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Observational study

Detection of nociceptive-related metabolic activity in the spinal cord of low back pain patients using ^{18}F-FDG PET/CT

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HIGHLIGHTS

- We compared PET/CT scans of patients with low back pain (LBP) to those without LBP.
- Increased ^{18}F-FDG uptake was found in the spinal cords of patients with LBP.
- ^{18}F-FDG PET/CT shows potential as an objective biomarker in the setting of LBP.

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ABSTRACT

Background: Over the past couple of decades, a number of centers in the brain have been identified as important sites of nociceptive processing and are collectively known as the 'pain matrix.' Imaging tools such as functional magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) have played roles in defining these pain-relevant, physiologically active brain regions. Similarly, certain segments of the spinal cord are likely more metabolically active in the setting of pain conditions, the location of which is dependent upon location of symptoms. However, little is known about the physiologic changes in the spinal cord in the context of pain. This study aimed to determine whether uptake of ^{18}F-FDG in the spinal cord on positron emission tomography/computed tomography (PET/CT) of patients with low back pain (LBP) differs from that of patients without LBP.

Methods: We conducted a retrospective review of ^{18}F-FDG PET/CT scans of 26 patients with non-central nervous system cancers, 13 of whom had reported LBP and 13 of whom were free of LBP (controls). No patients had spinal stenosis or significant ^{18}F-FDG contribution of degenerative changes of the spine into the spinal canal. Circular regions of interests were drawn within the spinal canal on transaxial images, excluding bony or discal elements of the spine, and the maximum standardized uptake value (SUVmax) of every slice from spinal nerves C1 to S1 was obtained. SUVmax were normalized by subtracting the SUVmax of spinal nerve L5, as minimal neural tissue is present at this level. Normalized SUVmax of LBP patients were compared to those of LBP-free patients at each vertebral level.

Results: We found the normalized SUVmax of patients with LBP to be significantly greater than those of control patients when jointly tested at spinal nerves of T7, T8, T9 and T10 ($p < 0.001$). No significant difference was found between the two groups at other levels of the spinal cord. Within the two groups, normalized SUVmax generally decreased cephalocaudally.

Conclusions: Patients with LBP show increased uptake of ^{18}F-FDG in the caudal aspect of the thoracic spinal cord, compared to patients without LBP.

Implications: This paper demonstrates the potential of ^{18}F-FDG PET/CT as a biomarker of increased metabolic activity in the spinal cord related to LBP. As such, it could potentially aid in the treatment of LBP by localizing physiologically active spinal cord regions and guiding minimally invasive delivery of analgesics or stimulators to relevant levels of the spinal cord.

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Abbreviations: MRI, magnetic resonance imaging; ^{18}F-FDG, fluorodeoxyglucose (^{18}F); PET, positron emission tomography; CT, computed tomography; LBP, low back pain; SUV, standardized uptake value; CNS, central nervous system; ROI, region of interest.

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1. Introduction

Low back pain (LBP) is the main reason for lost days at work and disability, with up to 20% of adults reporting an episode of back pain in a single year [1]. Clinical diagnosis of LBP includes history taking, physical exam, electromyography, discography, and imaging. These tests are relatively inaccurate in pinpointing specific locations of chronic back pain. For example, conventional magnetic resonance imaging (MRI) shows significant intervertebral disc abnormalities in 27–31% of asymptomatic subjects [2]. Additionally, the natural progression of degenerative disc disease does not correlate with the development of pain [3], and provocative discography and MRI-based morphometric measurements have only a weak association with back pain [4].

Imaging approaches with the potential to more accurately measure pain-related physiologic and functional changes in the central nervous system (CNS) include functional MRI, diffusion tensor imaging, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) and 15O-water-PET [5–8]. While these approaches have been helpful in identifying a variety of neural centers, studies have been restricted mainly to the brain. The spinal cord is important in the regulation of pain, as it facilitates both ascending and descending nerve impulses between the brain and peripheral nervous system.

Neuronal activity from pain generators in the spinal cord is dependent upon glucose metabolism. This metabolism has been investigated using glucose analogs in ex vivo specimens; 2-deoxyglucose (2-DG) autoradiography in animal models has shown increased metabolic activity in the spinal cord gray matter in response to peripheral inflammatory pain stimuli [9]. These findings are compatible with current theories that tissue inflammation, neuronal damage and/or various noxious stimuli result in neuroplastic changes that, in turn, result in neuronal hypersensitivity and increased metabolic demand [10,11]. ^{18}F-FDG positron emission tomography-computed tomography (PET/CT) has emerged as a powerful tool for evaluating glucose metabolism in various oncologic, neurologic and cardiac diseases [12]. The ability to provide functional and spatial information that correlates with pain sites would make ^{18}F-FDG PET/CT a promising modality for imaging the differential nociceptive activity in the spinal cord of LBP patients.

2. Materials and methods

2.1. Patients

Approval for this study was obtained from our institutional review board, and data was collected in compliance with The Health Insurance Portability and Accountability Act (HIPAA).

A retrospective review of 3500 PET/CT scans of patients with non-CNS cancers was performed between January 1, 2006 and April 1, 2007 at Stanford University Medical Center. Among the exclusion criteria were significant motion artifact, vertebral marrow hyperplasia, spinal arthritis, extreme kyphosis, extreme scoliosis, metastatic disease or local disease recurrence. Just prior to undergoing a PET/CT scan, each patient had filled out an entrance questionnaire documenting the presence and location of pain. Of the 3500 PET/CT scans reviewed, 253 met the above screening criteria.

Thirteen of these 253 patients had described LBP on their study questionnaire. These 13 LBP patients were then compared to 13 who had described absence of any pain at the time of their PET/CT study (controls). Twelve of the LBP patients had undergone their last chemotherapy and/or radiation therapy at least 6 months prior to the scan, and one had undergone chemotherapy 2 months prior to PET/CT. Seven of the control patients had undergone their last chemotherapy and/or radiation therapy at least 12 months prior to the PET/CT. Six patients had never received chemotherapy or radiation therapy, but had presented to the PET clinic for evaluation of solitary pulmonary nodules or other pulmonary disorders, such as sarcoidosis, and had negative results.

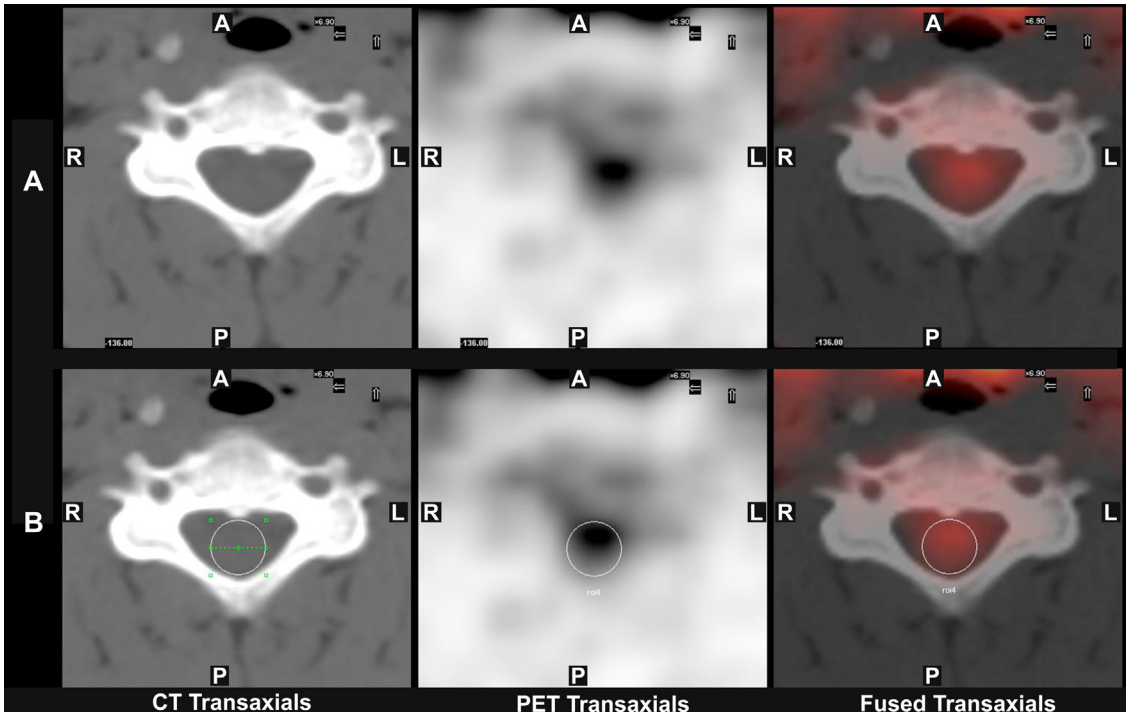

Fig. 1. Placement of ROIs. (A) Single transaxial ^{18}F-FDG PET/CT image obtained within the spinal cord. (B) Placement of an ROI (white circle) within the spinal canal on both the non-contrast CT image and attenuation corrected PET image. Data obtained from the ROI include total counts, SUVavg, SUVmax, and area. Designations of 'A', 'P', 'R' and 'L' represent the subject's anterior, posterior, right and left sides, respectively.

The average age of all subjects was 52.6 years, and the standard deviation (SD) was 21.0 years. Both the LBP and pain-free groups consisted of 8 males and 5 females. The average age was 40.7 years (SD = 14.2 years) in the LBP group and 64.5 years (SD = 20.3 years) in the LBP-free group.

2.2. ^{18}F-FDG PET/CT acquisition

All subjects were administered 15 mCi of ^{18}F-FDG intravenously. One hour after injection, PET emission scans in 2D mode were acquired from the head through the level of the thighs using a Discovery LS scanner (GE Medical Systems, Milwaukee, WI). Multiple 5 mm contiguous axial, four integrated multi-slice, helical CT transmission scans were obtained from the mid head to mid thighs, using 140 kV, 40 mAs, and a 512 × 512 matrix size. CT was used for attenuation correction and for assistance in anatomic localization of the spinal cord. Standard acquisition times were used over 6–7 bed positions to cover the area of interest. PET emission scans were corrected using segmented attenuation data of the CT transmission scan. CT data was reduced to an image matrix of 128 × 128 for adaptation to PET emission scans. PET images were reconstructed using a standard iterative algorithm (OSEM, two iterations, 28 subsets). The images were co-registered by overlaying the PET and CT images and were reviewed on a Xeleris workstation (GE Medical Systems, Milwaukee, WI).

2.3. Image analysis and statistical analysis

PET/CT image data sets were exported as DICOM files and analyzed using RT_image software (Stanford, version 6.2) [13]. Circular regions of interests (ROIs) were placed within the spinal canal, which was defined using transaxial CT images, and excluded bony elements of the spine (Fig. 1). These ROIs included the spinal cord, nerve roots, thecal sac, cerebrospinal fluid and epidural fat. Corresponding PET signal measurements (maximum standard uptake values (SUVmax)) were obtained for each slice from C1 to S1 within the spinal cord. The highest SUVmax among slices corresponding to each vertebra was recorded and then normalized in each patient by subtracting the SUVmax of L5, which served as an internal control; metabolic activity in the spinal canal at L5 is not expected to be affected by LBP, because there is minimal neural tissue at this level. The normalized SUVmax were compared between the LBP group and pain-free group at each vertebral body level from C1 to S1. A Mann Whitney test, stratified across vertebral levels, was performed at each vertebral body level, with statistical significance defined as $p < 0.05$.

3. Results

Normalized SUVmax of the LBP patients were higher than those of the pain-free patients in the lower thoracic segments, particularly at T7, T8, T9 and T10 (Fig. 2A and B). Although Mann Whitney tests for these vertebral levels individually and independently were not statistically significant, when jointly tested, there was a statistically significant difference between the LBP group and pain-free group ($U = 0$, $p < 0.001$) at these levels. No statistically significant differences were observed within the remainder of the spine.

Both the LBP and pain-free groups showed a general trend of decreasing normalized SUVmax moving caudally along the cord and demonstrated focal relative increases in normalized SUVmax at T11 and T12 (Fig. 2A and B). These increases are likely a result of increased cord volume due to the normal lumbar anatomic enlargement. The increase in cord volume at this level has been studied via anatomic and quantitative analysis of spinal cord gray matter, myelographic data, CT myelography, and MRI images of the cord [14,15].

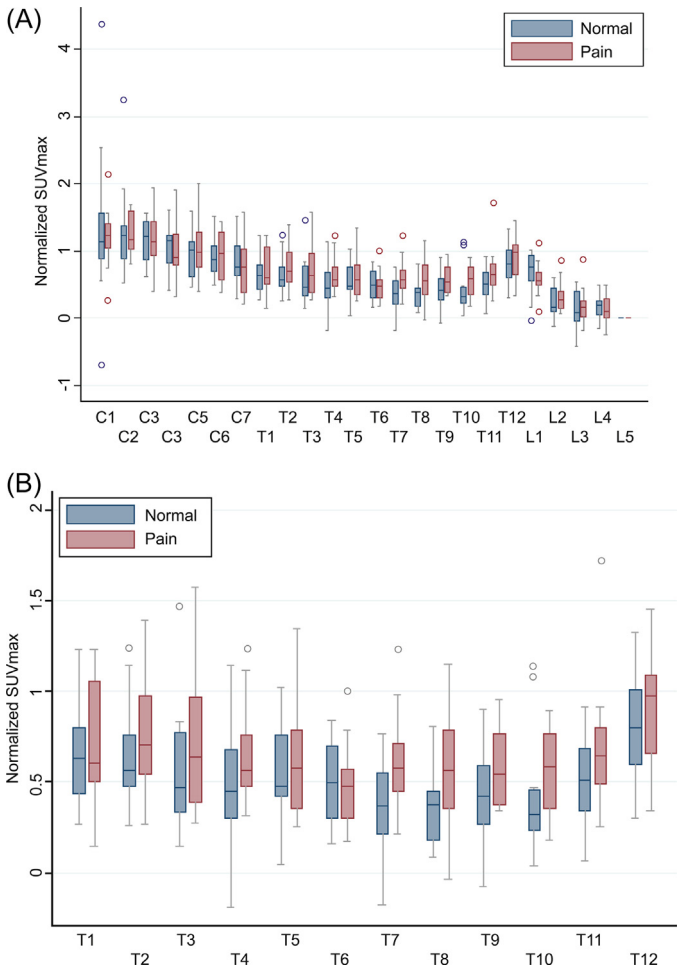

Fig. 2. (A) Normalized SUVmax as a function of vertebral body level is compared between patients with LBP and control subjects. Levels T7, T8, T9, T10, when analyzed jointly, stratified across segment demonstrated statistical significance. (B) Data from thoracic vertebral body levels is presented here only to better illustrate the difference between LBP (Pain) and control patients (Normal).

Representative ^{18}F-FDG PET/CT images from an LBP patient and an asymptomatic patient show differences in ^{18}F-FDG uptake intensity within the spinal canal of the lower thoracic spine (Fig. 3).

4. Discussion

Evaluation of the nervous system's involvement in pain pathways presents many challenges secondary to the relative low metabolic uptake in the spinal canal, small size of the spinal cord, and difficulty in obtaining accurate data. ^{18}F-FDG PET (without CT) has existed for several decades, but significant challenges arise when attempting to localize 18F-FDG uptake in the canal without the aid of the anatomic landmarks provided by CT. To date, only a few ^{18}F-FDG PET studies have attempted to evaluate the spinal cord. One such study used ^{18}F-FDG PET to successfully evaluate patients with cervical myelopathy [16].

Functional and metabolic imaging of the spinal cord using PET/CT is limited but has been growing in popularity. A few studies have attempted to use ^{18}F-FDG PET/CT to evaluate the contents of the spinal canal, including a recent study that identified the normal physiologic uptake of ^{18}F-FDG in the spinal cord in children [17]. There have been additional reports demonstrating the ability of ^{18}F-FDG-PET to predict and follow outcomes in patients with compressive or radiation induced cervical myelopathy [16,18]. In an isolated case, increased ^{18}F-FDG uptake was found in the sciatic

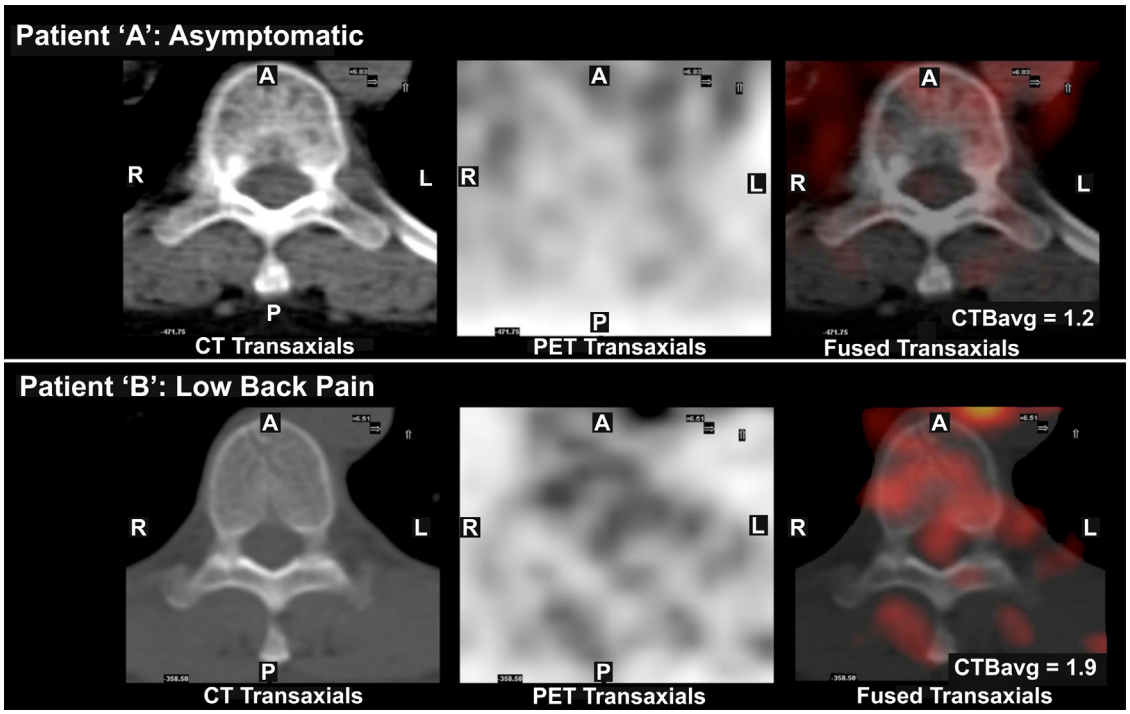

Fig. 3. Representative transaxial ^{18}F-FDG PET/CT images at level T10 (at the mid-vertebral level) from Patient 'A', who was asymptomatic, and patient 'B', who described 'LBP' on the pre-study questionnaire. From left to right, a non-contrast CT, an attenuation corrected ^{18}F-FDG PET only, and an ^{18}F-FDG PET/CT fusion image have been provided for both patients. Increased radiotracer uptake is observed within the spinal canal of patient 'B' relative to patient 'A'. Calculated SUV from ROIs drawn within the spinal canal at this level (ROIs not shown) had values of 1.2 and 1.9 from Patients 'A' and 'B' respectively.

nerve and lower spinal cord in a 78 year-old individual suffering from neuropathy [19].

In this study, we imaged the metabolic activity within the entire length of the spinal canal using ^{18}F-FDG PET/CT and are the first to identify differences in metabolic activity within the spinal canal between LBP patients and pain-free patients. We observed greater ^{18}F-FDG uptake in the caudal aspect of the thoracic spinal canal in subjects describing LBP than in those without pain. Although this increased ^{18}F-FDG uptake could result from inflammation, this observation may be explained partly by increased neurosensory and neuromotor activity in the spinal cord at these levels related to LBP. While there was a significant difference in average age between LBP (mean = 64.5 years) and pain-free groups (mean = 40.7 years), it has been published that cord activity is independent of age during locomotion [20]. Age was not felt to be a confounding factor in this study.

One limitation of this study was the difficulty in obtaining SUVs in the spinal canal, due to the overall low SUVs observed. We compensated for this by using a normalized SUVmax, rather than a normalized average SUV (SUVavg), in order to increase sensitivity for detection of differences in canal metabolism. Other limitations of this study include its retrospective design, lack of a semi-quantitative measure of pain, and lack of more detailed information regarding the location and duration of pain. With the exception of one patient, we minimized the potentially confounding factors of prior chemotherapy, radiation, and surgery by excluding patients who had received these therapies within a 6-month period prior to ^{18}F-PET/CT [21]. Despite these limitations, our initial results support the need for a larger prospective study involving non-cancer patients mirroring the general pain population. Larger patient sample sizes will allow for comparing normalized SUVmax within the spinal canal of patients with pain in other locations, such as the shoulder, knee and hip. Additionally, the use of MRI rather than CT in future studies will be helpful in more accurately delineating the spinal cord and other relevant structures.

This study may help lay the groundwork for the clinical use of ^{18}F-FDG PET/CT for the localization and quantification of pain generators. The ability of ^{18}F-FDG PET/CT to localize tumors has improved cancer treatment, allowing for only the necessary areas to be targeted [22]. Similarly, the ability of ^{18}F-FDG PET/CT to localize nociceptive-related metabolic activity would aid in the treatment of chronic pain, guiding placement of spinal catheters for delivery of analgesics to hypersensitive nerve roots and dorsal root ganglia. Finally, just as ^{18}F-FDG PET/CT is used to evaluate the efficacy of chemotherapy agents in drug development, it could also emerge as an important tool in evaluating both existing pain medications and those in phase II and III clinical drug development trials.

Ethical issues

Informed consent was not required or obtained for this retrospective study, but Ethic Board Approval was obtained. The study protocol was registered with the Stanford University Institutional Review Board but was not registered outside of Stanford University.

Conflicts of interest

The authors have no conflicts of interest to declare.

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