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The Role 18F-FDG and 18F-NaF PET/CT in Assessment of Temporomandibular Joint Metabolic Activity in Rheumatoid Arthritis

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Abstract

Objective: The aim of this study was to evaluate the efficacy of ^{18}F-fluorodeoxyglucose (FDG) and ^{18}F-sodium fluoride (NaF)PET/CT for assessing the status of the temporomandibular joint (TMJ) of rheumatoid arthritis (RA) patients compared with healthy (non-RA) individuals.

Method:

Eighteen patients diagnosed with RA (mean age 55±12.1years: 4 females and 14 males) were included in the test group. Eighteen age-, sex- and race-matched healthy control subjects were selected from the CAMONA clinical trial. PET/CT images were acquired 180-minute post-intravenous administration of FDG and NaF (2.2 MBq/kg). For FDG analysis, regions of interest (ROIs) were manually assigned per anatomical boundaries using a closed polygon tool. The first ROI of the mask was assigned on the trans-axial CT slice with the first evidence of the glenoid fossa down to two to three slices inferiorly. The ROI followed the anatomy of the TMJ. For NaF, a three-dimensional ball tool of 1.5 cm was used to assign ROIs with the head of the mandibular condyle located at the center including the osseous compartment of the joint extending inferiorly to the neck of the condyle. Averaged SUVmean was used to semi-quantify FDG and NaF uptake in each joint. Then average SUVmean of the right and the left TMJ was determined. For normalization, a Target to Background Ratio (TBR) was used. For statistical analysis, the student's t-test and regression analysis were used. The severity of RA was assessed by determining the Disease Activity Score of serum C reactive protein (DAS-28 CRP) and erythrocyte sedimentation rate (DAS-28 ESR) for each subject.

Results:

FDG TBRmean for the test group was 1.21±0.33 compared to 0.91±0.2 in controls, (p=0.003.) No correlation was found between FDG uptake and DAS28-CRP or DAS28-ESR. The NaF average SUVmean was significantly higher in RA patients than healthy control subjects (2.4±0.8 versus 1.9±0.4, p=0.02). Similarly, the TMJ TBRmean was also higher in RA patients relative to healthy controls (4.2±2.1 versus 2.7±0.9, p=0.01) A significant positive correlation was found between TBRmean and DAS28-CRP (r=0.49, p=0.03), while there was positive trend in the correlation between TBRmean with DAS28-ESR that was not statistically significance (r=0.37, p=0.12).

Conclusion:

RA patients appear to have significantly higher metabolic activity in the TMJ than age-, sex- and race-matched healthy control subjects. Our results illustrate the potential value of using FDG and NaF-PET/CT for evaluation of TMJ disorders and suggest that this modality may useful for monitoring the effects of treatment regimens.

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Introduction:

Temporomandibular Joint:

The temporomandibular joint (TMJ) is a dynamic synovial joint that is formed by the articulation of the articular eminence and fossa of the temporal bone superiorly with the condylar head of the mandible inferiorly. In humans, the embryonic development of the joint starts at week 8 of gestation as evidenced by the appearance of bony and cartilaginous structures. The various components of the joint are derived from the first pharyngeal arch that contains a mesodermal component that yields the vasculature and musculature and neural crest mesenchyme that gives rise to the bony and cartilaginous portions. Three stages have been identified in normal TMJ development. The first (blastemic stage) is defined by the appearance of two blastemas. The glenoid fossa blastema, derived from the otic capsule, undergoes intramembranous bone ossification. The second blastema eventually gives rise to the condyle via endochondral bone formation. The second stage of TMJ development (cavitation stage) begins during weeks 9 to 11 of gestation and is characterized by the presence of a mesenchymal layer that forms between the two blastemas that develops into the articular disc. The fibrous disc separates the space between the temporal bone and condyle into an upper and a lower compartment. The final stage (maturation stage) extends from the 17th

week of gestation until birth culminating in the formation of the functional bony and cartilaginous elements of the joint.[1,2,3,4]

The temporomandibular joint is considered a ginglymoarthrodial joint characterized by the presence of a synovial cavity and articular disc. Unlike other joints, the articulating surfaces of the TMJ are covered by fibrous connective tissue containing cartilaginous cells.[5,6] Anatomically, the fully developed TMJ consists of a concavity in the temporal bone referred to as the glenoid fossa that accommodates the condylar head of the mandible. The postglenoid process represents the posterior aspect of the joint and forms the anterior part of the external auditory meatus. The anterior aspect of the TMJ corresponds to the articular eminence of the zygomatic bone. Inferiorly, the articular surface of the joint is the superior border of the condylar head of the mandible.

In the middle of the joint a biconcave, non-vascular fibrous disc is located between the glenoid fossa and the condylar head with the thinnest portion in the middle. The disc is firmly attached to the medial and lateral parts of the condyle thereby facilitating the simultaneous movement of the two structures with every jaw movement. The upper part of the disc is attached to the posterior part of the glenoid fossa preventing it from slipping during jaw movement while the lower component helps avoid excessive rotation of disk relative to the condyle.

Numerous ligaments and muscles associated with the TMJ play major roles relative to jaw movements, force management and perception. The sphenomandibular, stylomandibular, pterygomandibular and collateral ligaments are among the ligaments involved in jaw movement and maintaining the proximity of the condyle to the temporal bone during mouth opening. The temporalis, masseter and medial pterygoid muscles are responsible for closing the jaw while opening involves the lateral pterygoid, geniohyoid, mylohyoid and digastric muscles. The arterial blood supply to the TMJ is mainly derived from the superficial temporal, anterior tympani, deep temporal, auricular posterior, transverse facial, middle meningeal and maxillary arteries. Venous drainage occurs through the pterygoid plexus that channels into the internal maxillary, sphenopalatine, medial meningeal, deep temporal, masseterine and inferior alveolar veins. The anteriolateral portion of the capsule of theTMJ is innervated by the masseteric nerve while the lateral aspect of the joint is innervated by auriculotemporal nerve. The masseteric and auriculotemporal nerves originate from the second and third branches of the trigeminal nerve, respectively.

The TMJ plays an important role a in a number of processes associated with the oral cavity. Amongst these are mouth opening/closing, chewing, speaking and

swallowing. During mouth opening the condyle goes through a combination of rotational and translational movements.

Multiple pathological conditions can affect the TMJ and dramatically impact a patient's life style. Disc displacement is a common joint derangement involving excessive movement of the disc anteriorly, medially or laterally but rarely posteriorly. Typically, the disc returns to its original position when the mouth is opened (reduction) while in a small percentage of subjects the displaced disc remains anterior to the condylar head (displacement without reduction). Severe forms of displacement can result in perforation of the disc that can be accompanied by osseous changes such as joint flattening and formation of osteophytes on the condyle and/or the articular surface of the temporal bone. Clinical manifestations of disc displacement include pain, clicking sounds and/or tenderness upon palpation of the joint and associated muscles. Treatment of a displaced disc ranges from conservative treatment (reassurance, occlusal adjustment, bite splints, administration of non-steroidal anti-inflammatory drugs (NSAID) and physical therapy) to more invasive types of interventions (arthroscopy, open surgery, condylectomy with or without bone grafting and alloplastic join replacement) depending upon the severity of a patient's symptoms.

TMJ pathology is not limited to displacement of the articular disc. Conditions that can affect the TMJ resulting in various degrees of dysfunction are osteoarthritis (OA), rheumatoid arthritis (RA), psoriatic arthopathy, ankylosing spondylitis, fibromyalgia as well as tumor and tumor-like lesions, amongst others. Osteoarthritis is associated with breakdown of the cartilage and bone within a joint secondary to an inflammatory process.[8] The diagnosis of OA is based on both clinical and radiographic findings. Clinically, patients complain of pain, tenderness upon palpitation of the TMJ and crepitus. Typical radiographic findings include, degenerative erosion of the head of the condyle and the glenoid fossa, condylar flattening and/or osteophyte formation.[9] The clinical symptoms can be managed through physical therapy, asking the patient to avoid heavy forces on the joint by eating soft food and avoiding gum chewing, the use of occlusal appliances and administration of anti-inflammatory medications. [10]

Rheumatoid Arthritis:

Rheumatoid Arthritis (RA) is a chronic systemic autoimmune disease that

primarily affects joints including the TMJ. The condition is mediated by an inflammatory reaction within synovial tissue leading to degeneration of cartilage and bone. The exact mechanism(s) underlying the pathogenesis of RA remain under investigation. Clinical signs and symptoms of RA are often preceded by the appearance of rheumatoid factor (RF; autoantibodies against the Fc region of IgG) and anti–citrullinated protein antibody (ACPA)[11,12].

A local increase in the concentration of the proinflammatory cytokines Interleukin-1 (IL-1), Intereukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-α derived from antigen-activated CD4+ T cell has been reported in RA patients. These cytokines, especially TNF-*a* and IL-1, are believed to have a key role in the pathogenies of RA. Both cytokines have been detected in the serum and synovial fluid of subjects with RA. Together, they can induce mesenchymal cells to release tissue destructive matrix metalloproteinases that participate in degenerative alterations within the joint. Activated CD4+ cells stimulate B cells to immunoglobulin-secreting plasma cells some which produce RF.[13] Additionally, activated CD4+ cell expresss receptor activator of nuclear factor kappa-beta ligand (RANK) that interacts with it's cognate receptor RANK found on the surface of immature and mature osteoclasts (OC). Interaction of RANKL with RANK stimulates osteoclastogenesis and activation of OCs that mediate resorption of the osseous component of the joint.[14] Macrophages, lymphocytes and fibroblasts are

also stimulated which can promote angiogenesis and consequently an increase in the vascularity of the synovium.

The overall prevalence of in US population RA ranges from 0.5 - 1% with women being affected two to three times more frequently than men. [11.16] Epidemiologic studies have demonstrated variability in the prevalence of the disease between ethnic groups. For example, the estimated prevelance rate in Pima Indians was (5%), Chippewa Indians (6.8%), rural Africa (0.1%) and China/Japan (0.2%-0.3%). These differences suggest that both genetic and environmental factors contribute modulate the disease process.[17]

Diagnosis of RA is based on clinical, hematological and radiographic criteria. Clinical findings that are diagnostic for the diseases include joints pain, edema of three or more joints, morning joint stiffness and metacarpal or metatarsal joint involvement through positive squeeze test. The wrists, proximal interphalangeal, metacarpophalangeal, and metatarsophalangeal joints are commonly affected by RA while the distal interphalangeal and spinal joints are usually spared. [10]

Laboratory tests for RA should include a complete blood cell count with a differential, evaluation of serum RF/ACPA concentrations and determination of either the erythrocyte sedimentation rate (ESR) or serum C-reactive protein (CRP) level. Elevated serum RF and ACPA are parts of the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) diagnostic criteria for RA.[11] An increase in RF titer has been reported to be correlated with the risk of developing RA and increasing disease severity. A value of >100 IU/ml has 26 times more risk of having the disease.[12] Anti–citrullinated protein antibody can typically be detected in serum before the onset of clinical symptoms. Patients who are ACPA-positive tend to have more bone degeneration and severe progression compared to patients who tested negative. [18]

Increases in ESR and serum CRP are general biomarkers that have been used by rheumatologists to develop indices to quantify disease activity in the joints. One of the most widely index is the Disease Activity Score of 28 joints that can be calculated in the context of the ESR (DAS28-ESR) or serum CRP level (DAS28-CRP) and used to quantify disease activity as well as assess the response to treatment. [8,20] Swelling and tenderness in a standard set of joints is determined along with a global health assessment scored on a scale of 0 to 100. Formulas that integrates these values along with the ESR or serum CRP level are then used to

calculate the actual DAS. The cutoff measures of disease activity for both CRP and ESR recommended by ACR: High disease activity >5.1, low disease activity <3.2, remission <2.6.

The goal in management of RA is disease remission or low disease activity taking into consideration the cost of treatment. Pharmacological approaches comprising disease-modifying antirheumatic drugs (DMARDs), NSAIDs and glucocorticoids have been used to successfully treat RA. The drugs are often used in conjunction with to manage the disease. In the European League Against Rheumatism (EULAR) task force multiple synthetic, biologic and targeted synthetic medication recommended for the management of RA. Some of the pharmacological drugs reported in this task force includes DMARDs (methotrexate) and glucocorticoids.[23]

Temporomandibular joint and rheumatoid arthritis:

Thee TMJ is one of the body joints that can be affected by RA. In the ACR and EULAR meeting on classification of RA, the TMJ was identified as one of the joints that need to be considered in the classification system.[11] When the TMJ is involved in RA it can result in patient discomfort, crepitation, stiffness and limitation in mouth opening [5]. Garrot in 1859 was the first to describe TMJ

involvement in rheumatic disease [24]. The prevalence of TMJ involvement in cohorts of RA patients is variable and has been reported to range from 10-58 % of subjects.[15,19] TMJ involvement can be examined clinically or radiographically. One of the most common structural imaging modalities used to evaluate the TMJ is the panoramic radiograph that provides a 2-dimensional view of the osseous structures within the joint. Currently, computed tomography (CT) and cone-beam computed tomography (CBCT) are considered the gold standards for imaging the TMJ. These methodologies provide high resolution and accurate 3-dimenional images that can demonstrate osseous changes within the joint. When deemed necessary, magnetic resonance imaging (MRI) can be used to evaluate soft tissue abnormalities in the joint. [25]

Imaging of temporomandibular joint:

In 1895, Röntgen discovered the so-called "X-ray" and described a method for visualizing internal anatomical structures. His work provided the foundation for modern radiographic imaging. Since Röntgen's scientific breakthrough, numerous technological advances have been made taking the concept of x-ray examination of patients from a curiosity to a routine and vital component of dentistry and

medicine. Recent major innovations include CT, CBCT, MRI and a variety of molecular imaging techniques. Conventional radiographs yield two-dimesional (2D) images that can delineate anatomical structures and to some extent, demonstrate anatomical anomalies or pathological changes. A major step forward occurred in 1973 with the introduction of CT, a method that provides three-dimentional (3D) images that can be used to evaluate anatomical structures in their transvers, coronal and sagittal dimensions. Although extremely useful for assessing hard tissues a drawback to CT is that it is not ideally suited for appraising soft tissues. In response to this, MRI was developed and is now considered the method of choice for soft tissue imaging. When considering the pathogenesis of many diseases, it is critical to appreciate that cellular and molecular alterations occur in a tissue prior to the onset of discernible structural changes. In the context of treatment outcomes, it is undoubtedly more desirable to detect the earliest stages of a disease process as opposed to the subsequent gross anatomic changes. Thus, a significant limitation of CT and MRI is their relative inability to demonstrate subclinical stages of a disease process. Along a similar line of thought, efficacious treatment of many conditions starts at the cellular and molecular levels with subsequent favorable structural changes taking protracted periods of time to manifest themselves. If CT and/or MRI are used to gauge a patient's response to a particular form of therapy it is feasible that the resultant images mislead a clinician

to conclude that the therapy is not working and should either be increased in "intensity" or even discontinued when in fact, the treatment is having a desirable effect . Both situations can have highly undesirable outcomes for the patient. In recognition of this, research has led to the advent of functional imaging protocols that have the capacity to detect subclinical cellular and molecular changes providing a diagnostic advantage over CT and MRI, Furthermore, it has been proposed that functional imaging can be used to effectively monitor physiological responses to therapeutic interventions.

Over the last two decades, a number of functional imaging techniques have been introduced into medical radiology including optical imaging, magnetic resonace spectroscopy, functional magnetic resonance imaging (fMR imaging) and positron emission tomography (PET). Positron emission tomography involves the use of radioactive isotopes such as ^{99m}Ti, ^{123}I ^{11}C, ^{13}N, ^{15}O, ^{18}F, ^{31}Ga , ^{93}Zr or ^{82}Rb that are injected into the patient. [27,28] These isotopes are characterized by the ability to bind to different biological substrate without altering their activity, also theses Isotopes have relatively short half-lives and can be excreted from the body after variable period of time. The atoms of the isotopes are in an unstable state and exhibit a high level of energy. Their nuclei are densely packed with protons and neutrons that undergo decay to arrive at a less energetic and more stable state. The

rate of decay is usually determined by the half-life of isotopes, i.e., the time it takes for half of the original nuclei to decay. As the decay proceeds positrons ($\boldsymbol{\beta}$+) are emitted that annhilate after contact with an electron releasing two high energy two photons (γ radiation) in two different directions. A cylindrical scintillation detector is used to to detect and measure the amount of γ radiation. Via sonogram the information is processed (coincidence process) for data correction and image reconstruction.

On a cellular level, cells with high metabolic activity exhibit increases glucose uptake. Most of the common radionuclides can be easily incorporate into biological substrates such as glucose or H_2O. The labeled substrates have short have lives and do not interfere with normal cellular processes when taken up by cells. ^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) exhibits a high affinity for malignant and inflammatory cells due to their increased rate of glucose metabolism relative to other cells. For these reasons, it was used as the tracer in the first total human body PET scan done in 1976 by a group of investigators at University of Pennsylvania. They were able to detect uptake of the tracer in the brain, heart and kidneys. The effectiveness of ^{18}F-FDG has been in validated in numerous subsequent investigations. One of the most important characteristics of ^{18}F-FDG is the similarity to glucose in structure and function such that it circulates, migrates

and is transported into cells in the same manner as glucose via GLUT transport protein. Once inside cells, ^{18}F-FDG is metabolized through the identical pathways used for glucose. As a result, ^{18}F-FDG is incorporated into metabolically active cells including inflammatory cells, cancer cells and proliferating cells in the kidneys, gland tissue or brain. Therefore, ^{18}F-FDG -PET can detect localized inflammatory changes at the molecular level. The tracer is now commonly used in PET to evaluate soft tissues but is not considered ideal for detecting metabolic changes in hard tissue structures.

Historically, ^{18}F-NaF was utilized as a standard radiotracer for bone scans before it was replaced by technetium polyphosphonates that have more desirable physical properties.[41] Due to its ability to interact with bone, it was shown that could be used as a tracer in PET ^{18}F-NaF to evaluate bone disease. The integration of ^{18}F-NaF into hard tissues is highly dependent on blood flow to the bony structure where it can easily cross cellular membranes and be rapidly cleared from plasma.[42] After absorption into ninhydroxyapatite, ^{18}F rapidly replaces a hydroxyl group on the surface of the hydroxyapatite matrix ($Ca_{10}(PO_4)_6OH_2$) of bone to form fluoroapatite ($Ca_{10}(PO_4)_6F_2$).[43] This extent of ^{18}F incorporation is determined by the amount of bone affected by a malignant tumor or osteoblastic/osteoclastic activity.[44] Moreover, the uptake of ^{18}F-NaF into bone structure has been reported to

be twice that achieved with Tc-99m and is also cleared from blood more rapidly than Tc-99m.[31] Due to these characteristics ^{18}F-NaF is considered a reliable radiotracer in regards to detecting bone metastasis, bone cancers and metabolic bony lesions with inflammatory etiologies.

Several imaging strategies have been used to evaluate the structures of the TMJ. One common approach is the panoramic radiograph due to the fact that most dental offices are equipped with Panorex units and the relatively low cost of the study. A major limitation of this type of radiograph is it provides only 2D views of the condyle, ramus and body of the mandible. It can be used to identify gross osseous structural changes but does not provide information regarding the soft tissue component of the joint. In a study using panoramic images to evaluate 97 patients diagnosed with juvenile idiopathic arthritis, 55% of the subjects were found to have radiographic evidence of hard tissue alterations of the TMJ. In individuals with clinical symptoms of joint pain and dysfunction, panoramic radiographic analysis showed good specificity and low sensitivity.[32] Cone-beam computed tomography provides and medical-grade CT provide 3D alternatives to panoramic radiography that enable clinicians to more accurately diagnose TMJ pathology and treat them appropriately. CBCT scans as an alternative for the 2-D imaging. Although CBCT images the images are of relatively high quality, the scanners are more expensive than a typical Panorex unit and expose patients to more radiation.

Additionally, the scatter of radiation caused by the presence of metal significantly affects CBCT images. Thus, in individuals with numerous metallic dental restorations, implants or orthodontic appliances, artifacts are generated in CBCT images that can influence their diagnostic accuracy and limit a clinician's ability to evaluate minor changes within the joint.

When an osseous lesion cannot be accurately defined by the previously mentioned modalities, MRI represents the next alternative. It has the ability to detect lesions within the soft tissues of the TMJ and can therefore provide additional critical information beyond acquired from panoramic radiographs or CBCT. It has been shown that MRI can be utilized for assessment of bisphosphonate-related osteonecrosis, condylar bone marrow edema and ossification within soft tissue compartment of the joints.[33,34,35]

As suggested earlier in this review, functional imaging techniques have the potential to identify early stages of a disease process that precede the overt structural changes demonstrated by panoramic radiography, CBCT or MRI. Two radionucleotide-based methodologies are single positron emission computed tomography (SPECT) and positron emission tomography (PET). Both methods involve injecting the patient with radioactively labeled substrates after which the

subject undergoes a CT scan. The resultant 3D images reveal in a quantifiable manner the areas where metabolically active cells associated with a disease process took up the tracer. In a study evaluating patients complaining of idiopathic jaw pain using SPECT scanning with Tc-99m-methyl diphosphonate (MDP) as the tracer, the images from 20 patients were compared to those from age-matched control. The scans of 15 patients showed uptake of the tracer in the area of pain while 12 control subjects showed increased uptake in their healed TMJ that had been successfully treated. The authors concluded that the sensitivity and specificity of SPECT bone scans in detecting painful sites were low. These findings suggest that SPECT bone scanning with Tc-99m MDP is not indicated as a routine imaging procedure for the detection of jaw pathoses.[36] Additional limitations of SPECT scan are the high number of false positive results, suboptimal spatial resolution of images and relative inaccuracy of the quantification of tracer uptake.

Positron emission tomography has become a widely used molecular imaging modality for detecting maxillofacial cancerous lesions and monitoring the effect of treatment. It is considered a powerful diagnostic tool capable of detecting early stages of a pathologic process and disease resolution. Ng and colleagues conducted a study evaluating different imaging techniques for their ability to identify oral squamous cell carcinoma and found that ^{18}F-FDG-PET had an accuracy of 98.4%

when compared to 87.1% and 99.2% for CT and MRI, respectively. The sensitivity of ^{18}F-F-FDG for the identification of nodal metastases on a level-by-level basis was 22.1% higher than that of CT/MRI (74.7% vs. 52.6%, $P < 0.001$) whereas the specificity of ^{18}F-FDG-PET was 1.5% lower than that of CT/MRI (93.0% vs. 94.5%, $P = 0.345$). The authors concluded that ^{18}F-FDG-PET is a superior and more sensitive approach for detecting oral SCC. [37] In a systematic review and meta-analysis assessing a variety of diagnostic imaging techniques for excluding or confirming a diagnosis of chronic osteomyelitis, FDG-PET scans were shown to have the highest diagnostic accuracy 96% compared to bone scintigraphy and MRI (82% and 84%, respectively).[38] In addition, Lee et al recently demonstrated that ^{18}F-PET/CT is superior to conventional Tc 99m MDP bone scanning when used to diagnose TMD associated with osteoarthritis.[39] finally, PET/CT scans can quantify tracer uptake within metabolically active tissues and thus possibly yield an early diagnosis prior to the onset of osseous degeneration. Collectively, these properties suggest that PET/CT has great potential as a tool for evaluating hard and soft tissue lesions of the TMJ. Of course, there are limitations associated with PET. The scans do not readily detect smaller lesions (<1 cm in size) nor lesions exhibiting low metabolic activity. Additional drawbacks are the cost of scanners and reagents as well as the dose of radiation.

Appreciating that a major component of the pathophysiology of RA is the induction of an inflammatory reaction that mediates the destruction of both soft and hard tissue within joints we speculate that molecular imaging can be used to detect early stages of the disease. It is commonly accepted that the definitive diagnosis of TMJ disease cannot be based on clinical examination alone.[17,18] Thus, future research should be conducted to critically determine whether molecular imagining techniques such as PET can be used to detect inflammatory changes in the joint prior to the onset of structural breakdown.

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Manuscript

Introduction:

Rheumatoid Arthritis (RA) is a systemic chronic inflammatory disease that affect body joints by inflammation of synovial tissue and destruction of bone and

cartilage. It is considered as an autoimmune disease that has various serological finding that may appears before clinical manifestations [1,2]. It manifested clinically by swelling, tenderness, increased inflammatory activity, degenerative changes and disability [3,4]. In clinical examination, rheumatologists have been widely using disease activity score of 28 joints using erythrocyte sedimentation rate (DAS28-ESR) and C-reactive protein(DAS28-CRP) to quantify the disease activity as well as assessment to treatment responses[5,6].

Temporomandibular joint (TMJ) is a dynamic joint that is formed by the articulation of articular eminence and articular fossa of temporal bone superiorly and the condylar head of the mandible inferiorly. In addition, TMJ is considered a special joint due to the presence of articular disk between the articulating surfaces separating it to upper and lower compartment. Unlike other body joint, TMJ articulating surfaces is covered by fibrous connective tissue with presence of cartilaginous cell [8,9]. TMJ plays an important part in daily activity such as chewing, speaking and swallowing. When TMJ is involved in RA it can result in patient discomfort, crepitation, stiffness and limitation in mouth opening [4]. Garrot in 1859 was the first to describe involvement of TMJ in rheumatic disease [13]. Affection of TMJ in RA has been reported with a prevalence ranging from 10- 58 %[8.9]. It can be examined clinically and radiographically, structural imaging modalities are used to evaluate TMJ involvement including Panoramic X-ray which provides a 2-

dimensional information limited to the osseous structure of the joint. Also, computed tomography (CT) and con-beam computed tomography (CBCT) considered as the gold standard in terms of TMJ imaging. As it shows 3-dimnsional image of osseous changes within the joint with good accuracy and resolution. Moreover, magnetic resonance imaging (MRI) can be used to delignate soft tissue abnormities in the joint[14].

Molecular imagining approaches such as positron emission tomography (PET) assessing TMJ in RA patients hasn't been widely investigated. Such technique offer an alternative that might demonstrate inflammatory changes in the joint prior to the onset of structural breakdown. The ability of ^{18}F-sodium fluoride (NaF) and ^{18}F-fluorodeoxyglucose (FDG) to assess metabolic activity in osseous structure and soft tissue of the joint respectively, has been reported in the other body joints [17,26]. The aim of this study was to investigate the role of NaF and FDG- PET/CT imaging of the TMJ taken in cohorts of RA and control (non-rheumatoid arthritis) subjects.

Material and methods:

Scans of RA patients were obtained from the Corporal Michael J. Crescenz Veterans Affairs Medical Center in Philadelphia. While, control subjects scans

were part of the “Cardiovascular Molecular Calcification Assessed by 18F-NaF PET/CT (CAMONA) study”. The CAMONA study was approved by the Danish National Committee on Health Research Ethics and conducted following the principles of the Declaration of Helsinki. All study participants provided written informed consent. Eighteen patients diagnosed with RA (mean age 55±12.1years: 4 females and 14 males) were included in the test group. Control group includes 18 subjects age and gender- matched selected from the CAMONA clinical trial (mean age 56±12 years). Clinical data including Disease Activity Score of C-reactive protein (DAS28-CPR) and erythrocyte sedimentation rate (DAS28-ESR) were calculated for RA patients.

Included test group diagnosed with RA according to the 2010 American College of Rheumatology classification criteria for RA. Exclusion criteria included: patient with evidence of active malignancy, metabolic bone disease, or recent computed tomography (CT) imaging within 6 months (due to concerns about radiation exposure). Inclusion criteria in control group were: patients free of oncological disease, autoimmune disease, immunodeficiency syndromes, alcohol abuse, illicit drug use, symptoms suggesting cardiovascular disease, or any prescription medication patients evaluated for chest pain syndromes were recruited from those referred for coronary CT angiography. Also, subjects with a 10-year risk of fatal

cardiovascular disease included. Pregnant women were not included in the study.[22,23]

Imaging protocol: The imaging protocol performed on the PET/CT system. After 180 minutes of intravenous injection of (4.0 MBq/kg) of F-FDG per kilogram of body weigh ^{18}F-FDG PET/CT scan obtained. Within an average of two weeks ^{18}F-NaF were taken. PET/CT images were acquired 90 minutes post intravenous administration of NaF (2.2 MBq/kg). For attenuation correction and anatomical variation low–dose CT imaging (140 kV, 30 – 110 mA, noise index 25, 0.8 s per rotation, slice thickness 3.75 mm) was taken.

Image analysis: To analyze soft tissue within the joint, Regions of interest (ROIs) of FDG scans were manually assigned per predetermined anatomical criteria. The first ROI of the mask was assigned on the trans-axial CT slice with the first evidence of the glenoid fossa. The ROI followed the anatomy of TMJ where it bounded anteriorly by articular eminence of temporal bone, posteriorly by tympanic portion of temporal bone, medially by sphenoid bone and laterally by the root of zygomatic process of temporal bone (Figure 1). In addition, ROI included the head of condyle where it forms the inferior border articulating surface of TMJ. ROI were taken in transverse section in two to three consecutive slices for both

right and left joint. Making sure that the mask included the capsular soft tissue excluding bony boundaries.

For NaF scans, ROI were assigned to ensure involvement osseous compartment of the joint. A 3D ball tool of 1.5 cm was used, where the head of the mandibular condyle was located at the center of ROI including the osseous compartment of the joint extending inferiorly to the neck of the condyle (Figure 2). Averaged SUVmean of the right and the left TMJ was used to semi-quantify FDG and NaF uptake in the joint. SUVmean was calculated based on the following equations:

$$\text{Total Tissue Metabolism} = \sum (\text{Slice SUV}_{\text{mean}} * \text{Slice ROI}_{\text{volume}})$$

$$\text{Averaged SUV}_{\text{mean}} = \frac{\text{Total Tissue Metabolism}}{\text{ROI}_{\text{total\_volume}}}$$

For normalization, the target-to-background ratio (TBR) was calculated for each subject by dividing the average TMJ SUVmean by the SUVmean in the superior vena cava taking by assigning ROI of 0.5 cm in the lumen of the vein. The scans were independently analyzed twice by the same investigator and second investigator for intra/interobserver agreement.

Statistical Analysis: student's t-test was used for parametric analysis to compare SUVmen and TBRmean in RA and control subjects. linear regression analysis was used to evaluate the correlation between TMJ uptake and clinical disease activity scores. Intraclass correlation coefficient test was used to calculate intra/ interobservers agreement. The analysis conducted using IBM SPSS Statistics version 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY: IBM Corp).

Result:

Subjects demographic and clinical characteristics are presented in (table 1). High level of agreement in both intraobserver and interobserver analysis was found in evaluating PET/CT scan of the TMJ (0.99 and 0.97 respectively). The FDG average SUVmean of RA patients was 1.18±0.47 compared to 1.09±0.27 in healthy controls (p=0.48). FDG TBRmean for the test group was 1.21±0.33 compared to 0.91±0.2 in controls, (p=0.003.) (Figure 3). No correlation was found between FDG TBRmean and DAS28-CRP or DAS28-ESR. The NaF average SUVmean was significantly higher in RA patients than healthy control subjects (2.4±0.8 versus 1.9±0.4, p=0.02). Similarly, the TMJ TBRmean was also higher in RA patients relative to healthy controls (4.2±2.1 versus 2.7±0.9, p=0.01). A significant positive correlation was found between TBRmean and DAS28-CPR

(r=0.49, *p*=0.03), while an insignificant one was observed between DAS28-ESR (r=0.37, *p*=0.12) (Figure 4).

Discussion:

The result of our study illustrates that higher TMJ metabolic activity in RA patients when compared to age/gender matched non-arthritis subjects. Which was determined by the significant TMJ TBRmean of FDG (1.21±0.33 vs 0.91±0.2, *p*=0.003) and NaF (4.2±2.1 versus 2.7±0.9, *p*=0.01). Our finding is in agreement with what have been reported in the literature of involvement of TMJ in rheumatoid arthritis with a prevalence up to 58%.[9]

RA is an autoimmune inflammatory disease of multifactorial origin. The underlying cause of RA is still poorly defined. Inflammation of synovial fluid and degenerative joint changes are among the reported characteristics of the disease. Cartilage erosion and progressive bone degeneration affect the articular surface and bony structure of TMJ. Proinflammatory cytokines reported to be in a higher level in RA including IL1, IL6 and TNF. [20,21] FDG can detect molecular metabolic activity within the soft tissue component of the joint. In this study the ROI for FDG analysis were manually drawn to including as much of the soft tissue within the joint trying to exclude adjacent bony structures. While NaF, evaluate

uptake in the osseous compartment, analysis in our method included the head of the condyle and articular surface of temporal bone with a goal to assess potential bony destruction.

Radiographic analysis is an essential armamentarium in diagnosing and monitoring treatment responses of TMJ disorders. Many studies have verified the utility of NaF and FDG-PET/CT in assessing osteoarthritis changes in other body joints. [17] Lee et al. were also able to demonstrate that PET has scan higher sensitivity and accuracy when compared to conventional bone scan for detecting TMD with osteoarthritis[18]. Moreover, in a systematic review of imaging techniques evaluating chronic osteomyelitis, FDG-PET imaging demonstrated the highest diagnostic accuracy 92% compared with 82% bone scintigraphy, and 84% MRI [19]. In evaluating arthralgic TMJs, SUVmax using NaF PET/CT was consistently showed to have a fair performance it detection and exclusion of affected joints. Moreover, SUVmax was significantly higher values in the temporomandibular joints in subtypes 4 than in the other subtypes. The study found out that NaF PET/CT is superior to ^{99m} Tc-HDP SPECT/CT in regards to regarding the measurement of SUVmax as a diagnostic criterion for TMD[15,16].

Since, diseases usually occur at cellular level before destructive changes appear clinically or radiographically. PET scan could be an asset in terms of detecting and

objectively assessing changes at molecular level. This could an essential way of managing disease at its early stages before structural breakdown takes place. But, research regarding the practical application of PET/CT in TMJ disorder is lacking.

Evaluating the disease activity score, we found correlation between DAS28-CRP & DAS28-ESR and NaF TBRmean (r=0.49, *p*=0.03 & r=0.37, *p*=0.12, respectively). But no correlation was found between activity score and FDG TBRmean. This finding could be attributed to the differences in disease initiation of RA patients included in this study. Another potential explanation is that osseous destruction is more pronounced in the joint of RA patients than soft tissue inflammation. In animal studies, Irmler et al. was able to demonstrate that Naf and FDG was correlated with joints distraction. NaF uptake was a sustained after 11 days of disease initiation with significant increase in uptake between day 18 and 25. While FDG uptake reached its peak at day 13 followed by subsequent reduction at day 21. Thus, indicating that inflammation is followed by bone destruction. [24,25]

Among the limitation of the current study, is the small sample size of population. Also, our quantitative results lack the clinical information related to TMJ analysis such as pain, crepitation or limitation of mouth opening that could have supported our results. In addition, TMJ is a small joint which requires a high-resolution

imaging modalities to define anatomical boundaries in a precise manner. However, the main purpose of this study was to develop an analysis scheme for quantifying TMJ with PET/CT scan and it has shown a promising sensitivity to detect the activity of inflammation and bone turn over. This will aid in achieving an earlier disease diagnosis and provide an objective tool to follow disease activity and progression as well as evaluate response to treatment approaches. Future longitudinal studies with larger sample size and clinical information of TMJ disease severity are required to quantify degenerative changes within the joint.

Conclusion:

Our results illustrate the potential value of using FDG and NaF-PET/CT for evaluation of TMJ disorders and other inflammatory conditions within the oral cavity. Since this approach yields structural images along with data that can be quantified it provides more information than conventional structural imaging techniques. The RA patients appeared to have significantly higher metabolic activity in the TMJ relative to the healthy control subjects. The degree of NaF uptake in the TMJ correlated with biochemical parameters of RA disease severity based on DAS28-CRP and DAS28-ESR scores. Thus, the results suggest that NaF uptake does have the capacity to detect inflammatory changes prior to overt

structural breakdown of the joint. In the future, this could allow for earlier and more efficacious treatment of degenerative disorders affecting the TMJ. Furthermore, NaF-PET/CT might also serve as a means of objectively assessing treatment outcomes especially those aimed at regeneration of damaged components of the TMJ.

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	RA	Control
n	18	18
Age years (mean±SD)	57±12	56±12
Female gender n (%)	4/18 (22.2%)	4/18 (22.2%)
BMI (mean±SD)	26.9 ±6	27± 3.4
Disease duration n (%)	12.5 (11.1)	
TJC, median (min, max)	6.5 (0, 15)	
SJT median (min, max)	6 (0, 6.5)	
DAS28-ESR (mean ±SD)	4.4 ±1.6	
DAS28-CRP (mean ±SD)	3.74 ±1.3	

Table 1: Patients' demographic and clinical characteristics; Min: minimum; max, maximum; TJC: tender joint count; SJC, swollen joint count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, Disease Activity Score based on 28 joint count.

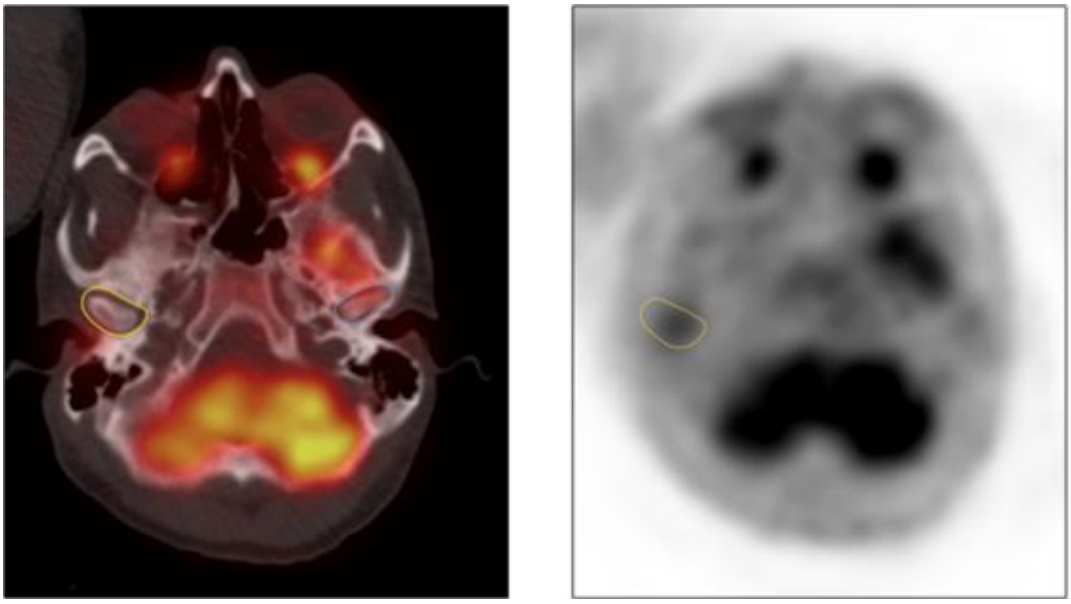

Figure 1: ROI was manually drawn following the anatomical boundaries of the TMJ and is here shown as it appears on the trans-axial slice on the fused (a) and the PET (b) images.

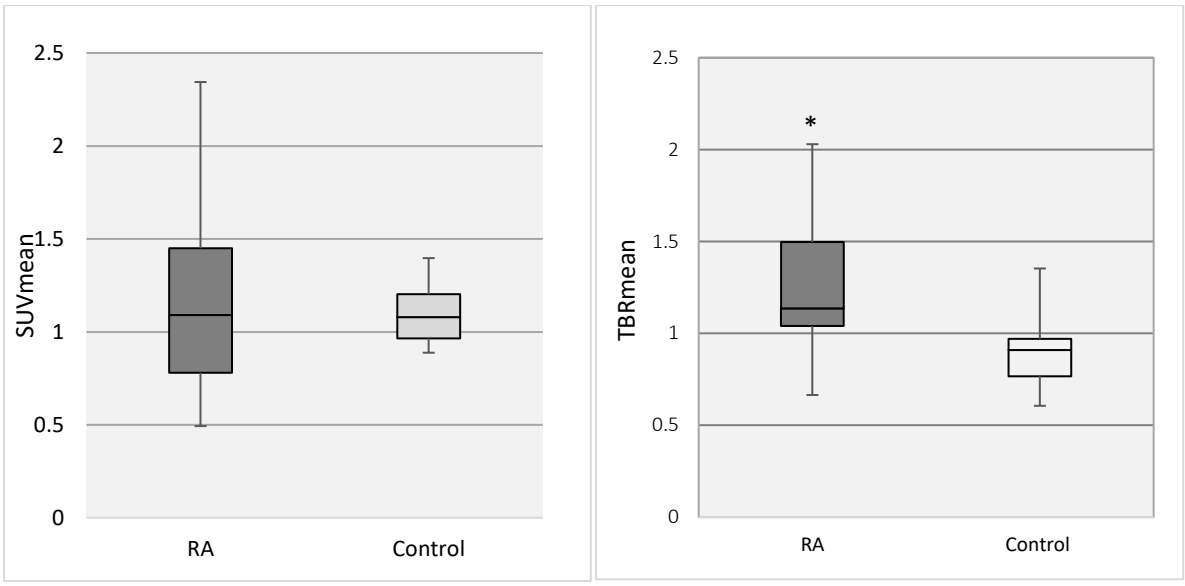

Figure 3 : Box plots of the average FDG SUVmean (a) and TBRmean (b) of RA patients compared tohealthy control.

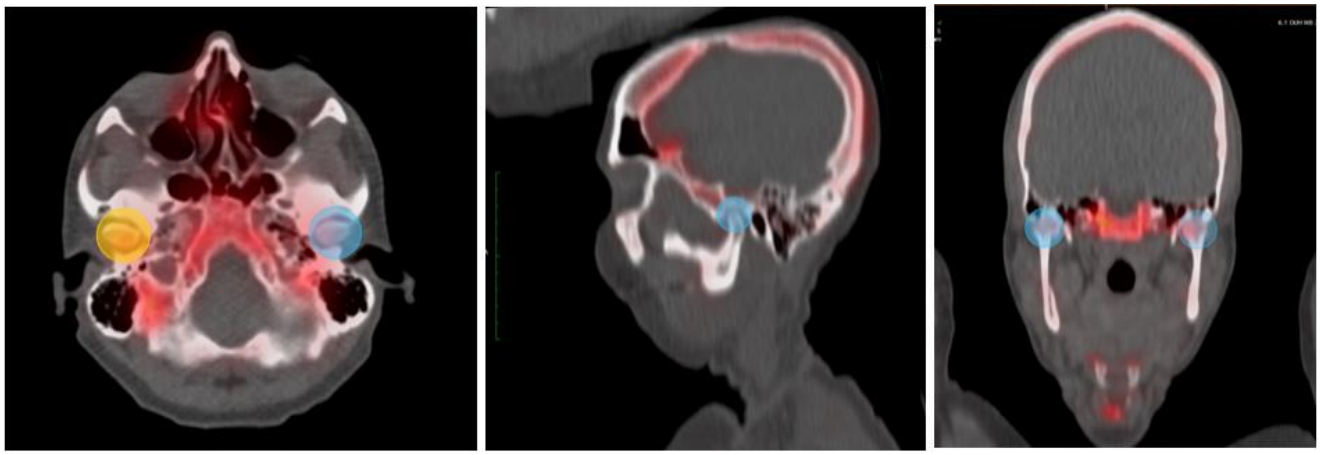

Figure 2: ROI including the osseous compartment of TMJ in transvers, sagittal and coronal slice of a fused PET/CT scan.

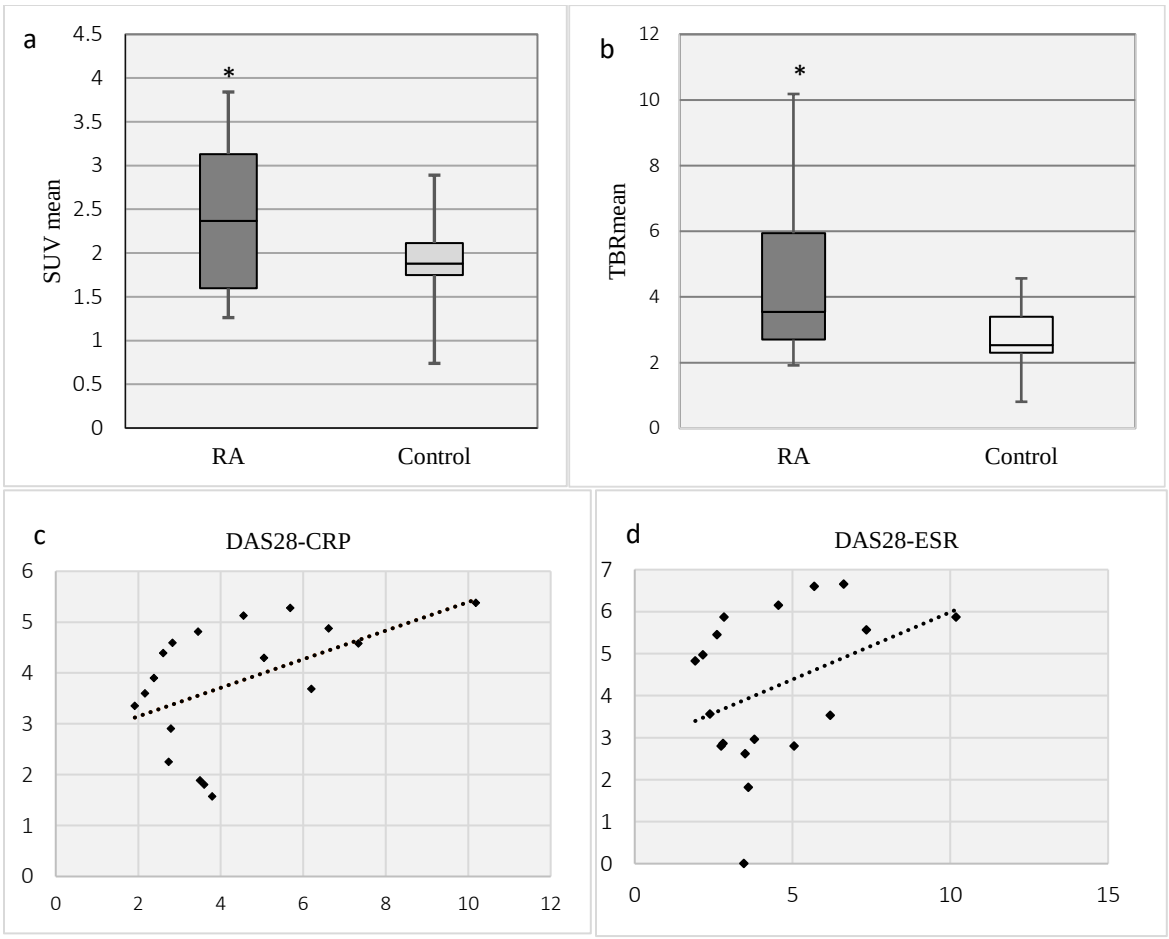

Figure 4: Box plots of the average NaF SUVmean (a) and TBRmean (b) of RA patients compared to healthy control. (c,d). The assossiation between TBRmean with DAS28-CPR and DAS28-ESR.