the neutrophils and macrophages. Thus, the processes in which these cells predominate will most probably be visualized with 18F-FDG.

Similar to the conventional scintigraphic techniques, 18F-FDG PET/CT provides functional and molecular information of the inflammatory process and also has advantages such as excellent spatial resolution, high lesion/background contrast, the use of a relatively low dose of radiation and the diagnosis may be more rapidly achieved than with other radiotracers such as 67Ga.

### Contribution of molecular imaging with PET to different inflammatory diseases

In the last decade there has been a notable increase in studies aimed at assessing different applications of PET radiotracers, mainly 18F-FDG in numerous inflammatory diseases (Table 2). As a consequence of this interest, the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) have very recently published a joint guideline for the use of 18F-FDG in inflammation and infection.5

In this review we will focus on the most relevant diseases such as in large vessel vasculitis, sarcoidosis, rheumatoid arthritis, inflammatory bowel disease and the study of atheroma plaque.

### Large vessel vasculitis

This is an inflammatory process which affects large vessels and is characterized by the accumulation of leucocytes in the vascular walls and their damage. Early diagnosis is fundamental to establish adequate therapeutic management and, frequently, relatively rapid treatment must be started. However, early diagnosis and assessment of the real extension of the disease may be difficult since unspecific symptoms and analytic parameters are frequently present (being the cause of fever of unknown origin in 17% of elderly patients8). In addition, biopsy of the temporal artery is often negative (in more than 45% of the patients7), since the involvement may be segmentary or exclusively extracranial and the sample obtained is not always sufficient.

The main limitation of structural imaging techniques (angiography, echo-doppler, CT and MR) is their low sensitivity to detect subtle alterations of the vessels early since they only show late anatomical changes and indirect signs of inflammation (wall thickening, stenosis, thrombosis and calcifications) making it difficult to differentiate between active and residual inflammatory
lesions. Likewise, ultrasonography does not allow the evaluation of deep large vessels.

Conventional scintigraphic techniques (scintigraphy with $^{67}$Ga and with labeled leucocytes) have been used on scarce occasions with limited results. In the last years there has produced an increase in publications on the use of $^{18}$F-FDG PET and PET/CT in giant cell arteritis (GCA) and Takayasu disease (TD). The main advantage is that they provide direct images of the early metabolic changes produced by the activation of the inflammatory cells (mainly the leucocytes) which infiltrate the vascular walls. Their potential applications are diagnosis, assessment of the degree of metabolic activity and extension, treatment monitoring and the early diagnosis of relapse.

The reported sensitivity of $^{18}$F-FDG in the early detection of active arterial inflammation is from 60 to 92% with a specificity of 88–100%, according to the series. However, it is currently not considered as a routine diagnostic tool in GCA, being especially indicated in atypical presentations with unpecific signs and symptoms (weight loss, general malaise, fever of unknown origin in older patients), in young patients or in clinical and biochemical suspicion and a negative temporal biopsy. Its main limitation is that the $^{18}$F-FDG uptake is not specific for vasculitis. Moreover, it does not allow the evaluation of temporal arteries because of its spatial resolution and physiologic uptake by the brain and soft tissue. Greater sensitivity has been described in patients with an elevation of the acute phase reactants, especially C-reactive protein (95.5% vs. 60% of global sensitivity).

$^{18}$F-FDG provides good results for the assessment of the degree of disease extension (Fig. 1). It allows all the large-sized arteries to be studied in a single scan, showing more affected regions than with MR and providing more precise evaluation of aortic involvement. Aortitis is a particular entity which occurs in 15% of the patients and early treatment is important due to the risk of aneurysm and dissection. However, its diagnosis is difficult due to the unpecific or absent clinical manifestations, to the negative temporal biopsy because frequently only the aorta is involved and to the delayed detection by the structural techniques. In one study carried out in GCA in the acute phase with confirmation by biopsy and positive $^{18}$F-FDG a correlation was observed between the increased uptake of $^{18}$F-FDG in the thoracic and abdominal aorta and the diameter measured by CT. Thus, $^{18}$F-FDG may have prognostic value for the posterior development of aortic dilatation and aneurysms.

With regard to the evaluation of response to treatment and the use in the therapeutic management of the patients, although not conclusive, the results suggest its utility. A normalization of the $^{18}$F-FDG uptake has been reported after treatment in 80% of the regions affected and a correlation has been observed with clinical and analytical improvement. However, in another prospective study although an initial decrease of the uptake was observed at 3 months of treatment, this uptake persisted at 6 months, being attributed to remodeling and tissue repair phenomenon or to an immune resistance of the vascular wall. Fuchs et al. described a global sensitivity and specificity of 73.3% and 83.9%, respectively, which increased in patients without immunosuppression (99.6% and 86.1%, respectively) versus those with immunosuppressive treatment (sensitivity: 52.9%, specificity: 78.6%). The incorporation of PET with $^{18}$F-FDG increased the clinical diagnostic efficacy from 54.1 to 70.5% and lead to a change in treatment in 26.7% of patients without immunosuppressants and in 22.6% of those with immunosuppressants. Patients under steroid therapy at the time of the study presented lower uptake of $^{18}$F-FDG and, thus, it is recommended that, whenever possible, the study should be performed in an interval without immunosuppressive treatment.

The studies published have not demonstrated that the initial intensity of $^{18}$F-FDG uptake and its evolution after treatment have a predictive value of relapse in patients with GCA. Rheumatic polymyalgia is a clinical syndrome which is frequently associated with GCA and currently numerous authors consider both as a single entity, detecting uptake of $^{18}$F-FDG in the large arteries in 30% of the patients. Thus, some patients apparently presenting isolated rheumatic polymyalgia in fact have an associated large vessel inflammation, even with a negative temporal biopsy and without signs or symptoms of GCA, with the consequent therapeutic and prognostic implications.

Takayasu disease (TD) is the most common cause of vasculitis in adolescents and affects the aorta and its main branches. Early diagnosis is important to prevent irreversible structural changes, although it is difficult to establish since the initial clinical manifestations and the biochemical parameters are often unpecific and structural techniques (angiography and angio-MR) only show late anatomical changes (stenosis, occlusion and aneurysms). This leads to a delay of months and even years in the diagnosis, with the degree of extension also generally being underevaluated.

The greater contribution of $^{18}$F-FDG would be in the clinical forms with an atypical onset and with normal or discordant inflammatory analytical parameters, in which the technique provides a more exact assessment of the extension and an early detection of reactivation. In a study with 32 patients, $^{18}$F-FDG PET/CT showed a sensitivity of 79% and a specificity of 87%, with a significant correlation of the uptake of $^{18}$F-FDG with the clinical manifestations and the analytical data at baseline and during follow-up. In addition, $^{18}$F-FDG PET/CT has shown to be superior to angiography in detecting early inflammation and monitoring the effectiveness of treatment (sensitivity of 92% and a specificity of 100%). Finally,
18F-FDG PET has shown similar results in comparison with MR in both the initial diagnosis and in the follow-up after immunosuppressive therapy, although it detected more involved regions.\textsuperscript{11}

As a result of all of the above, some guidelines are beginning to consider the use of 18F-FDG PET in the management of large vessel vasculitis within the investigation and clinical setting in specific situations such as in suspicion of the involvement of large vessels in GCA.\textsuperscript{21,22}

There are still issues which are in debate such as the standardization of the protocol,\textsuperscript{23} the validation of image reading,\textsuperscript{24} the influence of different factors on the 18F-FDG uptake, the interval between the completion of the treatment and the scan and the meaning of the persistence of uptake after the acute phase.

Other PET radiotracers are under evaluation in the study of vasculitis such as 11C-(R)-PK11195 which binds to the peripheral receptor of the benzodiazepines and is overexpressed in activated macrophages. Initial studies have shown the uptake of 11C-(R)-PK11195 in the arterial wall in symptomatic patients and not in asymptomatic patients.\textsuperscript{25}

Sarcoidosis

Sarcoidosis is a multisystemic disease of unknown etiology and is characterized by the presence of noncaseifying granulomas representing a clinical challenge since its mode of presentation, clinical course and response to treatment vary greatly. Its intensity of activity and extension has important therapeutic implications. Structural techniques have limitations to differentiate foci of active inflammation, especially pulmonary, from fibrosis. Also, the changes found in the size of the lesions by structural techniques do not always reflect the changes in metabolic activity.

Scintigraphy with 67Ga is the nuclear medicine technique most widely used for the diagnosis of sarcoidosis, evaluation of the grade of pulmonary and extrapulmonary involvement and the management of the patients. The disadvantages are the high radiation exposure, the low quality of the images and the need for late acquisitions which delay the diagnosis. In addition, although certain patterns of uptake have been considered as very indicative of sarcoidosis, the sensitivity and specificity described by the different groups vary greatly and, at present, their value is limited.

18F-FDG PET/CT has the advantage of high spatial resolution which allows the detection of smaller lesions such as pulmonary lesions, lower patient irradiation and a shorter time to obtain the diagnosis. However, at present it is not indicated in the initial diagnosis of the disease since the findings are indistinguishable from metastatic tumoral or lymphomatous involvement.\textsuperscript{26} Nevertheless, it has been reported that a pattern of symmetric uptake in the hilar and mediastinal lymph nodes or extranodal involvement associated with erythema nodosum and uptake in the parotid glands is more probably due to sarcoidosis and not to a tumoral process.\textsuperscript{27}

The indications with greater scientific evidence are the evaluation of disease extension, the degree of inflammatory activity, the detection of the involvement of unsuspected sites (Fig. 2) and as a guide for the biopsy of metabolically more active and accessible lesions. 18F-FDG has shown greater sensitivity than 67Ga, especially in extrapulmonary (100% and 81%, respectively) as well as pulmonary involvement (90% and 48%, respectively). A recent study has confirmed this greater sensitivity of 18F-FDG versus 67Ga (97% vs. 88%). 18F-FDG has demonstrated greater interobserver concordance and the detection of more extrapulmonary and mediastinal lesions and lymph nodes. In another study in 137 patients 18F-FDG PET detected clinical and radiological unknown occult sites of involvement in 15% of the cases, being positive in two thirds of the patients with radiologic stages I and III.\textsuperscript{30}

18F-FDG is also indicated for the monitoring of response to treatment. A decrease of pulmonary and extrapulmonary uptake has been observed after therapy with high dose corticoids in parallel with clinical and radiological improvement.\textsuperscript{28,30} One situation in which 18F-FDG may be of great value is in stage IV in which it is difficult to differentiate active pulmonary inflammation from fibrosis with structural imaging techniques. In one retrospective report including 188 studies 18F-FDG differentiated active reversible disease from irreversible fibrosis and also showed a decrease in pulmonary uptake in patients with active inflammation after treatment with corticoids.\textsuperscript{30} Milman et al. performed an interesting study using 18F-FDG as a tool to evaluate the efficacy of the treatment in the same patient according to the route of administration, with no differences being observed in pulmonary inflammatory activity measured by 18F-FDG after therapy with inhaled corticoids, although a reduction in pulmonary uptake was observed after oral administration.\textsuperscript{21}

Fig. 2. A 38-year-old man with histologically confirmed sarcoidosis. 18F-FDG PET/CT (A: maximum intensity projection image, B: coronal slices and C: axial slices) showing extensive lymph node involvement (mediastinal, laterocervical, supraclavicular and bilateral axillary).
In a very recent study $^{18}$F-FDG PET/CT showed discordant results with respect to high resolution thoracic CT in more than half of the studies (54.3%), demonstrating more extensive unsuspected pulmonary or extrapulmonary involvement in 14 out of 19 patients and less extension in 5. The information provided by $^{18}$F-FDG had a direct clinical impact on therapeutic management in 63% of the patients. The presence of cardiac involvement by sarcoidosis is an important prognostic factor, with early diagnosis and treatment being fundamental to reduce the associated morbimortality. However, its incidence is probably underestimated due to scarce or absent symptomatology and to the lack of standardized criteria for diagnosis. Endomyocardial biopsy is difficult to achieve and is positive in less than 10% of the patients, and the findings of the echocardiogram and radionuclide studies of myocardial perfusion are not pathognomonic. This is the context in which the contribution of $^{18}$F-FDG PET/CT is promising. One important limitation is the previously mentioned physiological uptake of $^{18}$F-FDG by the myocardium which may vary greatly depending on numerous factors (diet, age, blood glucose levels, and obesity). Similar to coroanary atheromatosis, attempts to solve this inconvenience include a low-carbohydrates and high-fat diet and a longer fasting period to reduce the cardiac uptake of $^{18}$F-FDG and to improve the sensitivity. However, this has not been confirmed by other authors. Although studies specifically aimed at the study of cardiac sarcoidosis with $^{18}$F-FDG are scarce, they include a small number of patients and do not always have histologic confirmation, the initial results are promising, especially compared to $^{11}$Ga. Okumura et al. reported that $^{18}$F-FDG PET can detect active cardiac inflammation in an early phase before the development of advanced fibrosis with a greater sensitivity than that of $^{67}$Ga (100% vs. 36%). A lower sensitivity has been described in patients receiving treatment with steroids (75% vs. 100%) and a lower specificity that of $^{18}$F-FDG. A focal uptake or foci of uptake within a diffuse pattern would be more suggestive of active inflammation and could be a predictor of good response to therapy with steroids in addition to being useful for monitoring. It has been reported that heterogeneous uptake of $^{18}$F-FDG in patients with cardiac sarcoidosis may disappear as quickly as 1 month after treatment with corticoids. Further studies are needed in larger populations to confirm these results, to standardize the technique, to validate the method of image interpretation and to establish the most specific patterns of uptake.

Other more tumor-specific PET radiotracers have been evaluated for the study of sarcoidosis with the aim of improving the differential diagnosis between malignant tumors and granulomas. Zhao et al. compared $^{18}$F-FDG with $^{11}$C-methionine (MET) and $^{18}$F-fluorothymidine (FLT) and found that although there were no differences for FDG and FLT, the uptake of MET was lower in the granulomatous lesions than in the tumors and would be useful for their differential diagnosis. Combined studies with $^{18}$FDG and $^{18}$F-fluoromethyl-tyrosine (FMT) have also demonstrated that FMT allowed a better discrimination between sarcoidosis, which did not show FMT uptake, and malignant lesions, which evidenced FMT uptake.

**Rheumatoid arthritis**

This is a systemic autoimmune disease characterized by a massive infiltration of activated macrophages, the proliferation of fibroblasts, hypertrophy of the synovial membrane, and neovascularization which cause chronic inflammation of the joints. Early diagnosis and treatment may help to slow down joint destruction although the early symptoms are not specific, and conventional radiologic studies are not able to assess synovial inflammation early. High resolution ultrasonography and MR with gadolinium and fat suppression allow visualization of the pannus, increase in vascularization, synovial thickening of the inflamed joint and bone erosions. Molecular imaging with $^{18}$F-FDG PET provides direct information of the early metabolic changes which take place in the synovia, evaluating the grade of inflammation and also allowing the study of all the joints in the human body in a single study. The most characteristic finding is an increase in uptake in the joint space or in the thickened synovia which may extend to the tendinous sheaths (Fig. 3). In 1995 the first study on the use of $^{18}$F-FDG PET in rheumatoid arthritis was published, demonstrating increased uptake in swollen joints in parallel with the synovial volume estimated with MR. In another study in which 366 joints of 21 patients with active rheumatoid arthritis were evaluated, $^{18}$F-FDG was found to be useful to establish synovial metabolic activity, and a greater intensity of uptake was found to correspond with a greater clinical, analytical and ultrasonography severity, with PET being positive in 63% of the joints studied versus 56% by ultrasonography. Moreover, it has been observed that $^{18}$F-FDG shows more inflamed joints than those found by clinical manifestations and bone scintigraphy, with the detection of atlanto-axial joint involvement (which is frequently asymptomatic and is an early phase of subclinical synovitis prior to subluxation) in up to 28% of the patients.

One important aspect in which the utility of $^{18}$F-FDG may be promising is in the monitoring of treatment for optimization and individualization, being of special relevance in the case of new biological treatments. In the initial studies a decrease of $^{18}$F-FDG uptake after treatment with prednisone and methotrexate was already observed. In more recent studies a correlation has been reported between the reduction in the intensity of articular uptake of $^{18}$F-FDG and the clinical activity after 2 weeks of treatment with infliximab (a new blocker of the tumor necrosis alpha factor) and after 2 and 4 weeks of combined oral therapy with methotrexate, sulfasalazine and hydroxychloroquine, and it may, thus, be an early predictor of the efficacy of the treatment and clinical evolution.

We want to emphasize the superiority of PET/CT over PET as it allows more precise anatomical localization of the foci of increased activity which is especially relevant in the evaluation of small joints such as the interphalangeal or metacarpophalangeal. In addition, the CT component provides anatomical information of bone involvement such as erosions.

However, there is still insufficient scientific evidence supporting the routine use of $^{18}$F-FDG PET/CT in these patients. Currently this technique is restricted to investigation, for the identification of affected joints and the quantification of the grade of inflammatory activity. Also, its contribution in the context of the imaging techniques available today (especially ultrasonography and MR) remains to be established, although it may play a role in the early diagnosis of synovitis in the initial stages. Its use in the follow-up and evaluation of the response to different therapies has the disadvantage of requiring successive studies with the consequent exposure to radiation.

**Inflammatory bowel disease**

Inflammatory bowel disease is a chronic inflammation of the gastrointestinal tract with an unknown etiology related to immune phenomena. The signs and symptoms are often unspecific and common to other diseases, especially in children, thereby making the initial diagnosis erroneous or delayed. Diagnosis is achieved with the combination of radiologic studies (barium contrast radiography, upper endoscopy and colonoscopy with biopsy) and invasive tests which generate patient discomfort and, on occasions, only allow incomplete evaluation due to the impossibility to explore all the intestinal segments. In addition, the assessment of the real
extension of the disease and the intensity of inflammatory activity is often difficult to establish with structural techniques.

Scintigraphy with leucocytes labeled with $^{99m}$Tc or $^{111}$In is the nuclear medicine test of choice and is of great utility in different clinical situations such as the evaluation of the grade of disease activity in cases with discordance between the clinical and analytical data, assessment of extension and the monitoring of response to treatment.\(^{47}\) It has a high sensitivity and specificity (ranging from 84 to 95\%), similar to those of ultrasonography and MR,\(^{48}\) which increases with SPECT and SPECT/CT and has a high negative predictive value. As mentioned previously, the main inconveniences are related to the time-consumption of cellular labeling and the manipulation of blood.

$^{18}$F-FDG PET/CT is a noninvasive method which has no inconveniences derived from cellular labeling and is an indicator of functional inflammatory activity and may, therefore, be superior to other techniques such as MR which detects the morphologic alterations such as stenosis and fistulas later. However, the physiologic uptake of $^{18}$F-FDG in the bowel varies depending on several factors,\(^{49}\) being frequently observed in the cecum. This affects the sensitivity and the specificity of the test and initially represents a limitation for its use in this disease. It has been observed that physiologic intestinal uptake is more intense in older patients.

The potential applications of $^{18}$F-FDG PET/CT are in early diagnosis, evaluation of the activity, disease localization and extension (Fig. 4) and assessment of the efficacy of treatment. It would be especially indicated in cases with contraindication or intolerance to endoscopy (due to severe inflammation or obstruction with the risk of perforation), discordance between clinical data and analytical inflammatory parameters, in the diagnosis of fibrosis versus active inflammation and for the early detection of relapse. Another potential utility of $^{18}$F-FDG PET/CT is in the selection of patients who may benefit from surgery since, frequently, obstruction is more often due to active inflammation (which may be the result of medical treatment) than not only to fibrosis of the tissue.

Löffler et al. carried out a retrospective study of 23 children from 2 to 16 years of age with Crohn’s disease, ulcerative colitis and juvenile arthritis with or without enteritis. $^{18}$F-FDG was found to be an excellent non invasive tool to identify the involved bowel segments early, with a high sensitivity (98\%) which was greater

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Fig. 3. A 50-year-old women with an acute episode of rheumatoid arthritis. $^{18}$F-FDG PET/CT (A: maximum intensity projection image, B: coronal and axial slices of the shoulders and C: coronal and axial slices of the hips) demonstrating intense bilateral articular and periarticular uptake in the shoulders and hips.

Fig. 4. A 39-year-old male with an acute episode of Crohn’s disease. In the $^{18}$F-FDG PET/CT (A: maximum intensity projection image, B: coronal slices and C: axial slices) an increased $^{18}$F-FDG uptake was observed in the wall of the ascending colon (demonstrating areas of dilatation and thickening and other zones of stenosis), transverse colon and a large part of the descending colon, the distal portion of which also presented dilatation. The involvement demonstrated by PET/CT was more extensive than that determined by endoscopy.
In a prospective study carried out in patients with Crohn’s disease, the sensitivity of 18F-FDG PET/CT to detect lesions observed on endoscopy was greater than that of endoscopy (75%) and ultrasonography (92%). Thus, a negative PET excludes inflammation since it has a high negative predictive value (98%), and a positive PET should be evaluated within the clinical and analytical context as well as that of other tests (ultrasonography, endoscopy, and histology).

An excellent correlation has been observed between the inflammatory activity evaluated by 18F-FDG and the clinical activity measured by endoscopy, especially in the case of ulcerative colitis (95% vs. 81% in Crohn’s disease). In a prospective study carried out in 22 patients with Crohn’s disease, the sensitivity of 18F-FDG PET/CT to detect lesions observed on endoscopy was greater than 70%, being 100% in the detection of severe inflammation (deep ulcers, stenosis). In another study including 59 patients with Crohn’s disease, a greater sensitivity was reported for PET in the detection of active disease (85.4%) compared with MR (40.9%) and scintigraphy with antigranulocyte antibodies (66.7%).

Despite all of the above, there is still limited scientific evidence of the use of 18F-FDG PET/CT in inflammatory bowel disease. Although a very good correlation is generally found between the findings of 18F-FDG and both clinical and analytical inflammatory activity and with endoscopic findings, the sensitivity is similar to that of labeled leucocytes and the specificity is lower and cannot, at present, replace the conventional studies.

Study of atheroma plaque

The development of atheroma plaque is a dynamic phenomenon which silently progresses along the decades prior to the production of clinical events. It is characterized by the subendothelial accumulation of lipids, macrophages and monocytes, inflammation, necrosis and calcification of the vascular wall. The inflammation in the wall plays a critical role in the onset of the plaque, its progression and rupture. Histopathologic studies have demonstrated that unstable or vulnerable plaques have a larger necrotic nucleus rich in lipids and a more intense inflammatory component. Structural techniques show late changes such as wall thickening, calcification and stenosis without being able to determine whether the process is active. Molecular imaging allows in vivo characterization of the complex physiopathological processes involved in the different stages of plaque development, detecting the functional changes in the early phases and their grade of activity. In addition, the hybrid PET/CT equipment allows more precise anatomical localization of atheroma plaque and their correlation with the metabolic information.

Different studies have demonstrated that the activated macrophages present in plaque are closely involved in plaque initiation, development and rupture. These macrophages have elevated glucose consumption and, therefore, greater incorporation of 18F-FDG, which increases with the grade of inflammation. Thus, 18F-FDG is considered an early biological marker of plaque inflammation (Fig. 5). Its uptake has been closely related to cardiovascular risk factors and it is an independent predictor of future ischemic events. More intense uptake has been reported in symptomatic than in asymptomatic carotid plaque in the same patient. 18F-FDG is also used in the assessment of the effect of antiinflammatory therapies. The first study in humans included oncologic patients treated with simvastatin or diet, observing an 18F-FDG uptake decrease in the atheroma plaque at 3 months of therapy with simvastatin but not after diet. A decrease in uptake has also been observed at one year after the reduction of the cardiovascular risk factors and at 12 weeks after treatment with atorvastatin.

One very interesting subject is that of the evaluation of coronary atheromatosis. However, the technique has limitations due to the small size of the vessels, the physiologic uptake of 18F-FDG in the myocardium, the effect of partial volume and cardiac and respiratory movements. These limitations may largely be solved with PET 4D equipment and with time-of-flight, PET/MR and new image reconstruction algorithms. The use of a low-carbohydrates and high-fat diet has also been proposed to reduce physiologic myocardial uptake.

The initial results obtained with 18F-FDG are promising, although more studies are needed before considering their possible application in clinical health care. The pending issues to resolve are related to its prognostic significance, its utility in the development and monitoring of response to new treatments, the optimal time of image acquisition and its interpretation.

Leucocytes labeled with 18F-FDG

The implementation of their use is combined with the advantage of the use of leucocytes with those of 18F and PET/CT to increase the sensitivity and specificity of 18F-FDG. The main advantage over this is the minimum physiologic uptake in the gastrointestinal tract and renal system and the disadvantages are a more laborious labeling than that of leucocytes labeled with 111In or 99mTc, the need for trained personnel and special equipment. In addition, the efficiency
of the labeling is obtained is lower (from 72±8% for 18F-FDG versus 90±5% for 111In) and is influenced by the level of blood glucose, is less stable and delayed images cannot be acquired due to the period of semidisintegration of 18F, which reduces the specificity. Published studies are very scarce and their results have not been widely compared. In 1992 the viability of in vitro labeling of human leucocytes with 18F-FDG 66 was demonstrated and posterior studies in animals and humans reported that leucocytes labeled with 18F-FDG discriminated inflamed from normal tissue better than 18F-FDG. A good correlation has also been observed between the grade of inflammatory activity and the uptake of leucocytes labeled with 18F-FDG.

In conclusion, 18F-FDG PET/CT has demonstrated very promising results in the study of inflammatory disease, with greater scientific evidence in the case of vasculitis and sarcoidosis as recognized in the guidelines of the EANM and the SNMMI. The most accepted indications in the case of vasculitis are the diagnosis and assessment of inflammatory activity and its extension (especially in GCA). In sarcoidosis, the results obtained for the evaluation of extension of involvement and the grade of activity and therapeutic response are clearly superior to those achieved with 67Ga. The value of 18F-FDG in other inflammatory diseases at this stage is debatable since the advantages over the other techniques available have not been demonstrated. In view of the current great demand for 18F-FDG PET/CT in oncology we must adequately place the study within the context of the other conventional imaging (ultrasonography, CT, MR) and conventional nuclear medicine techniques. Prospective studies with a larger number of patients are necessary to clarify the many aspects pending response.

Points of interest

The fundamental indication of 18F-FDG PET/CT continues to be oncologic. 18F-FDG PET/CT has demonstrated to be a useful technique in the study of different inflammatory processes and its use is clearly expanding.

The principal indications of 18F-FDG PET/CT in large vessel vasculitis are diagnosis, assessment of the degree of activity, extension and treatment monitoring. 18F-FDG PET/CT has demonstrated clearly superior results to those of 67Ga in the study of sarcoidosis, with a greater sensitivity for the assessment of disease extension and the degree of inflammatory activity and the detection of involvement in unsuspected sites.

In other inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease 18F-FDG PET/CT is still not considered of first choice.

Conflict of interest

The authors have no conflicts of interest to declare.

References


