Chapter 2

Molecular Imaging

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Abstract

Mechanisms responsible for the course of the rheumatic diseases have not been fully explained. Among the available tools that may help in studies of these mechanisms is molecular imaging—especially techniques emphasized by nuclear medicine. In contrast to CT, MRI or US examination that show only structural pathologies, radionuclide methods allow imaging of functional changes that occur in the course of the disease and usually are featured by a very high specificity. Recent advances in nuclear medicine allowed to develop target-specific agents making it possible to reveal molecular level disturbances that take place on the course of the ongoing disease. The fundamental radionuclide studies include PET, SPECT, and classic scintigraphy. Technological advances (especially hybrid modalities) allow obtaining images of much better resolution and allow combining both structural and functional data.

Keywords: PET, SPECT, markers of inflamation, radiotracers cordially

1. Introduction

Mechanisms responsible for the course of the rheumatic diseases have not been fully explained till today. Molecular imaging sits among the available tools that may help in studies of these mechanisms, particularly techniques emphasized by nuclear medicine.

In contrast to such imaging modalities as CT, US or MRI, that reveal only structural pathologies, radionuclide methods enable imaging of functional changes that occur in the course of the disease and more importantly are usually featured by a very high specificity. Radionuclide studies also make it possible to determine the changes in the molar concentration of specific chemical compounds up to 10^{-11} or even 10^{-3}–10^{-4} if an MRI is used. It means that radionuclide studies enable the performance of diagnosis of disorders in the molar concentration of the

specific chemical compounds that take place in the course of the disease. It is important to note that the functional character of disorders should be the basis for the choice of treatment.

Over the last several decades, the introduction of new biological agents has greatly improved the effectiveness of treatment. Those agents influence the activity of specific receptor and metabolic pathways [1]. Along with the application of new agents, it has become necessary to introduce new diagnostic methods, which allow evaluation of the activity of those biological processes. Unfortunately, neither clinical examination nor laboratory tests nor conventional X-ray does not provide such findings. A clinical evaluation can be highly subjective; laboratory tests are frequently non-specific and inconsistent, while conventional X-ray shows structural changes only at the advanced stage of the disease.

It seems that the introduction of molecular imaging techniques may lift those limitations. The fundamental methods of molecular imaging are radionuclide studies. Recent advances in nuclear medicine allowed to develop target-specific agents making it possible to reveal molecular level disturbances that take place on the course of the ongoing disease [2]. The fundamental radionuclide studies include a PET, SPECT, and classic scintigraphy. Moreover, hybrid devices are used more frequently in diagnostics these days—these consist of gamma camera and CR/MRI. Thanks to hybrid techniques, it is possible to perform CT/MRI combined with scintigraphy (for example PET-CT, PET-MRI, and SPECT-CT). It is also important to mention that the combination of those techniques allows applying attenuation correction of the absorbed radiation that is being emitted by radioisotope, as well as making it possible to determine the exact location of the abnormal uptake of the radiopharmaceutical. Finally, the images obtained are of very high quality.

Technological advances allow obtaining images of much better resolution and allow combining both structural and functional data. Vogel et al. noted in his study that hybrid imaging technique ^{18}F-FDG PET-CT, apart from providing the capability of assessing the degree of inflammation localized in the tarsus of a rheumatoid arthritis (RA) patient, also allows precise localization of the disease activity in particular joints [3]. Neither physical examination nor X-ray can provide such relevant data. Furthermore, ^{18}F-FDG PET/CT allows to visualize and diagnose metabolically active subcutaneous nodules, activated lymph nodes or other affected joints in the course of the disease (such as those of the knee or atlantoaxial joints). This method allows better discrimination between juxtaarticular disease and articular processes as well as delineation of tendon sheath and bursal inflammation. Furthermore, this method makes it possible to delineate inflammation of the tendon sheaths and bursae. Miese et al. [4] also assessed the high suitability of PET/MRI apparatus in his work about the diagnosis of RA, in which he showed increased uptake of ^{18}F-FDG in the corresponding metacarpophalangeal joints that were affected by synovitis and tenovaginitis as identified on contrast-enhanced MRI.

MRI is second modern imaging modality that is very useful in the diagnosis of rheumatic diseases. This method features a very high resolution and similarly good contrast between the soft tissues. Thanks to the new sequences and specific contrast agents, and modern MRI allows imaging of vast amounts of pathologies.

Both of these methods provide the information about molecular pathological mechanisms that accompany the disease; thus allowing a better understanding of the pathophysiology of rheumatic diseases. Moreover, they allow a search of the new forms of molecular treatment

that allow for an early and accurate prognosis as well as monitoring of therapy [5]. Beyond any doubts, another important feature of these methods is the capability of making the diagnosis at the subclinical phase of the disease, thanks to which a proper treatment can be started long before irreversible morphological changes occur.

Procedures offered by nuclear medicine meet the number of important expectations associated with the development of modern medical sciences, such as:

a. The capability of putting a considerably early diagnosis of pathological changes as well as the determination of their character, which is crucial to make an appropriate diagnosis before irreversible structural changes occur.

b. The ability of accurate determination of the degree of pathological changes.

c. The ability to predict the course of the disease and the subsequent introduction of personalized therapy.

d. The reduction of constantly increasing the costs of medical procedures by use of such evaluation tools that provide a good assessment of the effectiveness of the applied treatment.

e. The need of the determination of remission of the pathological changes as well as an early diagnosis of their relapse.

Taking these facts into account, it is clear that radionuclide studies and MRI have proven to be useful in solving all of the clinical issues. Moreover, it is important to note that it meets economic and pharmacological criteria for cost-effectiveness.

2. Radiopharmaceuticals

2.1. ^{18}F-FDG

The most commonly used radiopharmaceutical used in PET-CT studies is fluorodeoxyglucose (^{18}F-FDG), which is a structural glucose analog. Areas of increased tracer uptake indicate the intensification of metabolic processes associated with increased glucose demand. This feature can be found both in a tumor and inflammatory setting. Increased uptake of ^{18}F-FDG is associated with increased activity of the GLUT1 and GLUT3 transport mechanisms as well as the activity of hexokinase—these phenomena are typical for cells that undergo fast proliferation as well as other types of cells such as macrophages, neutrophils and young granulation tissue [6–8].

2.2. ^{11}C-choline

Choline is another tracer that features high sensitivity for proliferative processes that occur in the course of the disease. This tracer is uptaken by quickly dividing cells where it undergoes phosphorylation by choline kinase into phosphorylcholine. Choline is essential for phospholipids synthesis, especially phosphatidylcholine (also known as lecithin) which serves as the building block of the cell membranes. Increased uptake of choline depends on the

mechanisms responsible for active transport via the cell membrane as well as on congestion-dependent passive diffusion. It has been found that increased uptake can be seen even in the early phase of the inflammation. Once present, its grade of accumulation corresponds with both the extent of the contrast-enhanced signal in an MRI study (with Gadovist as a tracer) and the accumulation of ^{18}FDG [9].

2.3. ^{67}Ga-citrate

This radiopharmaceutical has been used in both the diagnosis of cancer as well as acute and chronic foci of inflammation for several years. Gallium (administered via i.v. infusion) acts as an iron analog that binds to transferrin, ferritin, and leukocytes (primarily neutrophils) [10]. These molecules accumulate within the foci of inflammation secondary to increased capillary permeability. At the time when ^{67}Ga-bound macromolecules reach the inflammatory interstitial space, the isotope undergoes the process of transchelation into lactoferrin, ferritin and bacterial siderophores (if present). Moreover, lactoferrin is then being secreted by neutrophils that are present in the inflammatory foci caused by the disorders of the connective tissue [11]. Recently, ^{67}Ga-citrate is rarely used because of the vast availability of other—frequently much better—markers as well as other factors such as the unfavorable energetic profile of the emitted radiation, the long-lasting radioactivity of the blood (due to high affinity to the white blood cells) and relatively long half-life time. This results in significantly increased absorbed radiation dose in comparison to other radioisotopes, not to mention low quality of the obtained images. Another disadvantage of ^{67}Ga-citrate is the lack of specificity for inflammation because it accumulates similarly in neoplasms.

2.4. ^{99m}Tc and ^{111}In HIG

Both 99m-technetium and 111-indium can be used for labeling of human (polyclonal) immunoglobulins (HIG). HIG accumulate in the inflamed tissues because its mechanism of accumulation is related to the increased permeability of the vascular capillaries as well as increased blood flow to the inflamed area. This technique features very high sensitivity, not to mention that the grade of its accumulation highly corresponds to the severity of the inflammation, hence making it a useful prognostic tool. On the other hand, one of the disadvantages of this radiopharmaceutical includes lack of specificity [12].

2.5. ^{99m}Tc-diphosphonates

Similarly to gallium-67, ^{99m}Tc-diphosphonates are non-specific tracers used in the diagnosis of the inflammation—its mechanism of uptake relies on the metabolism of the osseous cells—its degree of uptake depends on the activity of osteoblasts (hence its perfect for imaging of the bone turnover). Bone scintigraphy is readily available and cheap method of evaluation of bones [13, 14]. As the severity of the inflammation progress, the uptake increases. In the setting of inflammation evaluation, the bone scan comes in the form of a triphasic examination, which consists of vascular, parenchymal, and late (bony) phase (**Figure 1**). Each phase presents a specific aspect of the pathology:

- Phase I—hyperemia,
- Phase II—increased volume of the vascular bed,
- Phase III—metabolic turnover and remodeling of the osseous tissue as a result of the ongoing pathology (inflammation and destruction of the cartilage).

This method is highly sensitive but features low specificity, which can be improved by hybrid SPECT-CT technique if one is available.

It is important to note that the accumulation of described radiopharmaceuticals in tissues affected by inflammation is non-specific because these tracers accumulate similarly in neoplastic foci. Due to that fact, there is recently ongoing research that aims to develop markers specific for inflammation occurring in the course of the rheumatic diseases.

2.6. Labeled leukocytes

Since the inflammation features the migration of leukocytes, there was an idea to use that mechanism in the diagnosis and localization of the inflammatory foci. Nuclear medicine has

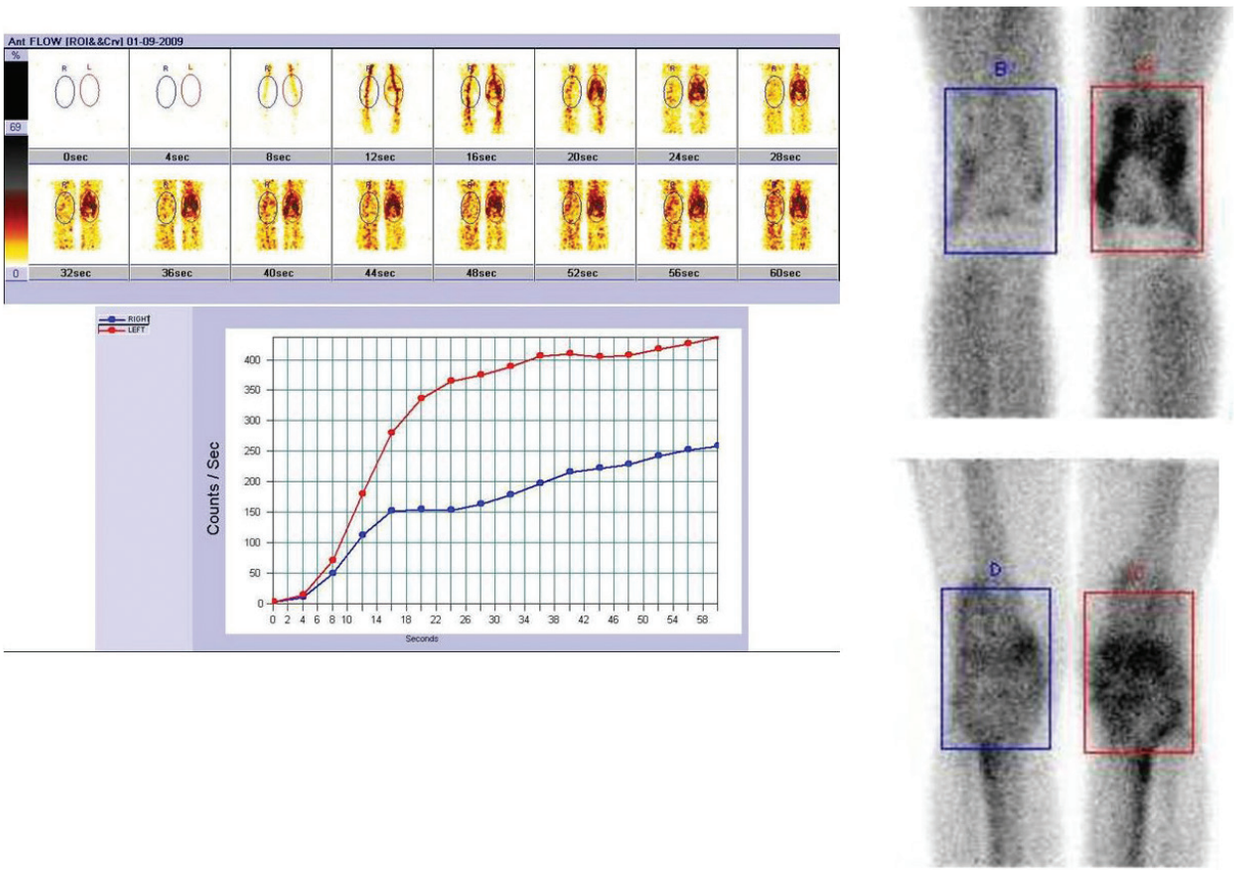

Figure 1. Triphasic bone scan after ^{99m}Tc-MDP administration in patient with RA shows increased blood flow (A), blood pool (B), and increased accumulation of the radiotracer in the bony phase (C) which indicates increased bony turnover in the affected left knee.

come to meet this need and has developed a radionuclide examination that makes it possible to label leukocytes of the patient (both in vitro and in vivo depending on the technique). In the setting of inflammation, neutrophils and monocytes are being recruited, and due to the phenomena of chemotaxis, they accumulate in the foci of inflammation. Thanks to this mechanism of accumulation, labeled leukocytes can be used in the diagnosis of RA as well as other inflammatory diseases. Labeled leukocytes emphasize two main techniques—in vivo and in vitro assay.

- *In vitro assay* is a technique that involves taking a blood sample, isolating a leukocyte suspension, labeling those leukocytes with ^{99m}Tc-HM-PAO or ^{111}In-oxine, and intravenous administration back to the patient. It is important to note that this procedure does not affect chemotaxis.
- *In vivo assay*, on the other hand, involves intravenous administration of ^{99m}Tc-labeled monoclonal antibodies against the specific NC-1 antigen that is present on the granulocyte cell membrane. In this procedure, the labeling process occurs directly in the blood of the patient. Moreland et al. [15] in his work have shown that there is a direct correlation between the foci of increased accumulation and the clinical picture in the course of rheumatoid arthritis. This examination may also be used as a tool to control anti-inflammatory treatment [15].

2.7. ^{11}C-PK11195

One of the proposals involved the introduction of ^{11}C-PK11195 isoquinoline carboxamide—this radiopharmaceutical binds to both monocytes and macrophages and serves as peripheral benzodiazepine receptor (PBR) antagonist also known as translocator protein (TSPO). This peptide is particularly active on the outer surface of the mitochondrial membrane of the activated macrophages, polymorphonuclear cells as well as nervous and lymphatic tissue [16–18]. It is responsible for the process of steroidogenesis, apoptosis, cell proliferation, and immune response. It has also been proved that this radiopharmaceutical is an effective marker in neuroinfection, due to the fact that peripheral benzodiazepine receptors can be typically found on activated glial cells.

2.8. ^{99m}Tc-J001X

Other noteworthy markers are those with the ability to label the macrophages. These kinds of cells are particularly active in inflammation based on the rheumatic disorders and play a major role in the inflammatory process. It was found that macrophages bind specifically to the proteoglycans of the bacteria. Hence a technique of proteoglycans labeling has been developed [19, 20].

Recently used tracer is called J001X—which is a poly-(1,3)-D-galactoside isolated from the cellular membrane of *Klebsiella pneumoniae*. This ^{99m}Tc labeled-substance allows tracing of the mononuclear phagocytes.

The effectiveness of this radiopharmaceutical in the diagnosis of RA-associated lung pathology appears to be promising, but until today there is no randomized study that would confirm its effectiveness. Lastly, this tracer was also used in imaging of sarcoidosis and scleroderma [21].

2.9. ^{99m}Tc-RP128

^{99m}Tc-RP128 is a peptide tracer used for imaging of leukocytes recruitment used for labeling of neutrophils and mononuclear phagocytes. ^{99m}Tc-RP128 is a pentapeptide tuftsin analog antagonist (TKPPR) that mediates the receptor-specific interaction and subsequently binds to tuftsin receptors. Tuftsin is an organic chemical compound consisting of amino acid residues such as threonine, lysine, proline, and arginine. It is produced by the spleen and its function is to stimulate macrophages and granulocytes to phagocytosis and chemotaxis. Tuftsin is derived from proteolytic cleavage of the Fc domain of the heavy chain of IgG. Tuftsin receptor's function is to mediate the immune functions; hence they represent important molecular targets. The mechanism of RP128 imaging is based on the upregulation of tuftsin receptors located in activated macrophages. Chaudhuri et al. [22] noted that the affinity of radiotracer is fourfold greater than their endogenous ligand. Despite that fact, this radiotracer was described only in a few works; thus there is a need for further research that would confirm its utility. Studies show that it accumulates in other organs to an only small extent (except kidneys). The grade of accumulation in healthy joints was moderate—in contrast to the affected joints, which featured a very high uptake. The sensitivity of the scan was 69% for swollen joints, 76% for painful joints, and 73% for joints with bone erosions [23].

2.10. ^{99m}Tc- and ^{111}In anti-E-selectin

Adhesion is another mechanism used in the diagnosis of the inflammation. Molecules responsible for this phenomena cause leukocytes to bind to the activated endothelial vessels resulting in their transendothelial migration. One of such molecules that are used in the diagnosis of the inflammation is E-selectin labeled with ^{99m}Tc or ^{111}In. E-selectin (CD62E, ELAM1) is a transmembrane glycoprotein that is transiently expressed on the luminal surface of activated vascular endothelium during a normal inflammatory response. E-selectin mediates the initial tethering and rolling of granulocytes, monocytes, and some lymphocytes via specific interactions with its carbohydrate-based ligands. It is then activated by interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α), and bacterial LPS—it has to be noted that this may occur only in the setting of inflammation [24]. ^{111}In-1.2B6 monoclonal antibody (mAb) is another antibody that was used for imaging of selectin activity. Since this is a murine antibody, the administration of this radiopharmaceutical comes with a risk of developing human anti-mouse antibody (HAMA) response, a possibly life-threatening state that requires immediate medical attention. This fact limits the repetition of the study in patients in whom treatment control is necessary. Therefore, F(ab')2 fragments of 1.2B6 mAb—devoid of its Fc portions—were introduced [25].

2.11. Octreotide

Octreotide is a long-acting somatostatin analog that targets the activation of endothelium and macrophage recruitment at any of five identified G-protein-coupled somatostatin receptor subtypes (SST1–5). Hyper-expression of these receptors has been thoroughly documented in numerous pathological conditions hence it can be considered as a basis for octreotide imaging. The synovia of affected joints in RA patients features overexpression of somatostatin receptors—those that are targeted by octreotide. The SST2 expression on activated venule of endothelial cells and infiltrating mononuclear phagocytes have been identified in histological and immunochemistry examinations both in the affected synovia and fibroblast-like synovial

cells. It is important to note that patients with favorable treatment results also show significantly lower expression of the somatostatin receptors; thus somatostatin scintigraphy may also be used in the prediction of the effectiveness of the treatment [26].

Somatostatin receptor expression also features a good correlation with the clinical data—its sensitivity estimates 75%. Vanhagen et al. [27] also noted that no radiotracer accumulation was observed in the joints of healthy individuals. Numerous works point that somatostatin analogs may be used in RA treatment as well. It has also been found that the administration of somatostatin analogs reduced the symptoms of the disease—presumably due to the inhibition of IL-6 and IL-8 production as well as inhibited proliferation that occurs in the affected synovium. Therefore, somatostatin scintigraphy may be used as a tool in the prediction of the somatostatin analog treatment effects, although until today there has been no randomized study to confirm it. Therefore, more research is required before its utility may be introduced to the guidelines [28].

2.12. Other radiopharmaceuticals

2.12.1. Anti-CD-3

Since mature T lymphocytes play a role in the development of RA, some radionuclide studies make it possible to label monoclonal antibodies against CD3 and T lymphocyte migration into the affected synovium. Recent advances allow Muromonab to be labeled with ^{99m}Tc and use it for imaging of rheumatic disease. It is essential to note that this examination correlates well with physical examination and patient history [29]. Moreover, scintigraphy with this tracer can be used in differential diagnosis of juvenile idiopathic arthritis and RA as well as other rheumatic diseases.

2.12.2. ^{99m}Tc-anti-CD4 mAb

Anti-CD4 imaging is also used for the evaluation of T lymphocyte infiltration. CD4 is expressed on the cell surface of mature T helper cells, thymocytes, and dendritic cells [30]. ^{99m}Tc-MAX.16H5, murine IgG1 was used in patients and showed affected joints in all RA patients. Studies indicate that the sensitivity of the ^{99m}Tc-MAX.16H5 scan is better than the bone scan.

2.12.3. ^{99m}Tc-Anti-CD20 mAb

Almost 95% of circulating normal and malignant B lymphocytes expresses CD20 antigen [31]. Furthermore, its expression is exclusive to B lymphocytes simultaneously featuring the lack of expression in the hematopoietic stem cells. Due to this fact, Rituximab as a mouse/human monoclonal antibody can be labeled with ^{99m}Tc and used for B cell infiltration imaging [32].

2.12.4. TNF-alpha

TNF plays an essential role in the development of RA [33]. The promising results have been described in studies which involved the use of ^{123}I-anakinra, infliximab (a monoclonal antibody that binds to membrane-bound and soluble TNF [34]) and ^{99m}Tc-Adalimumab.

3. Clinical application of radionuclide studies in the setting of rheumatoid arthritis and other inflammatory diseases

3.1. Rheumatoid arthritis

3.1.1. Diagnosis and disease progression

In vitro studies of Matsui et al. [35] has shown that in the setting of a murine model of collagen-induced arthritis, the peak of ^{18}F-FDG uptake occurs both at the stage of pannus creation and during the destruction of the bone caused by inflammation caused by proliferating fibroblasts. Another prominent role of macrophages includes the fact that their inactivated form accumulates ^{18}F-FDG merely to a small extent, while glucose demands after their hypoxia-induced activation increases significantly.

The degree of ^{18}F-FDG uptake in correlation to the disorder severity:

- Moderate uptake can be seen in the initial period of the disease progression, at which interstitial inflammatory cells recruitment, synovial cells hyperplasia, and edema can be seen.
- Uptake of ^{18}F-FDG noticeably increases as the bony destruction and pannus creation progresses.

It has been shown that the highest grade of ^{18}F-FDG accumulation not only is related to the proliferation of fibroblasts but also to the neutrophils as well. On the other hand, resting macrophages feature moderate accumulation of ^{18}F-FDG. In the setting of hypoxia, the activity of various inflammatory cells changes, while the activity of proinflammatory cytokines (such as TNF-alpha) increases. It has been observed that in these conditions there is increased ^{18}F-FDG uptake by macrophages and fibroblasts, while in the case of neutrophils, it remains at the background level. T cells accumulate ^{18}F-FDG to a small extent regardless of the microenvironment.

Summarizing, the degree of ^{18}F-FDG uptake correlates with the activity of proliferating fibroblasts as well as macrophages activated by hypoxia; hence allowing the ^{18}F-FDG study to be used in the evaluation of the disease severity.

Beckers et al. [36] assessed that the sensitivity of this technique in the setting of rheumatoid arthritis equals approx. 90%. Some works indicate that the study allows the identification of lesions in the subclinical phase of the disease as well as at the stage of its clinical remission. This fact plays a particularly important role in the treatment [37].

^{18}F-FDG PET-CT study also allows the assessment of the disease severity in other maladies, such as spondyloarthritis, polymyalgia rheumatica, Still's disease, polychondritis, IgG4-related disease, polymyositis, and dermatomyositis [38].

Some of the studies aimed to assess the usefulness of ^{11}C-choline as a marker for both the diagnosis and the severity assessment tool in rheumatic diseases. These indicated that it might be a good marker for the proliferation progress, which occur not only in the setting of tumors but also in the rheumatic conditions as well.

Roivainen et al. [39] made a comparison between ^{11}C-choline PET-CT to ^{18}F-FDG and gadolinium-enhanced MRI. The authors have shown that there is very high compliance between the pharmacokinetics of ^{18}F-FDG and ^{11}C-choline at the site of the affected joints. Regardless of the clinical symptoms of the inflammatory process, the accumulation of both markers occurred in the same joints that featured a clear contrast enhancement in the MR study. Moreover, authors state that ^{11}C-choline may be a very promising tracer for quantitative imaging of proliferative arthritis changes. However, to characterize the relationship of PET-CT results with the clinical and functional measures of inflammation, a subsequent prospective study involving a larger number of patients is necessary [39]. Among other radiopharmaceuticals, ^{11}C-(R)-PK11195 isoquinoline carboxamide is also being used for both the diagnosis of RA as well as an assessment of the disease severity. It was noted that this tracer tends to accumulate primarily in the activated macrophages and its degree of uptake highly corresponds to the severity of synovitis priorly assessed by histopathological examination. This examination turned out to be highly sensitive in both localizations of acute phase inflammation spots and the assessment of initial phase of the disease. It is considered that increased PET signal in inflamed joints occurs as a result of specific PBR-mediated uptake of ^{11}C-(R)-PK11195 caused by activated macrophages.

Van der Laken et al. [40] performed one of the first studies in the setting of the rheumatic disease. The authors concluded in their work that ^{11}C-(R)-PK11195 uptake on the PET scans was significantly higher in severely inflamed joints in comparison to those with moderate or mild signs of inflammation. Additionally, tracer uptake in contralateral, unaffected by inflammation knee joints of RA patients was significantly higher than in joints of healthy individuals from the control group (with no history of inflammatory joint disease or the presence of any subclinical disease activity). PET tracer uptake in the affected joints is highly correlated with PBR staining of sub-lining of synovial tissue, which also proves its correlation to CD68 staining of macrophages.

It is believed that this tracer may allow imaging of the ongoing pathology prior to its clinical manifestation due to the fact that macrophages infiltration into synovial joints is a common feature of asymptomatic synovitis in early RA [41, 42]. Furthermore, the application of ^{11}C-(R)-PK11195 imaging to RA may prove to be relevant to patient management since the presence and the number of macrophages in rheumatoid synovium strictly correlates with the progression of joint erosions that can be seen in the X-ray. Another use of this trace encompasses diagnosis of subclinical synovitis in patients with arthralgia. Last but not least, increased uptake of the tracer correlates with the progression of the disease.

3.1.2. Treatment control

Numbers of works indicate that ^{18}F-FDG is an excellent marker in the assessment of treatment effectiveness. The utility of ^{18}F-FDG as the marker in this assessment was suggested by Palmer et al. back in 1995 [43]. The authors in their work studied the influence of prednisolone and subsequent methotrexate treatment on findings in MRI and ^{18}F-FDG PET-CT. Results showed that as the volume of the pannus seen on MRI decreased, so did the uptake of ^{18}F-FDG—not to mention the improvement of the clinical picture (such as reduction of pain sensation,

stiffness, and edema). However, none of the studied parameters correlated with the outcome of the treatment. Authors concluded that both morphological pictures visible in MRI study and the functional test of PET study allow the assessment of the quantitative effectiveness of the applied therapy.

Similar results were presented in 2004 by Beckers et al. who have shown a direct correlation between the clinical picture of a joint with the findings of an ultrasound examination and the degree of ^{18}F-FDG uptake in PET-CT [36]. Additionally, as it turned out, the degree of ^{18}F-FDG uptake in the affected joint highly correlates to the thickness of the synovial membrane priorly assessed in the ultrasound examination. Moreover, another correlation has been found between the number of joints with increased ^{18}F-FDG uptake (with consideration of their total uptake value) and the duration of the disease together with the degree of severity. In 2004, Brenner et al. indicated in his work that despite confirmed correlation between ^{18}F-FDG uptake and the effectiveness of the treatment, PET-CT is still not recommended as a routine evaluation tool due to its high costs and limited availability [44]. This technique would be more indicated if the findings could provide parameters that are not obtainable by other tests (such as MRI, bone scan or ultrasound examination). However, authors pinpoint few of such parameters, that is, the possibility of quantitative assessment of disease severity of each affected joint and the assessment of disease progression as well as monitoring of treatment effectiveness. Authors emphasize that further studies are necessary for the better determination of PET-CT study indications.

Beckers et al. [36] presented a noteworthy work which aimed to study the response to the anti-TNF-alpha treatment [44]. Authors in their work showed a significant correlation between the degree of ^{18}F-FDG uptake, MRI findings, synovial membrane thickness, and the concentration of matrix metalloproteinase (MMP)3 and CRP levels. Similarly, Elzinga et al. [45] showed in their work that decreased uptake of ^{18}F-FDG after application of anti-TNF therapy is an important prognostic factor that indicates the effectiveness of the treatment.

3.1.3. Prognosis

Elzinga et al. [45] concluded that decreased ^{18}F-FDG uptake in the metacarpophalangeal and wrist joints 2 weeks following the infliximab (anti-TNF-alpha) therapy allowed to predict the outcome of the treatment after 14 and 22 weeks. It was all possible to achieve that because of the presence of clear correlation between the fall of the tracer uptake and the severity of the disease, which has subsequently contributed to the development of disease activity score (DAS). However, this type of correlation was not found in later observations; thus it requires further research. Perhaps another radiopharmaceutical will turn out to be more useful in prognosis of anticipated outcomes of the given treatment.

3.2. Diagnosis of concomitant diseases

A PET-CT study is a useful tool in the diagnosis of concomitant neoplastic disorders in patients with lupus, systemic sclerosis, dermatomyositis/polymyositis or Sjögren syndrome. Epidemiological data in these groups of patients showed the occurrence is noticeably higher; especially lymphoma, pharyngeal, and pancreatic cancer [46–48].

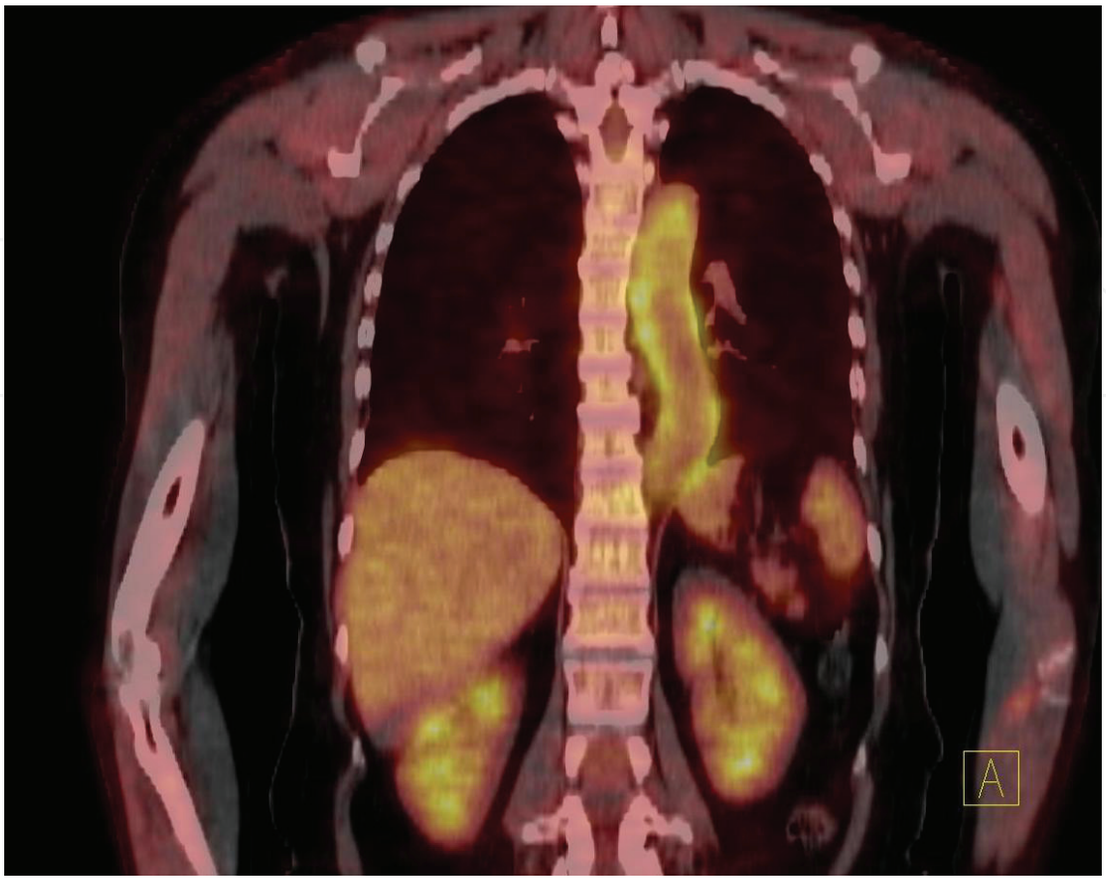

Figure 2. 18F-FDG PET-CT in patient with RA shows increased accumulation of the tracer in the wall of the aorta.

Autoimmune disease treatment involves the use of immunosuppressants, which aim to lower the immune response of the organism, simultaneously increasing the risk of infection (including a higher risk for relapse of tuberculosis) [49]. ^{18}F-FDG PET-CT study turns out to the most sensitive test for the diagnosis of infection. This examination can show abnormal focal uptake of the tracer in up to 90% of the patients suffering from autoimmune diseases; sensitivity and specificity in the diagnosis of neoplastic disorder equal 100 and 67%, respectively [50].

3.3. Fever of unknown origin

^{18}F-FDG PET-CT also showed to be promising in the diagnostic process in patients with the symptoms of FUO. In cases where other imaging studies showed to be inconclusive, ^{18}F-FDG PET-CT allows for the localization of pathological foci (either inflammation or a tumor based) in approx. 47% of the patients. Positive predictive value of this study has been assessed for 78% while negative predictive value—for 88% [51].

3.4. Vasculitis

Suspected large vascular vessels vasculitis is another indication for ^{18}F-FDG PET-CT. The term of vasculitis emphasizes the numbers of diseases, out of which Takayasu arteritis together with giant cell arteritis accounts for the most common types of vasculitis. Sensitivity and

specificity of ^{18}F-FDG PET-CT in this setting equal 90%. In a meta-analysis performed by Balink et al. [52], the authors point out that sensitivity of this modality is higher than in any other imaging method (**Figure 2**).

4. Conclusion

Indeed, we can say that recently used studies such as MRI, CT or US in the setting of rheumatology are the marriage of convenience while radionuclide studies may be considered as a marriage of love. Such complex disease processes that occur in rheumatic diseases require comprehensive data that can be obtained only by procedures from the field of nuclear medicine.

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References

[1] Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for the treatment of rheumatoid arthritis. Lancet. 2007;**370**:1861-1874

[2] Wunder A, Straub RH, Gay S, Funk J, Müller-Ladner U. Molecular imaging: Novel tools for visualizing rheumatoid arthritis. Rheumatology (Oxford). 2005;**44**:1341-1349

[3] Vogel WV, van Riel PL, Oyen WJ. FDG-PET/CT can visualise the extent of inflammation in rheumatoid arthritis of the tarsus. European Journal of Nuclear Medicine and Molecular Imaging. 2007;**34**:439

[4] Miese F, Scherer A, Ostendorf B, Heinzel A, Lanzman RS, Kropil P, Blondin D, Hautzel H, Wittsack HJ, Schneider M, Antoch G, Herzog H, Shah NJ. Hybrid 18F-FDG PET-MRI of the hand in rheumatoid arthritis: Initial results. Clinical Rheumatology. 2011;**30**:1247-1250

[5] Ladner U. Molecular imaging: Novel tools in visualizing rheumatoid arthritis. Rheumatology (Oxford). 2005;**44**:1341-1349

[6] Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: High accumulation in macrophages and granulation tissues studied by microautoradiography. Journal of Nuclear Medicine. 1992;**33**:1972-1980

[7] Kubota K, Kubota R, Yamada S. FDG accumulation in tumour tissue. Journal of Nuclear Medicine. 1993;**34**:419-421

[8] Yamada S, Kubota K, Kubota R, Ido T, Tamahashi N. High accumulation of fluorine-18-fluorodeoxyglucose in turpentine-induced inflammatory tissue. Journal of Nuclear Medicine. 1995;**36**:1301-1306

[9] Roivainen A, Parkkola R, Yli-Kerttula T, Lehikoinen P, Viljanen T, Möttönen T, Nuutila P, Minn H. Use of positron emission tomography with methyl-11C-choline and 2-18F-fluoro-2-deoxy-D-glucose in comparison with magnetic resonance imaging for the assessment of inflammatory proliferation of synovium. Arthritis and Rheumatism. 2003;**48**: 3077-3084

[10] Weiner R. The role of transferrin and other receptors in the mechanism of 67Ga localization. International Journal of Radiation Applications and Instrumentation. Part B. 1990;**17**:141-149

[11] Otsuki H, Brunetti A, Owens ES, Finn RD, Blasberg RG. Comparison of iron-59, indium111, and gallium-69 transferrin as a macromolecular tracer of vascular permeability and the transferrin receptor. Journal of Nuclear Medicine. 1989;**30**:1676-1685

[12] Pons F, Sanmarti R, Herranz R, Collado A, Piera C, Vidal-Sicart S, Muñoz-Gomez J, Setoain J. Scintigraphic evaluation of the severity of inflammation of the joints with 99Tcm-HIG in rheumatoid arthritis. Nuclear Medicine Communications. 1996;**17**:523-528

[13] Peepre K, Shah D, Solanki S, Tiwari AN, Pisal R. Clinical utility of nuclear medicine 99mTc-MDP bone scan in the early diagnosis of rheumatoid arthritis. The Turkish Journal of Pediatrics. 2008;**50**:194-195

[14] Rosenthall L. Nuclear medicine techniques in arthritis. Rheumatic Diseases Clinics of North America. 1991;**17**:585-597

[15] Moreland LW, Pratt PW, Mayes MD, Postlethwaite A, Weisman MH, Schnitzer T, Lightfoot R, Calabrese L, Zelinger DJ, Woody JN, Koopman WJ. Double-blind, placebo-controlled multicenter trial using chimeric monoclonal anti-CD4 antibody, cM-T412, in rheumatoid arthritis patients receiving concomitant methotrexate. Arthritis and Rheumatism. 1995;**38**:15811588

[16] Canat X, Carayon P, Bouaboula M, Cahard D, Shire D, Roque C, Le Fur G, Casellas P. Distribution profile and properties of peripheral type benzodiazepine receptors on human hemopoietic cells. Life Sciences. 1993;**52**:107-118

[17] Bazzichi L, Betti L, Giannaccini G, Rossi A, Lucacchini A. Peripheral-type benzodiazepine receptors in human mononuclear cells of patients affected by osteoarthritis, rheumatoid arthritis or psoriasic arthritis. Clinical Biochemistry. 2003;**36**:57-60

[18] Giusti L, Betti L, Giannaccini G, Mascia G, Bazzichi L, Lucacchini A. [3H]PK11195 binding sites in human neutrophils: Effect of fMLP stimulation and modulation in rheumatic diseases. Clinical Biochemistry. 2004;**37**:61-66

[19] Hmama Z, Kouassi E, Panaye G, Delassan S, Normier G, Binz H, Revillard JP. Binding of a bacterial acylpoly(1,3)galactoside to human blood leucocytes. Scandinavian Journal of Immunology. 1992;**36**:11-20

[20] Hmama Z, Normier G, Kouassi E, Flacher M, Binz H, Revillard JP. Binding of a membrane proteoglycan from *Klebsiella pneumoniae* and its derivatives to human leukocytes. Immunobiology. 1992;**186**:183-198

[21] Diot P, Diot E, Lemarie E, Guilmot JL, Baulieu JL, Asquier E, Valat C, Delarue A, Le Pape A. Imaging of pulmonary disease in scleroderma with J001X scintigraphy. Thorax. 1994;**49**:504508

[22] Chaudhuri MK, Konopinska D, Bump NJ, Najjar VA. The similarity between tuftsin (Thr-Lys-Pro-Arg) receptors and tuftsin antibody: A case of induced molecular mimicry. Annals of the New York Academy of Sciences. 1983;**419**:135-142

[23] Caveliers V, Goodbody AE, Tran LL, Peers SH, Thornback JR, Bossuyt A. Evaluation of 99mTc-RP128 as a potential inflammation imaging agent: Human dosimetry and first clinical results. Journal of Nuclear Medicine. 2001;**42**:154-161

[24] Koch AE, Burrows JC, Haines GK, Carlos TM, Harlan JM, Leibovich SJ. Immunolocalization of endothelial and leukocyte adhesion molecules in human rheumatoid and osteoarthritic synovial tissues. Laboratory Investigation. 1991;**64**:313-320

[25] Chapman PT, Jamar F, Keelan ET, Peters AM, Haskard DO. Use of a radiolabeled monoclonal antibody against E-selectin for imaging of endothelial activation in rheumatoid arthritis. Arthritis and Rheumatism. 1996;**39**:1371-1375

[26] Takeba Y, Suzuki N, Takeno M, Asai T, Tsuboi S, Hoshino T, Sakane T. Modulation of synovial cell function by somatostatin in patients with rheumatoid arthritis. Arthritis and Rheumatism. 1997;**40**:2128-2138

[27] Vanhagen PM, Markusse HM, Lamberts SW, Kwekkeboom DJ, Reubi JC, Krenning EP. Somatostatin receptor imaging. The presence of somatostatin receptors in rheumatoid arthritis. Arthritis and Rheumatism. 1994;**37**:1521-1527

[28] Paran D, Kidron D, Mayo A, Ziv O, Chowers Y, Caspi D, Yaron M, Paran H. Somatostatin analogue treatment attenuates histological findings of inflammation and increases mRNA expression of interleukin-1 beta in the articular tissues of rats with ongoing adjuvant-induced arthritis. Rheumatology International. 2005;**25**:350-356

[29] Marcus C, Thakur ML, Huynh TV, Louie JS, Leibling M, Minami C, Diggles L. Imaging rheumatic joint diseases with anti-T lymphocyte antibody OKT-3. Nuclear Medicine Communications. 1994;**15**:824-830

[30] Scoazec JY, Feldmann G. Both macrophages and endothelial cells of the human hepatic sinusoid express the CD4 molecule, a receptor for the human immunodeficiency virus. Hepatology. 1990;**12**:505-510

[31] Stashenko P, Nadler LM, Hardy R, Schlossman SF. Characterization of a human B lymphocyte-specific antigen. Journal of Immunology. 1980;**125**:1678-1685

[32] Malviya G, Laganà B, Milanetti F, Del Mastro C, Familiari D, Dierckx RA, Scopinaro F, D'Amelio R, Signore A. Use of 99m-technetium labelled Rituximab for imaging of patients with chronic inflammatory diseases. European Journal of Nuclear Medicine and Molecular Imaging. 2008;**35**(Suppl 2):S142-S143

[33] Tetta C, Camussi G, Modena V, Di Vittorio C, Baglioni C. Tumour necrosis factor in serum and synovial fluid of patients with active and severe rheumatoid arthritis. Annals of the Rheumatic Diseases. 1990;**49**:665-667

[34] Knight DM, Trinh H, Le J, Siegel S, Shealy D, McDonough M, Scallon B, Moore MA, Vilcek J, Daddona P, Ghrayeb J. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. Molecular Immunology. 1993;**30**:1443-1453

[35] Matsui T, Nakata N, Nagai S, Nakatani A, Takahashi M, Momose T, Ohtomo K, Koyasu S. Inflammatory cytokines and hypoxia contribute to 18F-FDG uptake by cells involved in pannus formation in rheumatoid arthritis. Journal of Nuclear Medicine. 2009;**50**:920-926

[36] Beckers C, Ribbens C, André B, Marcelis S, Kaye O, Mathy L, Kaiser MJ, Hustinx R, Foidart J, Malaise MG. Assessment of disease activity in rheumatoid arthritis with (18) F-FDG PET. Journal of Nuclear Medicine. 2004;**45**:956-964

[37] Brown AK, Conaghan PG, Karim Z, Quinn MA, Ikeda K, Peterfy CG, Hensor E, Wakefield RJ, O'Connor PJ, Emery P. An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis. Arthritis and Rheumatism. 2008;**58**:2958-2967

[38] Yamashita H, Kubota K, Mimori A. Clinical value of whole-body PET/CT in patients with active rheumatic diseases. Arthritis Research & Therapy. 2014;**16**:423

[39] Roivainen A, Yli-Kerttula T. Whole-body distribution of 11C-choline and uptake in knee synovitis. European Journal of Nuclear Medicine and Molecular Imaging. 2006; **33**:1372-1373

[40] van der Laken CJ, Elzinga EH, Kropholler MA, Molthoff CF, van der Heijden JW, Maruyama K, Boellaard R, Dijkmans BA, Lammertsma AA, Voskuyl AE. Noninvasive imaging of macrophages in rheumatoid synovitis using 11C-(R)PK11195 and positron emission tomography. Arthritis and Rheumatism. 2008;**58**:3350-3355

[41] Tak PP, Smeets TJ, Daha MR, Kluin PM, Meijers KA, Brand R, Meinders AE, Breedveld FC. Analysis of the synovial cell infiltrates in early rheumatoid synovial tissue in relation to local disease activity. Arthritis and Rheumatism. 1997;**40**:217-225

[42] Kraan MC, Versendaal H, Jonker M, Bresnihan B, Post WJ, t Hart BA, Breedveld FC, Tak PP. Asymptomatic synovitis precedes clinically manifest arthritis. Arthritis and Rheumatism. 1998;**41**:1481-1488

[43] Palmer WE, Rosenthal DI, Schoenberg OI, Fischman AJ, Simon LS, Rubin R, Polisson RP. Quantification of inflammation in the wrist with gadolinium-enhanced MR imaging and PET with 2-[F-18]-fluoro-2-deoxy-ɒ-glucose. Radiology. 1995;**196**:647-655

[44] Brenner W. 18F-FDG PET in rheumatoid arthritis: There still is a long way to go. Journal of Nuclear Medicine. 2004;**45**:927-929

[45] Elzinga EH, van der Laken CJ, Comans EF, Boellaard R, Hoekstra OS, Dijkmans BA, Lammertsma AA, Voskuyl AE. 18F-FDG PET as a tool to predict the clinical outcome of infliximab treatment of rheumatoid arthritis: An explorative study. Journal of Nuclear Medicine. 2011;**52**:77-80

[46] Kiss E, Kovacs L, Szodoray P. Malignancies in systemic lupus erythematosus. Autoimmunity Reviews. 2010;**9**:195-199

[47] O'Byrne KJ, Dalgleish AG. Chronic immune activation and inflammation as the cause of malignancy. British Journal of Cancer. 2001;**85**:473-483

[48] Sela O, Shoenfeld Y. Cancer in autoimmune diseases. Seminars in Arthritis and Rheumatism. 1988;**18**:77-87

[49] Carter PH, Zhao Q. Clinically validated approaches to the treatment of autoimmune diseases. Expert Opinion on Investigational Drugs. 2010;**19**:195-213

[50] Oh JR, Song HC, Kang SR. The clinical usefulness of ^{18}F-FDG PET/CT in patients with systemic autoimmune disease. Nuclear Medicine and Molecular Imaging. 2011;**45**:177-184

[51] Ergül N, Çermik TF. FDG-PET or PET/CT in fever of unknown origin: The diagnostic role of underlying primary disease. International Journal of Molecular Imaging. 2011:318051

[52] Balink H, Bennink RJ, van Eck-Smit BLF, Verberne HJ. The role of ^{18}F-FDG PET/CT in large-vessel vasculitis: Appropriateness of current classification criteria? BioMed Research International. 2014;**2014**:687608

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