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***In vivo* quantification of mouse autoimmune arthritis by PET/CT**

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Abstract

Aim—To quantify the progression and severity of mouse collagen-induced arthritis (CIA) using an *in vivo* imaging tool, ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET/CT, and validate it against gold standard ‘histopathological’ evaluation.

Method—The PET radiotracer ¹⁸F-FDG, a marker for glucose metabolism, was injected in mice at different stages during the development of CIA and the radiotracer distribution was imaged using a PET scanner. A sequential CT scan provided correlated anatomy. Radiotracer concentration was derived from PET/CT images for individual limb joints and on a per-limb basis at different stages of the disease. The imaging outcomes were subjected to correlation analysis with concurrently-measured clinical and histological score.

Results—Clinical and histological score, and hence disease severity, showed a strong linear correlation ($R^2=0.71$, $p=0.001$, and $R^2=0.87$, $p<0.001$, respectively) with radiotracer concentration measured from PET/CT during the progression of CIA.

Conclusions—The strong positive correlation of the ¹⁸F-FDG PET/CT findings with the histopathological evaluation at different stages of the disease suggest the potential of this imaging tool for the non-invasive assessment of progression and severity in mouse autoimmune arthritis.

Thus, ¹⁸F-FDG PET/CT can be considered as a non invasive tool in preclinical studies for development of novel therapies of inflammatory arthritis.

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AUTHOR'S CONTRIBUTIONS: SKR, SPR, AJC and AM designed the experiments. SKR, AM, ADM and AJC performed all experiments. SKR, AM and AJC did the statistical analysis. SPR and AJC conceived the study and helped in designing experiments. All authors have contributed to the conception and/or acquisition of data and analysis for this project and to either drafting or revising the manuscript. All authors read and approved the final manuscript.

Keywords

Mouse CIA; *in vivo* imaging; PET/CT; quantification; inflammation

INTRODUCTION

The collagen-induced arthritis (CIA) mouse model shares key pathological events of human rheumatoid arthritis (RA) such as activation and migration of lymphocytes, proliferation of synovial tissue, hypoxia, angiogenesis and bone erosion.[1, 2] Conventionally, disease severity in mouse CIA is assessed by a clinical score (visual assessment) along with the histopathological evaluation of the joint tissues.[3] These techniques have limitations; (a) mice need to be sacrificed for histopathologic studies and therefore the same animal cannot be studied at different stages of the disease, (b) the disease severity as measured by clinical/histopathological scores is semi-quantitative, is subject to observer bias and therefore has poor sensitivity to change, (c) the analysis of cellular-molecular interactions in the native *in vivo* environment of affected tissue cannot be performed, especially in the longitudinal setting.

Molecular imaging has the potential to offer an unparalleled insight into the arthritic disease process in the native *in vivo* environment of the human or animal body.[4] Briefly, in positron emission tomography (PET), a radiotracer such as ^{18}F -fluorodeoxyglucose (^{18}F -FDG), a glucose analogue, is injected intravenously into the subject. The ^{18}F -FDG is readily taken up by metabolically active cells such as malignant or inflammatory cells, followed by phosphorylation, and thus get trapped within the cell. The radiotracer emits positrons that annihilate with a nearby electron to produce a pair of annihilation photons propagating in opposite directions. A PET scanner detects this pair of annihilation photons in coincidence, allowing the reconstruction of three-dimensional images of the distribution of the radiotracer. ^{18}F -FDG-PET is quantitative, that is, the signal intensity in the images is directly proportional to the underlying concentration of the radiotracer. Elevated ^{18}F -FDG uptake observed on PET images corresponds to regions of active inflammation in arthritis. [5-8] Current preclinical PET scanners, such as the one used in this study, has a high spatial resolution (~1 mm) and excellent sensitivity (~10%) allowing radiotracer concentrations in nM or less to be visualized. Co-registration of PET with X-ray computed tomography (CT) provides an anatomical frame-of-reference for the former, allows for the precise localization of areas of inflammation in joints, and provides a means for correcting the PET images for photon attenuation of the body. Combined PET/CT devices are now widely available worldwide. An added advantage of PET/CT is that findings in a preclinical setting may be directly translated to the clinic. Conceptually, the same experiments can be performed in mice/humans and this provides an important experimental bridge that may accelerate the transition of new therapies and diagnostic tools into the clinic.

^{18}F -FDG-PET/CT has been widely employed for staging and assessment of therapeutic response in the field of oncology [9, 10], but its deployment in rheumatology has been limited.[6, 7, 11-14] The mouse CIA model is widely believed as a well representative model to study the pathogenesis of autoimmune arthritis, as it uses the native articular type

II collagen as an antigen.[1, 2] So far, Cha et al. showed at a single time point that ^{18}F -FDG can quantify arthritis in mouse CIA model [8], however, till date detail studies have not been done to validate the combined use of ^{18}F -FDG-PET and CT in this model as an *in vivo* marker of disease severity at multiple time points during the disease progression. In this background, we wanted to evaluate the positive correlation of ^{18}F -FDG PET/CT with the gold standard 'histopathology' analysis at different stages of the disease, so that longitudinal studies can be performed in the same animal. In this proof-of-principle study, we observed that in mouse CIA model, ^{18}F -FDG PET/CT quantify severity and progression of mouse autoimmune arthritis in an *in vivo* settings as good as the gold standard histopathology studies.

METHODS

Induction of CIA

Animal handling was performed in accordance with an approved protocol by the UC Davis Institutional Animal Care and Use Committee. 8-12 weeks old arthritis susceptible male DBA/1 mice were purchased from Jackson Laboratory (Bar Harbor, ME). Arthritis was induced using bovine type II collagen (CII) in 18 mice out of which 14 mice completed the study. Briefly, 100 μg bovine CII emulsified in 100 μl of complete Freund's adjuvant (CFA) was injected intra-dermally (I.D) into the proximal tail of male DBA/1 mice followed by a second intradermal injection on day 21 with emulsified incomplete Freund's adjuvant (IFA). [15-17] After the second injection of CII, mice were examined daily for the onset and severity of the arthritis (Figure 1).

Clinical score (CS)

Before the PET/CT scan, at each time point, the severity of the arthritis was scored using an algorithm (clinical score, CS) by two independent investigators (SKR, AM). A CS was allocated for each mouse based on the following criteria: 0=no erythema/swelling, 1=one toe inflamed or swollen, 2= > one toe but not entire paw inflamed /swollen or mild swelling of the entire paw, 3=entire paw inflamed or ankylosed paw.[18] Thus, the score ranged from 0 to 12 for each mouse (Figure 1).

^{18}F -FDG PET/CT scan

Mice were scanned using ^{18}F -FDG-PET/CT at day 0 (before first collagen injection, n=18) followed by subsequent scans at day 28 ± 1 (n=4) and 56 ± 1 (n=5) (Figure 1). Briefly, mice were anesthetized following an IV injection of 7.4 MBq ^{18}F -FDG and scanned sequentially, starting at 30 min post-injection, on a small animal PET and CT (both Siemens Healthcare, Knoxville, TN) systems using a detachable animal bed for maintaining animal position. PET images were reconstructed using the 'fastMAP' method (OSEM3D: 16 subsets, 2 iterations; MAP: 18 iterations). This method provides higher recovery coefficients, lower spill-over fraction and optimized quantitative accuracy[19] compared to previous studies.[7, 20] Regions-of-interest (ROI) were manually drawn at carpal and tarsal joints of each paw using CT as a reference by an investigator (AJC) blinded to the clinical or histopathological scores. The maximum ^{18}F -FDG uptake per ROI was averaged over the four paws at each time point to generate a total uptake value.

Histological score (HS)

To validate the PET/CT findings with the current gold standard “histopathology”, mice were sacrificed (day 0: n=5, day 28: n=4, day 56: n=5) for histopathological analyses after the PET/CT scan at each time point (Figure 1). Briefly, after euthanizing with CO₂ inhalation and cervical dislocation, limbs were dissected and processed, followed by staining with hematoxylin-eosin (H&E) for pathological alterations- inflammatory infiltrates, pannus, cartilage destruction and bone erosion. Each parameter was graded on a scale of 0-3 by two investigators (AM, AD-M), where 0=normal; 1=mild; 2=moderate and 3=severe). The maximum HS for each paw was 12.[21]

Statistical Analysis

CS, HS and the PET/CT measures were presented as Mean±SD. T-tests were used to determine the statistical differences between groups/time points. One-sided tests at level 0.05 were used based on known increase in CS, HS, and PET/CT measures over time (day 0 to 56). Graphical and Pearson correlation between measures over time were computed. A p-value of <0.05 was considered statistically significant. Regression analyses with PET/CT measures quantifying the association with the CS and HS were also performed.

RESULTS

¹⁸F-FDG PET distribution in mice extremities with disease progression

We examined the distribution of ¹⁸F-FDG uptake in the extremity joints in the animals by PET during CIA progression. Representative images are shown in the Figure 2C. At baseline, physiologically normal distribution of activity was noted in the paws, with near-uniform baseline accumulation of the radiotracer (Figure 2C, top). This uptake distribution was treated as that corresponding to healthy controls. The quantitative assessment is provided in the subsequent section. At day 28, an overall increase in ¹⁸F-FDG-PET activity was noted, particularly for the carpal and tarsal regions, based on co-registered anatomy from CT (Figure 2C, middle). On day 56, a higher accumulation of ¹⁸F-FDG compared to that at day 28 was detected in the carpal and tarsal joints, indicating elevated metabolic activity corresponding to disease progression (Figure 2C, bottom). Further, “hot spots” were noted for the distal phalangeal joints of several digits of the fore- and hind-limbs indicating increased severity of disease. The improved resolving power in the images for these minuscule pockets of ¹⁸F-FDG activity was a byproduct of the optimized performance of the ‘fastMAP’ image reconstruction method, and is expected to contribute to an improvement in quantitative assessment of the images.

¹⁸F-FDG PET/CT quantifies disease severity and progression in the CIA mouse model

Macroscopic signs of arthritis started to appear on day 20 after the first injection of CII. The total mean clinical score (CS) on day 28 was 3.75±1.5 (n=4), and progressed with time to 7.4±1.3 (n=5) on day 56. This value was significantly greater than day 28 (p=0.009) (Figure 2A & 3A). Histological score (HS) of the joint tissues on day 56 (15.2±5.2) showed more pannus and diffuse cellular infiltrates compared to that of day 28 (9±2; p=0.027) (Figure 2B & 3A). On day 28, the PET/CT scans showed increased ¹⁸F-FDG uptake in the carpal and

tarsal joints (306.9 ± 32.9 kBq/cc) compared to the pre-immunization status (day 0) of the same (216.7 ± 7.6 kBq/cc, $p < 0.01$) (Figure 2C & 3A). The highest ^{18}F -FDG uptake was measured on day 56 (375.7 ± 113.8 kBq/cc) and was statistically significantly different compared to the pre-immunization status (day 0) $p < 0.01$. In combined ^{18}F -FDG PET/CT scan, we observed that at day 56 the tibio-talar joint showed maximum ^{18}F -FDG uptake (Figure 2D), which corroborated well with the clinical score (Figure 2A, day 56) and histopathology (Figure 2B, day 56). ^{18}F -FDG uptake was measured on day 56 was (375.7 ± 113.8 kBq/cc) overall higher than that from day 28 (306.9 ± 32.9 kBq/cc), but was found to not be statistically significantly different compared to that from day 28 ($p = 0.128$) – a possible by-product of the small sample size.

^{18}F -FDG PET/CT uptake significantly correlates with the longitudinal change in clinical and histological score during CIA progression

CS and HS at different time points showed progressive increase in disease severity compared to that of day 0 (Figure 2A, 2B, 3A). Similarly, the ^{18}F -FDG PET/CT uptake showed progression of the disease severity in an *in vivo* setting (Figure 2C, 3A). With disease progression the *in vivo* PET/CT uptake significantly correlated with the respective CS ($R^2 = 0.71$, $p = 0.001$) and HS ($R^2 = 0.87$, $p < 0.001$). Among CS and HS, the correlation of PET/CT with HS was higher than that observed with CS (Figure 3B). We also performed linear regression analysis of CS alone, PET/CT alone and CS and PET/CT as independent predictors with HS as the outcome variable. Adjusted R-squared values of CS alone (0.90), PET/CT alone (0.87) and CS and PET/CT (0.97) were obtained with respect to HS. These results demonstrate that while the correlation between CS and HS is marginally better (0.90) than that between PET/CT and HS (0.87), the use of CS and PET/CT indeed improved upon the clinical evaluation of disease than each individual method.

DISCUSSION

In this proof-of-principle study, ^{18}F -FDG PET/CT imaging tracked disease progression closely with respect to both clinical and histopathological evaluation. The strong correlation of ^{18}F -FDG PET/CT findings at different stages (day 28 and 56) of CIA with the gold standard “histopathology” vouches for the further investigation of this novel non-invasive multimodality imaging as a tool for *in vivo* quantification of disease progression and severity (Figure 3). In this study, PET/CT signals were compared with CS and HS at different stages of the disease. PET/CT produces continuous measurements that vary linearly with radiotracer activity concentration as opposed to CS and HS, which are discrete measurements. It is therefore important to interpret the PET/CT signal magnitude with respect to its baseline value and not as a fold-change compared to CS or HS.

Disease progression and severity in CIA, the most widely studied mouse model of autoimmune arthritis, is conventionally assessed by clinical score (CS) and histological score (HS). Histopathological analyses provide a direct evidence for the disease activity but these analyses do not lend themselves to longitudinal studies of the disease process in the same animal. Further, these studies are limited to only a regions-of-interest (ROI), sample error can be considerable and cellular-molecular characteristics associated with autoimmune

arthritis initiation and progression may be altered in *ex vivo* settings. Since PET/CT is an *in vivo* imaging technique [22, 23], it allows for the same animal to be studied at multiple time-points during progression of autoimmune arthritis and individual joints can be studied to document molecular-level processes like metabolism in their natural environment. As a consequence PET/CT studies are expected to require a smaller sample size. Further, PET/CT allows the simultaneous assessment of all joints of the animal body, thus reducing sample error typical of histopathology. Further investigations to be undertaken include studies to document whether PET/CT has improved sensitivity to subclinical disease compared to clinical score, and whether PET/CT is able to provide markers for assessing response to therapies such as TNF-alpha inhibitors and other anti-inflammatory agents. We demonstrate in our study that the 'fastMAP' method [19] has the potential to provide improved image quality when radiotracer activity in small regions such as the limbs and digits needs to be quantified.

The novelty of this study is that we have established the ^{18}F -FDG-PET/CT technique for *in vivo* quantification of the diseases severity and progression in the mouse CIA model. In the recent past, two studies reported the use of ^{18}F -FDG-PET alone for assessing disease activity in a rat and mouse CIA model [7, 8], but none of them conducted the detailed head-to-head comparison of histopathology and ^{18}F -FDG activity at different time points of the disease. Therefore correlations of histopathological outcomes with radiotracer uptake at each individual time-point during disease progression were not available. Moreover, none of these studies have used computed tomography (CT) with ^{18}F -FDG-PET, thus the anatomical reference of ^{18}F -FDG-PET uptake are not accurate. In this context, only two studies by Irmeler et al. and Zhang et al. used ^{18}F -FDG-PET/CT to quantify arthritis in the glucose-6-phosphate isomerase (G6PI)-induced mouse arthritis [20] and rat collagen induced arthritis model [24] respectively. Arthritis progression in the G6PI-induced arthritis model occurs on a different scale than the CIA model and there are fundamental differences in the underlying molecular processes during arthritis induction in the two models.[25]. Here we have validate the use of ^{18}F -FDG-PET/CT to quantify the degree disease activity at different time points in the mouse CIA model, the most widely used model of human autoimmune arthritis. We expect that this unique *in vivo* imaging tool will be broadly used for development of novel therapies of inflammatory arthritis.

Inter- and intra-observer variability is a common problem in HS and CS-based studies. ^{18}F -FDG-PET/CT alternatively provides markers (such as maximum radiotracer uptake) that are determined objectively based on the intensity in the resulting images, thus reducing this variability.[26] These imaging markers can therefore be capitalized upon as surrogate end points in preclinical studies of new arthritis therapies, as is currently under active investigation in the context of oncologic disease. In this context, at least we found that the correlation of ^{18}F -FDG PET with histological score (0.87) is very much comparable with that of clinical and histological score (0.90).

Limitations of using ^{18}F -FDG PET/CT include costs of the radiotracer and the scanning machine, the requirement of trained personnel to conduct the imaging study, and the challenge of obtaining precise quantification in small regions-of-interest owing to limited resolving power (currently of the order of 1 mm).

A limitation of our study is that we compared a single measure from PET/CT (average of the maximum signal over the 4 paws) with CS and HS. Our future studies will evaluate CS and HS on a per limb and per digit basis to better quantify the merits of quantification using PET/CT. Our research group [6, 27] and others [13] have demonstrated recently in our studies using PET/CT in humans, the technique also provides tremendous potential for early monitoring of response to RA treatment.

CONCLUSION

Based on these observations, we conclude that ^{18}F -FDG PET/CT shows promise as a key quantitative imaging tool for the non-invasive *in vivo* assessment of progression and severity of mouse collagen induced arthritis. Further, ^{18}F -FDG PET/CT might prove useful in preclinical studies of new drugs for arthritis by providing more objective information in the native *in vivo* environment without sacrificing the study animals. ^{18}F -FDG PET/CT is particularly suitable for longitudinal studies required for novel drug discovery and has the potential to replace the conventionally used histopathological studies.

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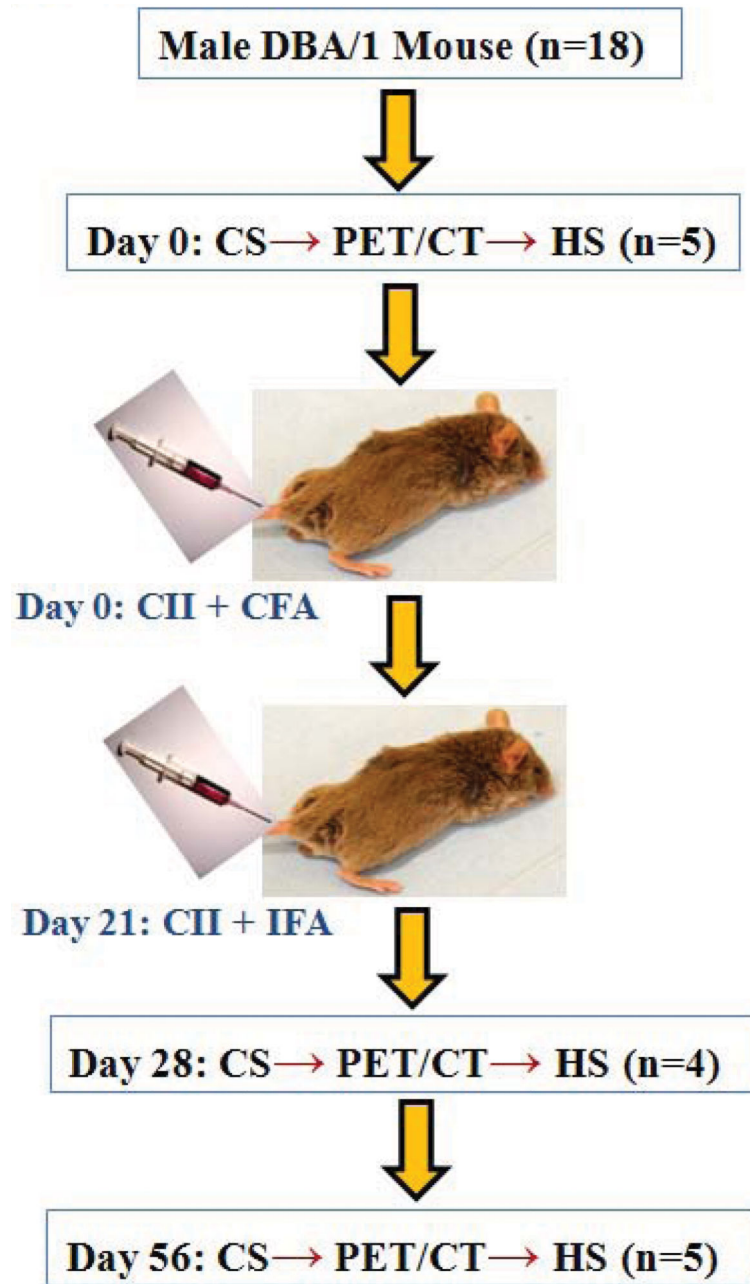


Figure 1. Study flowchart. CS: clinical score; HS: histological score; CII: type II bovine collagen; CFA: complete Freund's adjuvant; IFA: incomplete Freund's adjuvant

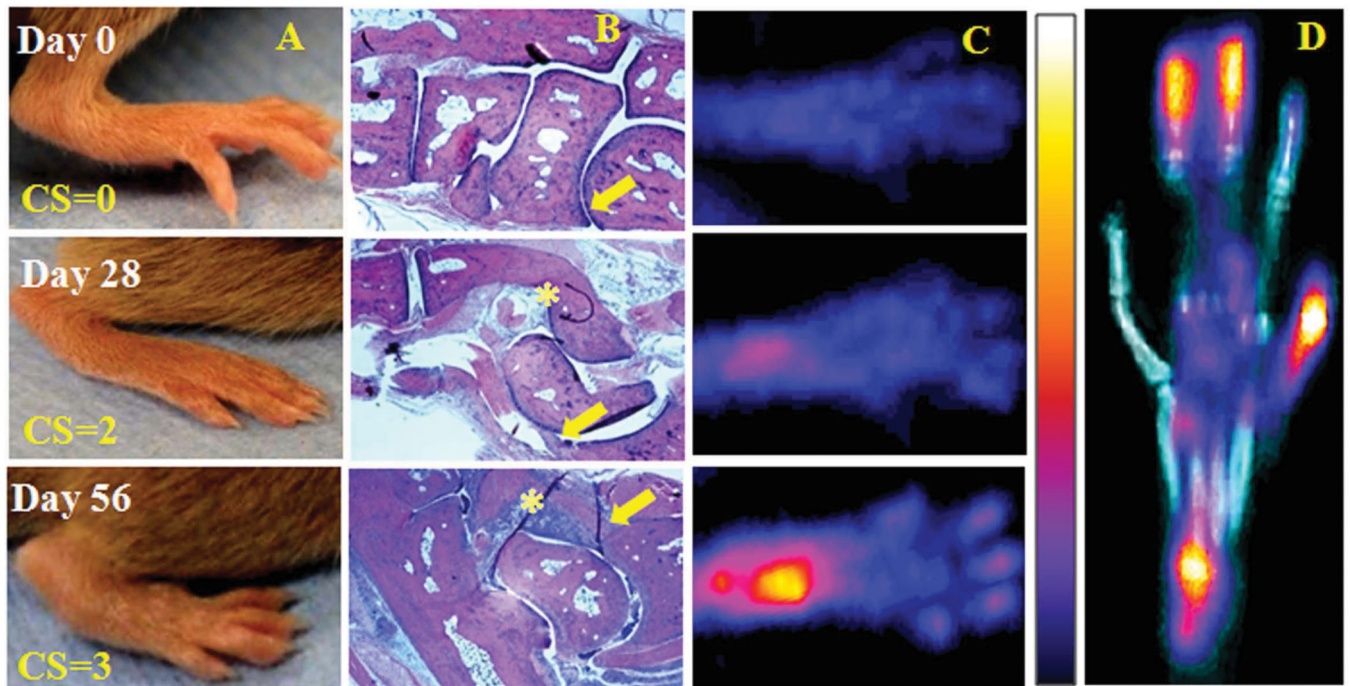


Figure 2. ^{18}F -FDG PET/CT quantifies *in vivo* disease severity in mouse CIA model; a montage of representative photographs of the hind limb of the same mouse as disease progressed; (A) Clinical score (CS); (B) histopathology (5x); and (C) representative maximum-intensity projection of ^{18}F -FDG PET. The pseudo-color in PET indicates higher glucose metabolism, hence increased cellular metabolic activity. The yellow arrows in (B) represent sites of pannus and yellow stars represent cellular infiltrates. (D) Representative fused ^{18}F -FDG PET/CT image showing the increased uptake of ^{18}F -FDG in the affected joints of CIA mouse at day 56. Data were presented as Mean \pm SD. T-tests were used to determine the statistical differences between groups/time points.

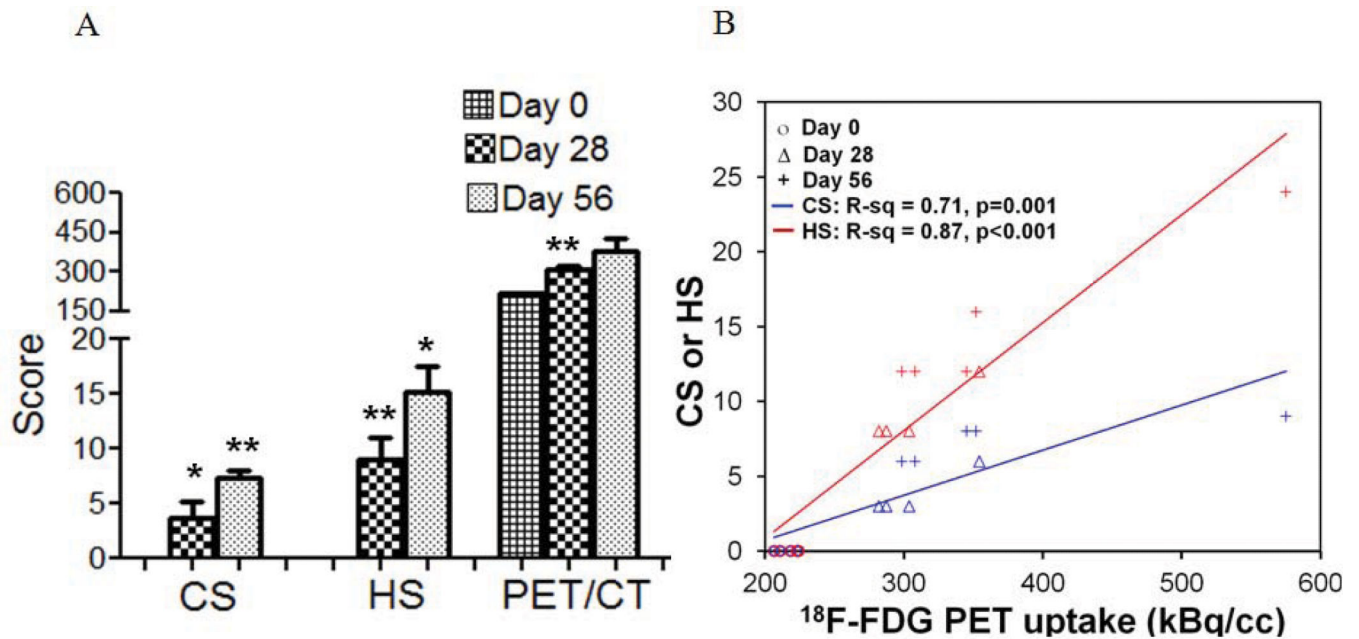


Figure 3.

^{18}F -FDG PET/CT uptake positively correlated with clinical and histopathological score at different stages of CIA. (A) Bar diagram showing the progression of clinical score (CS), histological score (HS) and ^{18}F -FDG PET/CT uptake (PET/CT) at different stages of the disease. (B) Line diagram showing the correlation of PET/CT uptake (kBq/cc) with clinical (CS) and histopathological score (HS) at different stages of CIA (n=14). The coefficient of determination (R-squared) between measures over time was computed is shown. *p<0.05; **p<0.01