Review of Contemporary Philosophy
ISSN: 1841-5261, e-ISSN: 2471-089X
Vol 22 (1), 2023
Pp 3704 - 3714

The Role of Molecular Imaging in the Assessment of Inflammation in Metabolic Disorders: Review

[1]-Saeed Mohammed Ahmed Alzahrani,[2]-Khalid Daar Almotairi,[3]-Ahmed Ali Hmoud Mashykhei,[4]-Othman Mohammed A Mahzary,[5]-Riyadh Mohammed Hussain Khared,[6]-Mohammed Ahmed Kaylani,[7]-Hussain Mohammed Hussain Khared,[8]-Mansoor Theaby Jobran Ogdy,[9]- Aqeel Mohammad Ali Hadi,[10]- Mohanad Adel Ali Bejah,[11]- Ali Yahia Ibrahim Shabaani,[12]- Hasan Ahmed Yahya Abu Hashim,[13]-Sarah Farhan Alenizi,[14] - Abdulkarim Hameed Alanazi,[15]- Abdullah Fahad Mulhiyah

1. Ksa, Ministry Of Health, Dammam Health Network Eastern Health Cluster
2. Ksa, Ministry Of Health, Wathailan General Hospital
3. Ksa, Ministry Of Health, Al-Harth General Hospital
4. Ksa, Ministry Of Health, Ahad Almassarha Hospital Jazan Health Cluster
5. Ksa, Ministry Of Health, Middle Sector Of Jazan Health Cluster, Primary Health Care Center
6. Ksa, Ministry Of Health, King Fahd Central Hospital In Jazan
7. Ksa, Ministry Of Health, King Fahd Central Hospital In Jazan
8. Ksa, Ministry Of Health, Damad General Hospital
9. Ksa, Ministry Of Health, Damad General Hospital
10. Ksa, Ministry Of Health, Damad General Hospital
11. Ksa, Ministry Of Health, Damad General Hospital
12. Ksa, Ministry Of Health, Damad General Hospital
13. Ksa, Ministry Of Health, C2 Riyadh Healith Cluster
14. Ksa, Ministry Of Health, General Administration Of Medical Services
15. Ksa, Ministry Of Health, C2 Riyadh Healith Cluster

Abstract

Background: Inflammation plays a crucial role in various metabolic disorders, highlighting the need for innovative diagnostic techniques. Molecular imaging has emerged as a powerful tool for visualizing inflammation and assessing disease progression through targeted imaging of immune cells.

Methods: This review synthesizes current literature on molecular imaging modalities, including positron emission tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT). Specific emphasis is placed on the use of radiolabeled tracers and nanoparticles to enhance specificity in detecting inflammatory markers associated with cardiovascular disease, rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), and gastrointestinal disorders.

Results: The analysis reveals that 18F-fluorodeoxyglucose (FDG) PET is commonly employed to visualize macrophage activity in atherosclerosis, indicating heightened inflammation and plaque instability. Alternatives such as 11C-PK11195 and 68Ga-DOTATATE target specific receptors overexpressed in activated macrophages, offering improved specificity. Advances in MRI techniques, including superparamagnetic iron oxide nanoparticles (SPIONs) and chemical exchange saturation transfer (CEST), provide insights into metabolic alterations at inflammatory sites.

Conclusion: Molecular imaging techniques significantly enhance the ability to visualize and understand inflammatory processes at the cellular level. This has implications for early diagnosis and personalized treatment strategies in metabolic disorders. The ongoing development of novel imaging agents and

methodologies promises to further refine our understanding of disease mechanisms and improve patient outcomes.

Keywords: Molecular Imaging, Inflammation, Metabolic Disorders, Positron Emission Tomography, Magnetic Resonance Imaging.

Received: 07 october 2023 **Revised:** 22 November 2023 **Accepted:** 06 December 2023

1. Introduction

Inflammation may occur throughout the body and often serves as a common factor across several illnesses and infections. There is a current increase in preclinical and translational research to elucidate the precise function of inflammation in disease progression for more accurate diagnosis. This study primarily focuses on visualizing inflammation via the targeting of the immune system. Upon the introduction of a pathogen, there is an increase in immune cells, including macrophages, monocytes, and lymphocytes [1]. Monocytes and macrophages are attracted to the site of infection, where they multiply and engulf the pathogen; this phagocytic process allows for the internalization of exogenous imaging agents and the visualization of the inflammatory response [2]. Imaging of lymphocytes primarily utilizes radiolabeled antibodies [3-6]. Molecular imaging of these cells allows the non-invasive, in vivo viewing of immune cells to assess the degree and severity of the illness. The visualization of these immune cells as inflammatory biomarkers will profoundly impact customized treatment and the early diagnosis of inflammatory diseases.

Molecular imaging depends on endogenous or exogenous contrast chemicals to identify inflamed tissue. The dependence on endogenous contrast is noteworthy since it reduces patient risk; nevertheless, the lack of specificity of molecular processes constrains the precision and use of agents like hemoglobin and deoxyhemoglobin [7,8]. Molecular imaging has always necessitated tracer molecules that are particular to biological activities. These tracers include a contrast-generating substance, such as a fluorescent dye, which is directed toward a specific molecule or function inside the body. These tracers provide elevated, adjustable, and precise contrast, unattainable with endogenous contrast alone. Tracers have been employed in various modalities; for instance, radioactive atoms are used with sugars for metabolic tracking via positron emission tomography (PET)/SPECT, iodine-labeled tracers are utilized in X-ray imaging, and lanthanides that react to external magnetic fields are applied in MRI [9-11]. Nonetheless, the advancement of small molecule tracers has markedly decelerated owing to toxicity issues and inadequate sensitivity stemming from limited signal specificity and fast physiological elimination [1]. The use of nanoparticles is a promising approach to include exogenous contrast for molecular imaging, addressing the constraints often associated with fluorescent probes. Despite the promise of many nanoparticle forms, they often fail to meet expectations in clinical applications due to inadequate target specificity. Recent developments in active targeting have enhanced these prospects [12]. Methods for functionalizing nanoparticles enhance specificity by targeting extracellular receptors or critical characteristics of the target environment. The identification and use of the molecular signature of illnesses allow the creation of innovative imaging probes that disclose pathological information about tissue without invasive biopsies.

Conventional clinical imaging modalities, including computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US), primarily furnish anatomical data essential for diagnosis; however, they do not provide molecular information that may be pivotal for determining suitable treatments. The assessment of tumor response to treatment employs the Response Evaluation Criteria in Solid Tumors (RECIST) score, which depends on changes in tumor size [13]. A significant alteration in tumor size may need many weeks to manifest; yet, molecular alterations will occur before physical changes. Recent improvements in contrast agents enable the extraction of functional, molecular, and anatomical information from conventional imaging modalities.

The selection of a contrast agent for MRI is contingent upon the purpose of the imaging session. T1-weighted MRI requires the administration of a paramagnetic metal agent, often gadolinium-based, which reduces the T1 relaxation period, hence enhancing the signal [14]. The inadequate sensitivity and restricted

specificity of gadolinium-based contrast agents make T1-weighted MRI unsatisfactory for molecular imaging [15]. T2-weighted MRI often requires the administration of superparamagnetic iron oxide nanoparticles (SPIONs), leading to negative contrast enhancement. SPIONs typically measure between 10 and 100 nm and are often coated with dextran to enhance biocompatibility [16,17]. The absorption of SPIONs by active macrophages at inflammatory locations renders T2-weighted MRI a suitable option for molecular imaging of inflammation [16,18].

MR spectroscopy is an additional MR method that captures the molecular spectra of the target tissue to provide insights into the concentration and presence of various metabolites inside the tissue [19]. Although MR spectroscopy offers more information than conventional MRI, it is constrained by inadequate spatial resolution and low sensitivity, since the substances of interest are present in minimal amounts [20]. Chemical exchange saturation transfer (CEST) magnetic resonance imaging entails the transfer of magnetization from the target agent to adjacent water molecules, resulting in signal attenuation via the saturation effect that is observable only in the water molecules, not in the target agent. CEST imaging relies on the chemical composition of the target metabolite and the RF pulse that triggers the proton's chemical exchange [20]. The sensitivity of CEST imaging is strongly correlated with the chemical exchange rate of proton transfer, facilitating the molecular imaging of particular metabolites present in low quantities [21]. Although most research on CEST drugs mostly targets cancer, there has been a preclinical investigation into the use of CEST imaging and MR spectroscopy in neuroinflammation [22-25].

Given that inflammation is a characteristic of several illnesses, the capacity to visualize inflammatory indicators at the molecular level would enhance the comprehension of disease pathogenesis and, eventually, improve patient treatment. This study aims to elucidate the current molecular imaging methods used to evaluate the inflammatory conditions associated with cardiovascular disease, rheumatoid arthritis, chronic obstructive pulmonary disease, and gastrointestinal illnesses.

2. Imaging of Inflammatory Disease

Cardiovascular disease (CVD) is the predominant cause of mortality globally [26,27]. Cardiovascular disease (CVD) is an overarching term that includes several disorders affecting the heart and circulatory system, most of which progress gradually and are often recognized only upon the emergence of symptoms, frequently culminating in mortality, mostly due to heart attack or stroke [28]. In the United States, a person succumbs to cardiovascular disease (CVD) every 36 seconds. Given the rising prevalence of smoking and escalating obesity rates—two significant risk factors for CVD—it is imperative to prioritize the advancement of early screening tools to detect CVD markers before it becomes critical.

Atherosclerosis transpires when plaque accumulates inside the artery; with time, this plaque hardens, causing the artery to constrict and impeding blood flow, often leading to cardiovascular disease [29-32]. Plaque accumulation is often identified only when symptoms arise, such as myocardial infarction or stroke, which are among the leading causes of death in the United States and Europe [31]. Currently, catheter-based X-ray angiography or intravascular ultrasonography is used to detect coronary atherosclerosis; however, this method is very invasive and provides only anatomical data about the extent of stenosis [26,33,34]. Non-invasive molecular imaging methods should be used to assess plaque activity to identify individuals at very high risk who require prompt care. Coronary CT angiography (CCTA) is a technique for assessing the extent of stenosis and the makeup of plaques [35]. CCTA can quantify the extent of calcification in coronary plaques, serving as a robust predictor of significant cardiovascular events [36,37]. Although CCTA offers functional insights into cardiovascular disease, it cannot serve as a genuine molecular imaging tool, since it does not depict alterations at the molecular level.

Elevated macrophage activity, indicative of inflammation, is associated with an increased risk of plaque rupture; hence, molecular imaging of macrophage activity in the arteries might assist in pinpointing regions where plaque accumulation may occur [38-40]. 18F-Fluorodeoxyglucose (FDG) PET imaging is often used to visualize the inflammatory aspect of atherosclerosis [41-44]. 18F-FDG is a radiolabeled glucose compound that is absorbed by cells using the same process used for glucose metabolism. Both 18F-FDG and

glucose undergo phosphorylation by hexokinase, resulting in the formation of 18F-FDG-6-phosphate and glucose-6-phosphate, respectively. 18F-FDG-6-phosphate is not further metabolized by glucose-6-phosphate isomerase; hence it accumulates inside the cell for PET imaging [45]. Atherosclerosis involves the aggregation of macrophages at sites of active plaque formation, necessitating substantial glucose, which leads to the overexpression of glucose transporters on the macrophage surface. Consequently, elevated 18F-FDG uptake will be seen in areas of heightened macrophage density, indicative of inflammation and active plaque formation (Figure 1) [38,46]. The impact of 18F-FDG absorption from other cells, including neutrophils, endothelial cells, and lymphocytes, on the reported signal remains uncertain [33,40]. After the calcification of plaque cells, 18F-FDG uptake will significantly diminish, rendering this kind of PET imaging useless. PET imaging of atherosclerosis with 18F-FDG necessitates a circulation duration of 2–3 hours to facilitate buildup in the artery wall and the reduction or elimination of background levels of 18F-FDG [40]. In oncology, 18F-FDG PET imaging generally requires one hour of circulation time before the commencement of imaging.

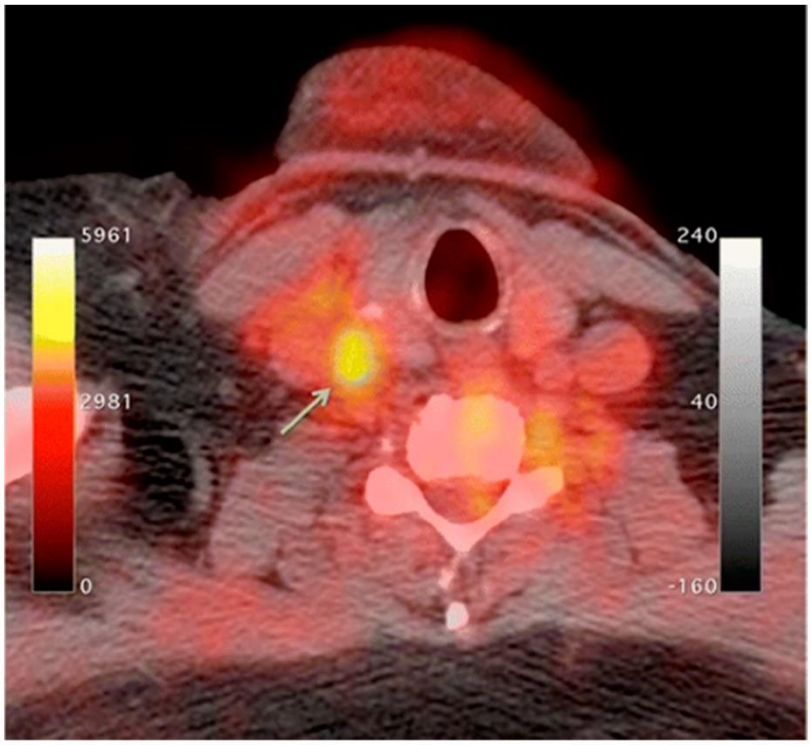

Figure 1. 18F-Fluorodeoxyglucose (18F-FDG) positron emission tomography (PET)/computed tomography (CT) imaging of activated macrophages to elucidate susceptible plaques via enhanced glucose metabolism.

18F-FDG PET imaging lacks specificity, complicating interpretations due to the presence of highly metabolic adjacent tissues, including cardiac cells and neurons [38,47,48]. The inhibition of myocardial 18F-FDG absorption may be accomplished by dietary modification (high-fat, low-carbohydrate) to transition the body to beta-oxidation of fatty acids, therefore reducing glucose metabolism as the principal energy source and attempting to minimize background activity [49,50]. Alternative radiotracers unique to macrophages may be used, therefore minimizing the influence of other highly metabolic cells. Translocator protein (TSPO)/peripheral benzodiazepine (PBR) receptors are significantly overexpressed in activated macrophages, presenting an advantageous opportunity for active targeting [51-54]. Uptake of 11C-PK11195 in individuals with atherosclerosis was elevated in those who had a myocardial infarction or stroke, in contrast to asymptomatic patients [53]. Additional radiolabeled TSPO-targeted ligands including 18F-GE-180, demonstrated an improved signal-to-noise ratio and reduced non-specific binding; further validation of this radiotracer is necessary [55-57].

68Ga-DOTATATE is a radiolabeled tracer used to target inflammatory plaques in atherosclerosis by binding to somatostatin receptor subtype 2 (SSR-2), which is overexpressed on activated macrophages. Copper radiolabel (64Cu) is often used in place of gallium because of its extended half-life and reduced positron range, enabling improved spatial resolution [47,58]. CXC-motif chemokine receptor 4 (CXCR-4) is overexpressed on several immune cells, including monocytes and macrophages, making this receptor an effective target for imaging inflammatory atherosclerotic plaques [59]. A radiolabeled ventilator, 68Ga-pentixafor, specifically targets the CXCR-4 receptor to quantify arterial inflammation in atherosclerotic plaques [59-61].

As plaque accumulates inside the artery, macrophages become activated, and the area often experiences hypoxia owing to diminished oxygen diffusion efficiency resulting from the thickness of the arterial wall. Active macrophages indicate areas of inflammation, suggesting that their activity is partly influenced by hypoxia since atherosclerotic plaques have elevated levels of hypoxia-inducible factor 1-alpha (HIF-1α) [33,47,62]. Current research is focused on imaging hypoxia as a surrogate biomarker for plaque inflammation and atherosclerosis. Radiolabeled ligands, such 18F-fluoromisonidazole (FMISO) and 18F-EF5, have been used to identify atherosclerotic plaques using PET imaging of hypoxia in preclinical studies; more research is necessary to translate these results to clinical applications [63-65].

3. Oncology

The interplay of inflammation, infection, the immune system, and cancer is intricate and is a subject of ongoing research. Tumor cells multiply and release various cytokines and chemokines that attract leukocytes, often resulting in an inflammatory response. Leukocytes, including tumor-associated macrophages (TAMs), play a crucial role in the formation of the tumor microenvironment [66]. As previously stated, 18F-FDG PET imaging is often used to view inflammation and malignancy via heightened glucose metabolism [67]. This poses challenges in distinguishing active malignancies from inflammatory lesions since both exhibit heightened perfusion and metabolic activity. CT imaging using glucose-functionalized gold nanoparticles (GF-GNPs) was used in preclinical murine models to distinguish between cancer and inflammation based on vascular changes. [68].

Enhanced MRI imaging of ultrasmall superparamagnetic iron oxide particles (USPIO) effectively distinguished between inflammatory lesions and malignancies [69]. Recent advancements in multispectral optoacoustic tomography (MSOT) provide a singular imaging technique that may distinguish cancer from just inflammatory lesions by simultaneously detecting numerous biomarkers. This research describes many inflammatory indicators; tagging these markers with an NIR-sensitive fluorophore will facilitate imaging using MSOT. The advancement of NIR-sensitive, tumor-targeted imaging probes is presently a primary emphasis of MSOT research [70-72]. MSOT may distinguish several NIR-sensitive compounds by using spectral unmixing of distinct spectral profiles. This indicates that if inflammatory and tumor-targeted imaging agents are spectrally different, it will be possible to see cancer and inflammation concurrently. The capacity to detect a little focus of cancer amongst extensive inflammation holds considerable promise for facilitating earlier-stage diagnosis in individuals with pancreatic or colorectal malignancies associated with pancreatitis or inflammatory bowel disease.

4. Imaging in Immunotherapy and Cellular Therapy

Recent advancements in malignancy therapy have transitioned from traditional chemotherapeutics, which primarily inhibit development via toxic metabolites, to medicines and cellular therapies designed to enhance and/or guide host immune responses. Checkpoint inhibitors that stimulate and augment T-cell activity are widely used in both solid tumors and hematologic malignancies. Recently, cellular therapies have been authorized for the targeting of modified T lymphocytes to receptor sites in both leukemia and lymphoma. This change in treatment renders the diagnostic modalities of CT and FDG-PET, often used in cancer imaging, inadequate for distinctly distinguishing an immune response from tumor development. Consequently, novel imaging agents are being investigated to assess and monitor illness and immunological responses in an activated immune system.

Recent efforts to enhance diagnostics in this field have concentrated on tagging T cells with PET probes to accurately monitor and discern the impacts of T-cell activation in cellular therapy and graft-versus-host disease (GVHD). In murine models, FLT-PET has been used to detect proliferation in the gastrointestinal tract, correlating with immune recognition and response in the context of graft-versus-host disease [73]. Furthermore, human T cells with anti-melanoma T-cell receptors have been transduced with F-L-MAU and hdCKEmut PET probes to track and assess responses to melanoma lesions [74]. HSV1-TK transduced lymphocytes and CD19 CAR T cells with truncated epithelial growth factor receptors have been utilized to establish a platform for imaging and monitoring cellular responses, alongside the integration of suicide genes to ensure safety in cases of severe T cell immunologic responses or graft versus host disease [75]. Recently, a rat model has used 89ZrDFO-Inducible T-Cell COStimulator (ICOS)-monoclonal antibody (ICOS-ImmunoPET) to exploit the heightened ICOS expression in activated CAR-T cells for monitoring responsiveness and localization [76]. Numerous investigations using innovative PET isotopes combined with either MRI or CT are being conducted to enhance diagnostic precision in GVHD, cellular therapy, and immune-based treatments. NCT03633955 FLT-CT in immunotherapy, F-18 ARA-G PET. As advancements in cellular therapy progress, the allogeneic and immunologic domains of cancer treatment extend to both hematologic and solid tumors, necessitating the ability to monitor, track, and quantitatively assess upregulated cellular components, which will require molecular imaging techniques. Moreover, the next investigations will need molecular imaging to monitor possible harm and early signs of effectiveness.

Numerous studies indicate a need for bigger training datasets to more accurately delineate bias across various imaging modalities and to enhance their performance and generalizability due to dataset heterogeneity [77,78]. These investigations further underscore the need for enhanced clinical importance. A recent study on sinusitis showed a correlation between CNN scores and Lund–MacKay (LM) scores, the clinical visual assessment, whereas the evaluation of clinical significance was designated for further research. Certain investigations indicate the want for more algorithmic advancement, particularly the requirement for dependable techniques to differentiate specific sinus cavities [78]. In the context of COPD and inflammatory lung illness, the accuracies of microscopic image scoring algorithms are claimed to be comparable to those of pathologists; yet, both computer algorithms and pathologists encounter difficulties in distinguishing red blood cells from inflammatory cells when the staining is very dark [79]. In research involving CD, IBD, and inflammatory gastrointestinal lesions, selecting the useful segments of endoscopy and colonoscopy movies is sometimes challenging due to interference from out-of-focus regions and picture quality issues. Future research is required to correlate clinical data with endoscopic results to establish a completely automated system. Multiple sclerosis (MS) is a chronic inflammatory condition of the brain that often necessitates the segmentation of brain MRI images. The 3D patch-wise CNN methodology has been used for brain segmentation, although significant spatial variability complicates the process. Moreover, the use of 3D CNN necessitates an increased amount of volumetric data (weights) to mitigate overfitting [80].

5. Conclusions

Inflammatory disorders are prevalent and exhibit significant morbidity and death rates in severe instances. Timely recognition of molecular traits offers the greatest opportunity to prevent irreparable harm. A non-invasive and highly precise method for imaging the pathophysiology of these disorders is needed. The immune system significantly influences inflammatory diseases, making immune cells and associated inflammatory cytokines the principal focus in the molecular imaging of such conditions. Advancements in molecular imaging provide early identification via particular biomarkers that may exist before symptom manifestation, resulting in improved patient treatment.

References

1. MacRitchie, N.; Frleta-Gilchrist, M.; Sugiyama, A.; Lawton, T.; McInnes, I.B.; Maffia, P. Molecular Imaging of inflammation—Current and Emerging Technologies for Diagnosis and Treatment. Pharmacol. Ther. 2020, 211, 107550.

2. Chiu, S.; Bharat, A. Role of Monocytes and Macrophages in Regulating Immune Response Following Lung Transplantation. Curr. Opin. Organ Transpl. 2016, 21, 239–245.
3. Malviya, G.; Galli, F.; Sonni, I.; Signore, A. Imaging T-lymphocytes in Inflammatory Diseases: A Nuclear Medicine Approach. Q. J. Nucl. Med. Mol. Imaging 2014, 58, 237–257.
4. Malviya, G.; Anzola, K.L.; Podestà, E.; Laganà, B.; Del Mastro, C.; Dierckx, R.A.; Scopinaro, F.; Signore, A. (99m)Tc-Labeled Rituximab for Imaging B Lymphocyte Infiltration in Inflammatory Autoimmune Disease Patients. Mol. Imaging Biol. 2012, 14, 637–646.
5. Moroz, M.A.; Zhang, H.; Lee, J.; Moroz, E.; Zurita, J.; Shenker, L.; Serganova, I.; Blasberg, R.; Ponomarev, V. Comparative Analysis of T Cell Imaging with Human Nuclear Reporter Genes. J. Nucl. Med. 2015, 56, 1055–1060.
6. Tavaré, R.; McCracken, M.N.; Zettlitz, K.A.; Salazar, F.B.; Olafsen, T.; Witte, O.N.; Wu, A.M. Immuno-PET of Murine T Cell Reconstitution Postadoptive Stem Cell Transplantation Using Anti-CD4 and Anti-CD8 Cys-Diabodies. J. Nucl. Med. 2015, 56, 1258–1264.
7. Zalev, J.; Richards, L.M.; Clingman, B.A.; Harris, J.; Cantu, E.; Menezes, G.L.; Avila, C.A.; Bertrand, A.; Saenz, X.R.; Miller, S.C. Opto-Acoustic Imaging of Relative Blood Oxygen Saturation and Total Hemoglobin for Breast Cancer Diagnosis. J. Biomed. Opt. 2019, 24, 121915.
8. Lee, J.; Hirano, Y.; Fukunaga, M.; Silva, A.C.; Duyn, J.H. On the Contribution of Deoxy-Hemoglobin to MRI Gray–White Matter Phase Contrast at High Field. Neuroimage 2010, 49, 193–198.
9. Uematsu, T.; Yuen, S.; Yukisawa, S.; Aramaki, T.; Morimoto, N.; Endo, M.; Furukawa, H.; Uchida, Y.; Watanabe, J. Comparison of FDG PET and SPECT for Detection of Bone Metastases in Breast Cancer. Am. J. Roentgenol. 2005, 184, 1266–1273.
10. Lee, N.; Choi, S.H.; Hyeon, T. Nano-Sized CT Contrast Agents. Adv. Mater. 2013, 25, 2641–2660.
11. Bottrill, M.; Kwok, L.; Long, N.J. Lanthanides in Magnetic Resonance Imaging. Chem. Soc. Rev. 2006, 35, 557–571.
12. Pearce, A.K.; O'Reilly, R.K. Insights into Active Targeting of Nanoparticles in Drug Delivery: Advances in Clinical Studies and Design Considerations for Cancer Nanomedicine. Bioconjug. Chem. 2019, 30, 2300–2311.
13. Desar, I.M.E.; van Herpen, C.M.L.; van Laarhoven, H.W.M.; Barentsz, J.O.; Oyen, W.J.G.; van der Graaf, W.T.A. Beyond RECIST: Molecular and Functional Imaging Techniques for Evaluation of Response to Targeted Therapy. Cancer Treat. Rev. 2009, 35, 309–321.
14. Gallagher, F.A. An Introduction to Functional and Molecular Imaging with MRI. Clin. Radiol. 2010, 65, 557–566.
15. Caravan, P. Strategies for Increasing the Sensitivity of Gadolinium Based MRI Contrast Agents. Chem. Soc. Rev. 2006, 35, 512–523.
16. Jin, R.; Lin, B.; Li, D.; Ai, H. Superparamagnetic Iron Oxide Nanoparticles for MR Imaging and Therapy: Design Considerations and Clinical Applications. Curr. Opin. Pharmacol. 2014, 18, 18–27.
17. Wahajuddin, S.A. Superparamagnetic Iron Oxide Nanoparticles: Magnetic Nanoplatforms as Drug Carriers. Int. J. Nanomed. 2012, 7, 3445–3471.
18. Neuwelt, A.; Sidhu, N.; Hu, C.-A.A.; Mlady, G.; Eberhardt, S.C.; Sillerud, L.O. Iron-Based Superparamagnetic Nanoparticle Contrast Agents for MRI of Infection and Inflammation. Am. J. Roentgenol. 2015, 204, W302–W313.
19. Manias, K.A.; Peet, A. What Is MR Spectroscopy? Arch. Dis. Child. Educ. Pract. Ed. 2018, 103, 213.
20. Wu, B.; Warnock, G.; Zaiss, M.; Lin, C.; Chen, M.; Zhou, Z.; Mu, L.; Nanz, D.; Tuura, R.; Delso, G. An Overview of CEST MRI for Non-MR Physicists. EJNMMI Phys. 2016, 3, 19.
21. Liu, G.; Bettegowda, C.; Qiao, Y.; Staedtke, V.; Chan, K.W.Y.; Bai, R.; Li, Y.; Riggins, G.J.; Kinzler, K.W.; Bulte, J.W.M.; et al. Noninvasive Imaging of Infection after Treatment with Tumor-Homing Bacteria Using Chemical Exchange Saturation Transfer (CEST) MRI. Magn. Reson. Med. 2013, 70, 1690–1698.
22. Consolino, L.; Anemone, A.; Capozza, M.; Carella, A.; Irrera, P.; Corrado, A.; Dhakan, C.; Bracesco, M.; Longo, D.L. Non-Invasive Investigation of Tumor Metabolism and Acidosis by MRI-CEST Imaging. Front. Oncol. 2020, 10, 161.

23. Chang, L.; Munsaka, S.M.; Kraft-Terry, S.; Ernst, T. Magnetic Resonance Spectroscopy to Assess Neuroinflammation and Neuropathic Pain. J. Neuroimmune Pharmacol. 2013, 8, 576–593.
24. Chen, Y.Z.; Dai, Z.Z.; Shen, Z.W.; Lin, G.S.; Zhuang, C.Y.; Li, H.J.; Wu, R.H. Magnetic Resonance Imaging of Glutamate in Neuroinflammation. Radiol. Infect. Dis. 2016, 3, 92–97.
25. Yanez Lopez, M.; Pardon, M.-C.; Baiker, K.; Prior, M.; Yuchun, D.; Agostini, A.; Bai, L.; Auer, D.P.; Faas, H.M. Myoinositol CEST Signal in Animals with Increased Iba-1 Levels in Response to an Inflammatory Challenge-Preliminary Findings. PLoS ONE 2019, 14, e0212002.
26. Tarkin, J.M.; Dweck, M.R.; Evans, N.R.; Takx, R.A.P.; Brown, A.J.; Tawakol, A.; Fayad, Z.A.; Rudd, J.H.F. Imaging Atherosclerosis. Circ. Res. 2016, 118, 750–769.
27. Van Camp, G. Cardiovascular Disease Prevention. Acta Clin/Belg. 2014, 69, 407–411.
28. Francula-Zaninovic, S.; Nola, I.A. Management of Measurable Variable Cardiovascular Disease Risk Factors. Curr. Cardiol. Rev. 2018, 14, 153–163.
29. Jokinen, E. Obesity and Cardiovascular Disease. Minerva Pediatr. 2015, 67, 25–32.
30. Kondo, T.; Nakano, Y.; Adachi, S.; Murohara, T. Effects of Tobacco Smoking on Cardiovascular Disease. Circ. J. 2019, 83, 1980–1985.
31. Virani, S.S.; Alonso, A.; Benjamin, E.J.; Bittencourt, M.S.; Callaway, C.W.; Carson, A.P.; Chamberlain, A.M.; Chang, A.R.; Cheng, S.; Delling, F.N.; et al. Heart Disease and Stroke Statistics—2020 Update: A Report from the American Heart Association. AHA/ASA J. 2020.
32. Frostegård, J. Immunity, Atherosclerosis and Cardiovascular Disease. BMC Med. 2013, 11, 117.
33. Rosenbaum, D.; Millon, A.; Fayad, Z.A. Molecular Imaging in Atherosclerosis: FDG PET. Curr. Atheroscler. Rep. 2012, 14, 429–437.
34. Syed, M.B.; Fletcher, A.J.; Forsythe, R.O.; Kaczynski, J.; Newby, D.E.; Dweck, M.R.; van Beek, E.J. Emerging Techniques in Atherosclerosis Imaging. Br. J. Radiol. 2019, 92, 20180309.
35. Sandfort, V.; Lima Joao, A.C.; Bluemke, D.A. Noninvasive Imaging of Atherosclerotic Plaque Progression. Circ. Cardiovasc. Imaging 2015, 8, e003316.
36. Detrano, R.; Guerci, A.D.; Carr, J.J.; Bild, D.E.; Burke, G.; Folsom, A.R.; Liu, K.; Shea, S.; Szklo, M.; Bluemke, D.A. Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups. N. Engl. J. Med. 2008, 358, 1336–1345.
37. Park, H.-B.; Heo, R.; Hartaigh, B.Ó.; Cho, I.; Gransar, H.; Nakazato, R.; Leipsic, J.; Mancini, G.B.J.; Koo, B.-K.; Otake, H.; et al. Atherosclerotic Plaque Characteristics by CT Angiography Identify Coronary Lesions That Cause Ischemia: A Direct Comparison to Fractional Flow Reserve. JACC Cardiovasc. Imaging 2015, 8, 1–10.
38. Dunphy, M.P.; Freiman, A.; Larson, S.M.; Strauss, H.W. Association of Vascular 18F-FDG Uptake with Vascular Calcification. J. Nucl. Med. 2005, 46, 1278–1284.
39. Moore, K.J.; Tabas, I. Macrophages in the Pathogenesis of Atherosclerosis. Cell 2011, 145, 341–355.
40. Tarkin, J.M.; Joshi, F.R.; Rudd, J.H.F. PET Imaging of Inflammation in Atherosclerosis. Nat. Rev. Cardiol. 2014, 11, 443–457.
41. Lederman, R.; Raylman, R.; Fisher, S.; Kison, P.; San, H.; Nabel, E.; Wahl, R. Detection of Atherosclerosis Using a Novel Positron-Sensitive Probe and 18-fluorodeoxyglucose (FDG). Nucl. Med. Commun. 2001, 22, 747–753.
42. Skagen, K.; Johnsrud, K.; Evensen, K.; Scott, H.; Krohg-Sørensen, K.; Reier-Nilsen, F.; Revheim, M.E.; Fjeld, J.G.; Skjelland, M.; Russell, D. Carotid Plaque Inflammation Assessed with (18)F-FDG PET/CT Is Higher in Symptomatic Compared with Asymptomatic Patients. Int. J. Stroke 2015, 10, 730–736.
43. Vallabhajosula, S.; Machac, J.; Knesaurek, K.; Telsey, J.; Lipszyc, H.; Bastidas, D.; Zhao, Q.; Buchsbaum, M. Imaging Atherosclerotic Macrophage Density by Positron Emission Tomography Using F-18-fluorodeoxyglucose (FDG). J. Nucl. Med. 1996, 37, 144.
44. Yun, M.; Yeh, D.; Araujo, L.I.; Jang, S.; Newberg, A.; Alavi, A. F-18 FDG Uptake in the Large Arteries: A New Observation. Clin. Nucl. Med. 2001, 26, 314–319.
45. Buck, A.K.; Reske, S.N. Cellular Origin and Molecular Mechanisms of 18F-FDG Uptake: Is There a Contribution of the Endothelium? J. Nucl. Med. 2004, 45, 461–463.

46. Rudd, J.H.; Warburton, E.; Fryer, T.D.; Jones, H.; Clark, J.; Antoun, N.; Johnstrom, P.; Davenport, A.P.; Kirkpatrick, P.J.; Arch, B.N. Imaging Atherosclerotic Plaque Inflammation with [18F]-fluorodeoxyglucose Positron Emission Tomography. Circulation 2002, 105, 2708–2711.
47. Evans, N.R.; Tarkin, J.M.; Chowdhury, M.M.; Warburton, E.A.; Rudd, J.H.F. PET Imaging of Atherosclerotic Disease: Advancing Plaque Assessment from Anatomy to Pathophysiology. Curr. Atheroscler. Rep. 2016, 18, 30.
48. Mazurek, T.; Kobylecka, M.; Zielenkiewicz, M.; Kurek, A.; Kochman, J.; Filipiak, K.J.; Mazurek, K.; Huczek, Z.; Królicki, L.; Opolski, G. PET/CT Evaluation of 18 F-FDG Uptake in Pericoronary Adipose Tissue in Patients with Stable Coronary Artery Disease: Independent Predictor of Atherosclerotic Lesions' Formation? J. Nucl. Cardiol. 2017, 24, 1075–1084.
49. Gullberg, G.T.; Shrestha, U.M.; Seo, Y. PET Imaging of Glucose and Fatty Acid Metabolism for NAFLD Patients. J. Nucl. Cardiol. 2020, 27, 1689–1697.
50. Wykrzykowska, J.; Lehman, S.; Williams, G.; Parker, J.A.; Palmer, M.R.; Varkey, S.; Kolodny, G.; Laham, R. Imaging of Inflamed and Vulnerable Plaque in Coronary Arteries with 18F-FDG PET/CT in Patients with Suppression of Myocardial Uptake Using a Low-Carbohydrate, High-Fat Preparation. J. Nucl. Med. 2009, 50, 563–568.
51. Bird, J.L.E.; Izquierdo-Garcia, D.; Davies, J.R.; Rudd, J.H.F.; Probst, K.C.; Figg, N.; Clark, J.C.; Weissberg, P.L.; Davenport, A.P.; Warburton, E.A. Evaluation of Translocator Protein Quantification as a Tool for Characterising Macrophage Burden in Human Carotid Atherosclerosis. Atherosclerosis 2010, 210, 388–391.
52. Fujimura, Y.; Hwang, P.M.; Iii, H.T.; Kozloff, L.; Imaizumi, M.; Innis, R.B.; Fujita, M. Increased Peripheral Benzodiazepine Receptors in Arterial Plaque of Patients with Atherosclerosis: An Autoradiographic Study with [(3)H]PK 11195. Atherosclerosis 2008, 201, 108–111.
53. Gaemperli, O.; Shalhoub, J.; Owen, D.R.; Lamare, F.; Johansson, S.; Fouladi, N.; Davies, A.H.; Rimoldi, O.E.; Camici, P.G. Imaging Intraplaque Inflammation in Carotid Atherosclerosis with 11C-PK11195 Positron Emission Tomography/Computed Tomography. Eur. Heart J. 2012, 33, 1902–1910.
54. Pugliese, F.; Gaemperli, O.; Kinderlerer, A.R.; Lamare, F.; Shalhoub, J.; Davies, A.H.; Rimoldi, O.E.; Mason, J.C.; Camici, P.G. Imaging of Vascular Inflammation With [11C]-PK11195 and Positron Emission Tomography/Computed Tomography Angiography. J. Am. Coll. Cardiol. 2010, 56, 653–661.
55. Boutin, H.; Murray, K.; Pradillo, J.; Maroy, R.; Smigova, A.; Gerhard, A.; Jones, P.A.; Trigg, W. 18F-GE-180: A Novel TSPO Radiotracer Compared to 11C-R-PK11195 in a Preclinical Model of Stroke. Eur. J. Nucl. Med. Mol. Imaging 2015, 42, 503–511.
56. Rinne, P.; Hellberg, S.; Kiugel, M.; Virta, J.; Li, X.-G.; Käkelä, M.; Helariutta, K.; Luoto, P.; Liljenbäck, H.; Hakovirta, H. Comparison of Somatostatin Receptor 2-targeting PET Tracers in the Detection of Mouse Atherosclerotic Plaques. Mol. Imaging Biol. 2016, 18, 99–108.
57. Tarkin, J.M.; Joshi, F.R.; Evans, N.R.; Chowdhury, M.M.; Figg, N.L.; Shah, A.V.; Starks, L.T.; Martin-Garrido, A.; Manavaki, R.; Yu, E. Detection of Atherosclerotic Inflammation by 68Ga-DOTATATE PET Compared to [18F] FDG PET Imaging. J. Am. Coll. Cardiol. 2017, 69, 1774–1791.
58. Pérez-Medina, C.; Fayad, Z.A.; Mulder, W.J.M. Atherosclerosis Immunoimaging by Positron Emission Tomography. Arter. Thromb. Vasc. Biol. 2020, 40, 865–873.
59. Hyafil, F.; Pelisek, J.; Laitinen, I.; Schottelius, M.; Mohring, M.; Döring, Y.; van der Vorst, E.P.; Kallmayer, M.; Steiger, K.; Poschenrieder, A. Imaging the Cytokine Receptor CXCR4 in Atherosclerotic Plaques with the Radiotracer 68Ga-pentixafor for PET. J. Nucl. Med. 2017, 58, 499–506.
60. Li, X.; Heber, D.; Leike, T.; Beitzke, D.; Lu, X.; Zhang, X.; Wei, Y.; Mitterhauser, M.; Wadsak, W.; Kropf, S.; et al. [68Ga]Pentixafor-PET/MRI for the Detection of Chemokine Receptor 4 Expression in Atherosclerotic Plaques. Eur. J. Nucl. Med. Mol. Imaging 2018, 45, 558–566.
61. Weiberg, D.; Thackeray, J.T.; Daum, G.; Sohns, J.M.; Kropf, S.; Wester, H.-J.; Ross, T.L.; Bengel, F.M.; Derlin, T. Clinical Molecular Imaging of Chemokine Receptor CXCR4 Expression in Atherosclerotic Plaque Using 68Ga-pentixafor PET: Correlation with Cardiovascular Risk Factors and Calcified Plaque Burden. J. Nucl. Med. 2018, 59, 266–272.

62. Marsch, E.; Sluimer, J.C.; Daemen, M.J. Hypoxia in Atherosclerosis and Inflammation. Curr. Opin. Lipidol. 2013, 24, 393–400.
63. Joshi, F.R.; Manavaki, R.; Fryer, T.D.; Figg, N.L.; Sluimer, J.C.; Aigbirhio, F.I.; Davenport, A.P.; Kirkpatrick, P.J.; Warburton, E.A.; Rudd, J.H.F. Vascular Imaging with (18)F-Fluorodeoxyglucose Positron Emission Tomography Is Influenced by Hypoxia. J. Am. Coll. Cardiol. 2017, 69, 1873–1874.
64. Mateo, J.; Izquierdo-Garcia, D.; Badimon, J.J.; Fayad, Z.A.; Fuster, V. Noninvasive Assessment of Hypoxia in Rabbit Advanced Atherosclerosis Using 18F-fluoromisonidazole Positron Emission Tomographic Imaging. Circ. Cardiovasc. Imaging 2014, 7, 312–320.
65. Silvola, J.M.; Saraste, A.; Forsback, S.; Laine, V.J.; Saukko, P.; Heinonen, S.E.; Ylä-Herttuala, S.; Roivainen, A.; Knuuti, J. Detection of Hypoxia by [18F]EF5 in Atherosclerotic Plaques in Mice. Arter. Thromb. Vasc. Biol. 2011, 31, 1011–1015.
66. Coussens, L.M.; Werb, Z. Inflammation and Cancer. Nature 2002, 420, 860–867.
67. Derlin, T.; Grünwald, V.; Steinbach, J.; Wester, H.-J.; Ross, T.L. Molecular Imaging in Oncology Using Positron Emission Tomography. Dtsch. Arztebl. Int. 2018, 115, 175–181.
68. Motiei, M.; Dreifuss, T.; Betzer, O.; Panet, H.; Popovtzer, A.; Santana, J.; Abourbeh, G.; Mishani, E.; Popovtzer, R. Differentiating between Cancer and Inflammation: A Metabolic-Based Method for Functional Computed Tomography Imaging. ACS Nano 2016, 10, 3469–3477.
69. Seyfer, P.; Pagenstecher, A.; Mandic, R.; Klose, K.-J.; Heverhagen, J.T. Cancer and Inflammation: Differentiation by USPIO-Enhanced MR Imaging. J. Magn. Reson. Imaging 2014, 39, 665–672.
70. Ntziachristos, V.; Razansky, D. Molecular Imaging using Multispectral Optoacoustic Tomography (MSOT). Chem. Rev. 2010, 110, 2783–2794.
71. Beziere, N.; Lozano, N.; Nunes, A.; Salichs, J.; Queiros, D.; Kostarelos, K.; Ntziachristos, V. Dynamic Imaging of PEGylated Indocyanine Green (ICG) Liposomes within the Tumor Microenvironment Using Multi-Spectral Optoacoustic Tomography (MSOT). Biomaterials 2015, 37, 415–424.
72. Khanal, A.; Ullum, C.; Kimbrough, C.W.; Garbett, N.C.; Burlison, J.A.; McNally, M.W.; Chuong, P.; El-Baz, A.S.; Jasinski, J.B.; McNally, L.R. Tumor Targeted Mesoporous Silica-Coated Gold Nanorods Facilitate Detection of Pancreatic Tumors Using Multispectral Optoacoustic Tomography. Nano Res. 2015, 8, 3864–3877.
73. Lee, S.J.; Nguyen, T.D.; Onstad, L.; Bar, M.; Krakow, E.F.; Salit, R.B.; Carpenter, P.A.; Rodrigues, M.; Hall, A.M.; Storer, B.E.; et al. The success of Immunosuppressive Treatments in Patients with Chronic Graft-Versus-Host Disease. Biol. Blood Marrow Transplant. 2018, 24, 555–562.
74. McCracken, M.N.; Gschweng, E.H.; Nair-Gill, E.; McLaughlin, J.; Cooper, A.R.; Riedinger, M.; Cheng, D.; Nosala, C.; Kohn, D.B.; Witte, O.N. Long-Term In Vivo Monitoring of Mouse and Human Hematopoietic Stem Cell Engraftment with a Human Positron Emission Tomography Reporter Gene. Proc. Natl. Acad. Sci. USA 2013, 110, 1857–1862.
75. Kao, R.L.; Truscott, L.C.; Chiou, T.T.; Tsai, W.; Wu, A.M.; De Oliveira, S.N. A Cetuximab-Mediated Suicide System in Chimeric Antigen Receptor-Modified Hematopoietic Stem Cells for Cancer Therapy. Hum. Gene Ther. 2019, 30, 413–428.
76. Miletic, H.; Fischer, Y.; Litwak, S.; Giroglou, T.; Waerzeggers, Y.; Winkeler, A.; Li, H.; Himmelreich, U.; Lange, C.; Stenzel, W.; et al. Bystander Killing of Malignant Glioma by Bone Marrow-Derived Tumor-Infiltrating Progenitor Cells Expressing a Suicide gene. Mol. Ther. 2007, 15, 1373–1381.
77. Brooks, S.G.; Trope, M.; Blasetti, M.; Doghramji, L.; Parasher, A.; Glicksman, J.T.; Kennedy, D.W.; Thaler, E.R.; Cohen, N.A.; Palmer, J.N. Preoperative Lund-Mackay Computed Tomography Score Is Associated with Preoperative Symptom Severity and Predicts Quality-of-Life Outcome Trajectories after Sinus Surgery. Int. Forum Allergy Rhinol. 2018, 8, 668–675.
78. Humphries, S.M.; Centeno, J.P.; Notary, A.M.; Gerow, J.; Cicchetti, G.; Katial, R.K.; Beswick, D.M.; Ramakrishnan, V.R.; Alam, R.; Lynch, D.A. Volumetric Assessment of Paranasal Sinus Opacification on Computed Tomography Can Be Automated Using a Convolutional Neural Network. Int. Forum Allergy Rhinol. 2020, 10.
79. Heinemann, F.; Birk, G.; Schoenberger, T.; Stierstorfer, B. Deep Neural Network Based Histological Scoring of Lung Fibrosis and Inflammation in the Mouse Model System. PLoS ONE 2018, 13, e0202708.

80. Essa, E.; Aldesouky, D.; Hussein, S.E.; Rashad, M. Neuro-Fuzzy Patch-Wise R-CNN for Multiple Sclerosis Segmentation. Med. Biol. Eng. Comput. 2020, 58, 2161–2175.

دور التصوير الجزيئي في تقييم الالتهاب في الاضطرابات الأيضية: مراجعة

الملخص

الخلفية :يلعب الالتهاب دورًا حاسمًا في العديد من الاضطرابات الأيضية، مما يبرز الحاجة إلى تقنيات تشخيصية مبتكرة. ظهر التصوير الجزيئي كأداة قوية لتصوير الالتهاب وتقييم تقدم المرض من خلال استهداف الخلايا المناعية.

الطرق :تستعرض هذه المراجعة الأدبيات الحالية حول تقنيات التصوير الجزيئي، بما في ذلك التصوير المقطعي بالإصدار البوزيتروني(PET) ، والتصوير بالرنين المغناطيسي(MRI) ، والتصوير المقطعي المحوسب .(CT) تركز الدراسة على استخدام المتتبعات المشعة والجسيمات النانوية لتحسين الدقة في الكشف عن العلامات الالتهابية المرتبطة بأمراض القلب والأوعية الدموية، والتهاب المفاصل الروماتويدي، ومرض الانسداد الرئوي المزمن(COPD) ، والاضطرابات المعوية.

النتائج :يكشف التحليل أن استخدام 18 (FDG) F-fluorodeoxyglucoseفي التصوير المقطعي بالإصدار البوزيتروني يُستخدم بشكل شائع لتصوير نشاط البلعميات في تصلب الشرايين، مما يشير إلى زيادة الالتهاب وعدم استقرار اللويحات. تشمل البدائل الأخرى مثل 11 C-PK11195 و68 Ga-DOTATATEاستهداف مستقبلات معينة مفرطة التعبير في البلعميات النشطة، مما يوفر دقة محسّنة. تقدم تقنيات التصوير بالرنين المغناطيسي، بما في ذلك جسيمات أكسيد الحديد الفائق المغناطيسية (SPIONs) وتقنية النقل المشبع بتبادل كيميائي(CEST) ، رؤى حول التغيرات الأيضية في مواقع الالتهاب.

الاستنتاج :تعزز تقنيات التصوير الجزيئي بشكل كبير القدرة على تصوير العمليات الالتهابية وفهمها على المستوى الخلوي. لهذه التقنيات آثار مهمة في التشخيص المبكر واستراتيجيات العلاج المخصصة للاضطرابات الأيضية. يعد التطوير المستمر لعوامل التصوير والمنهجيات الجديدة بتحسين فهمنا لآليات المرض وتحسين نتائج المرضى.

الكلمات المفتاحية :التصوير الجزيئي، الالتهاب، الاضطرابات الأيضية، التصوير المقطعي بالإصدار البوزيتروني، التصوير بالرنين المغناطيسي.