Effects of age and weight on the metabolic activities of the cervical, thoracic and lumbar spines as measured by fluorine-18 fluorodeoxyglucose-positron emission tomography in healthy males

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Abstract
Objective: This study aimed to explore the age and weight-related metabolic trends in the spines of healthy male subjects using fluorine-18 fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) imaging. **Subjects and Methods:** Forty three healthy male subjects (age 23-75 years, weight 50-145kg) were selected from the CAMONA study. A global assessment methodology was applied to the subjects' ^{18}F-FDG 180 minute scans, where each region of the spine (cervical, thoracic and lumbar) was individually encapsulated in a single region of interest, and standardized uptake value (SUVmean) was calculated per respective region. **Results:** SUVmean increased significantly with weight in both the thoracic spine (Slope=0.0066, P= 0.001) and lumbar spine (Slope=0.0087, P<0.0001), but not the cervical spine. There were no significant correlations between age and SUVmean in all three regions. The cervical spine (average SUVmean=1.84±0.31) illustrated elevated activity when compared to the thoracic (average SUVmean=1.46±0.27, P<0.0001) and lumbar (average SUVmean=1.41±0.28, P<0.0001) spines. **Conclusion:** This study illustrated the ability of ^{18}F-FDG PET to assess metabolic processes in the spine. The data provided evidence of weight dependent metabolic activity, likely related to inflammation. This study offers a methodological precedent that can be applied to studies in populations with back pain

Introduction

Survey based studies have estimated chronic back pain to be widely prevalent in the population, especially in older and overweight cohorts [1, 2]. Lower back pain (LBP) has become the principal cause of disability worldwide [3]. Most cases fail to be attributed to any disease or structural abnormality and are consequently classified as "non-specific" [4, 5]. Present clinical treatment of non-specific back pain has been ineffective and inefficient as evidence by the continued prevalence, rising disability [1-3] and economic burden on healthcare systems [6, 7]. Thus, the concise etiology of non-specific back pain has yet to be determined. Epidemiological survey based studies have purported an increasing occurrence of both neck pain (NP) and LBP with age [8]; others have suggested a correlation of weight with back pain, particularly LBP [9-13]. The present body of literature on back pain calls for quantitative studies to examine the influence of age and weight on etiological mechanisms in the spine that may underlie back pain.

Radiological imaging provides the ideal medium to gain insight into biological processes occurring in the spine. Positron emission tomography (PET) allows for quantitative assessment of various metabolic processes in the human body. Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) is the most widely used radiotracer; ^{18}F-FDG is a radioactive analog of glucose that reflects the magnitude of glucose usage in relevant tissues [14]. Tracer uptake is determined by local perfusion and the rate of cellular appropriation. Uptake is normalized to injection dose and body weight as standardized uptake value (SUV) [15]. While ^{18}F-FDG is primarily used in clinical oncology, relevant non-oncological uses of ^{18}F-FDG PET [16] include imaging inflammation [7, 8, 17-19] and red bone marrow activity [20-23]. Accordingly, ^{18}F-FDG PET can be used to study the relationships between the spine's metabolic processes with both age and weight.

Traditional PET image analysis involves a qualitative scoring of the structure of interest. Standard quantitative analysis involves a region of interest (ROI) to be defined within the structure of interest, known as punch biopsy. Quantitative analysis has been proven to be

Global assessment methodologies are more comprehensive than competing methodologies [24, 26, 27]. Instead of the minuscule ROI used in punch biopsy, global analysis encapsulates the whole structure. Global assessment is often accompanied by the use of SUVmean, which consolidates the complete uptake of a structure as opposed to SUVmax [24, 26, 27]. The use of global ROI and SUVmean has been shown to be superior regarding partial volume correction and determining the most representative values for the whole structure [24, 26, 27].

Uncovering the metabolic processes in the spine may lead to greater understanding of the underlying causes of spine related pain. Accordingly, this study aimed to assess inflammation and its correlations with age and weight in healthy males.

Methodology

Subjects and Methods

Forty-three healthy male subjects (age 23-75 years, weight 50-145kg) were selected from the CAMONA study (28-30). The complete number of CAMONA subjects (n=139) was limited to only healthy males (n=47); further, inadequately fasted (<6 hours) subjects were excluded (n=4). The original study, in which all subjects were recruited, deemed said subjects "healthy controls" based on a lack of potentially complicating conditions: illicit drug use, alcohol abuse, prescription medication use, cardiovascular disease, diabetes, oncological disease or immune disorder. Further, this study's subjects were confirmed to not suffer from any confounding spinal disorder (e.g. ankylosing spondylitis) as could be determined from the visual inspection CT data. Fluorine-18-FDG PET/CT imaging was performed according to previously published methods [28]. Subjects were scanned on a hybrid PET/ CT system (GE Discovery STE, VCT, RX, and 690/710 systems) 180 minutes after an intravenous injection of 4.0MBq of ^{18}F-FDG per kilogram of body weight. A longer time period of 180 minutes was chosen to limit the influence of the blood pool uptake on subsequent measurements.

Data Collection

Fluorine-18-FDG PET/CT images were analyzed using OsiriX software; Pixmeo SARL Bernex, Switzerland (version 7.04). Positron emission tomography and CT were co-registered, allowing us to identify anatomical landmarks in the spine with the CT and quantify functional information from the PET. The whole spine was divided into separate anatomical regions, cervical (C1-C7), thoracic (T1-T12) and lumbar (L1-L5), where each region was quantified individually with the following methodology. A maximum intensity projection (MIP) of the PET/CT was utilized to remove all bone unrelated to the structured desired (e.g. cervical or thoracic spine). Segmentation and quantification were based on a region growing threshold algorithm applying segmentation parameters with limits of (lower/upper bounds) 85/1500 Hounsfield units (HU) on the CT image. Seeding points were manually defined on the cortical bone of the desired vertebral region

to allow the application of the semi-automatic three-dimensional segmentation. The final computed region of interest was redefined by using morphology altering algorithms or manual additions and deletions. Regions of interest were placed to encapsulate the entire segmented spinal region. In each region of the spine that was analyzed, the ROI included vertebral bodies, intervertebral discs, facet joints, spinal processes, lamina and the spinal canal. Quantitative metrics were subsequently derived based on the segmented area.
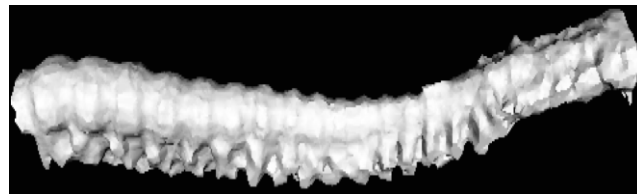

Figure 1. This image is the three-dimensional volumetric representation of the CT segmented axial spine ROI in a sample subject. The gross anatomy previously mentioned is represented. The ^{18}F-FDG uptake within this volume was used in further quantitative analysis (OsiriX software: version 7.04; Pixmeo SARL Bernex, Switzerland).

Global Assessment and Statistics

Points of uptake within the axial ROI were averaged and presented as ROImean. The axial ROI also provided its total area, ROIarea, in cm^2. The following computation (Figure 2) was utilized to derive the SUVmean, which represents the global uptake per area of the complete structure of interest. Bivariate correlations, including linear correlations, correlation t-tests and paired t-tests, were performed. P values of less than 0.01 were considered significant. The variables R^2 and P were used to represent coefficient of determination and P value, respectively.

$$ROI_{axialmean} * ROI_{axialarea} = Uptake_{axialnet} \quad (1)$$

$$\sum_{ExtremeAxial1}^{ExtremeAxial2} Uptake_{axialnet} = Uptake_{structurenet} \quad (2)$$

$$\sum_{ExtremeAxial1}^{ExtremeAxial2} ROI_{axialarea} = Area_{structurenet} \quad (3)$$

$$Uptake_{structurenet}/Area_{structurenet} = SUV_{mean} \quad (4)$$

Figure 2. The equations above mathematically express the derivation of the SUVmean (LaTeX).

Results

This study's subjects had a minimal relationship (R^2=0.01, P=0.51) between age and weight.

Multiple paired t-tests were performed to compare the regional uptakes within the spine. The cervical region (average SUVmean=1.84±0.31) expressed greater uptake as compared to the thoracic (average SUVmean=1.46±0.27, P<0.0001) and lumbar (average SUVmean=1.41±0.28, P<0.0001).

The thoracic spine had greater uptake than the lumbar (P= 0.02) though this was not deemed significant given our standards.
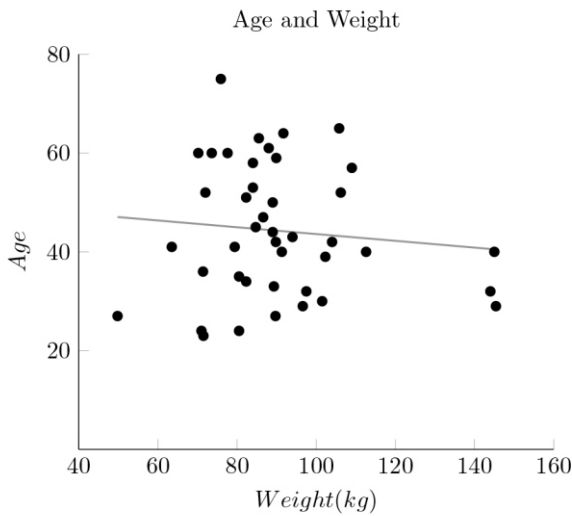

Figure 3. The plot illustrates the relationship between age and weight within the group of subjects in the study (LaTeX).
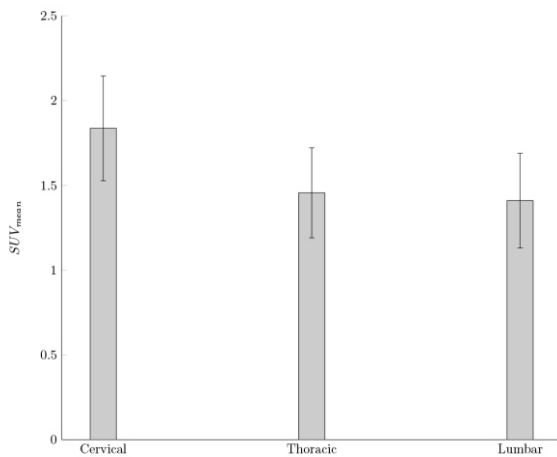

Figure 4. The average SUVmean of each region is illustrated with standard error bars expressing the relative standard deviation (LaTeX).

The cervical (R^2=0.10, P=0.04) spine lacked significant correlation with weight. Both the thoracic (R^2=0.24, P=0.001) and lumbar (R^2=0.24, P<0.001) regions illustrated statistically significant positive correlations with increasing weight; the lumbar yielded the largest increase in SUVmean per kilogram.

Age failed to yield statistically significant correlation with SUVmean in all three regions.

Discussion

This study derived SUVmean in the cervical, thoracic and lumbar spines of each subject. Weight proved to be significantly correlated to ^{18}F-FDG uptake in the thoracic (P=0.001) and lumbar (P<0.0001) spines but not in the cervical spine (P=

0.04). This is likely due to the weight bearing functions of the thoracic and lumbar spines. Higher body weight appears to place greater pressure on the osseous tissues in the weight bearing spines, given that every vertebra supports the weight above its axial position [31] and the surface area to volume ratio between bone and body mass [32]. Multiple osseous processes can culminate in greater ^{18}F-FDG activity in response to elevated mechanical load. Mechanical stress is sensed by the bone and subsequent cellular responses are demonstrated through a process known as mechanotransduction [33]. Physiologically acceptable increases in mechanical load result in stronger osseous tissue as a result of remodeling via cellular differentiation [34] and coordinated osteoclastic-osteoblastic activity [35]. In response to greater and more dynamic mechanotransduction, a pro-inflammatory response through the NF-kB signaling cascade is expressed [33]. Such mechanisms may be present in those of greater weight as such populations often have elevated levels of various pro-inflammatory cytokines [36] and such cytokines have been associated with increased bone turnover activity [37-39]. Inflammatory responses in the bone marrow would be expressed in elevated ^{18}F-FDG uptake [19, 23]. To note, elevated pressure on the spine increases the fracture rates, especially in osteoporotic populations [40]. Even minor indiscernible fractures will result in regions of cellular proliferation and inflammatory activity during the regenerative period [41-43]. Increased mechanical stress is transferred to the intervertebral discs, as well. Increased weight load compresses the discs and leads to a decrease in disc height [13]. This compressive force on the disc tissue leads to degeneration, namely expressed as inflammatory activity [10, 18, 44]. Increased cellular glycolic activity, observed as increased SUVmean, would arise in all such weight stimulated processes, especially in the weight bearing spines (thoracic and more so lumbar). The cervical spine would be expected to respond less significantly to weight given the minimal weight supported by the region; this aligned with our results.

Table 1. This table expresses the characteristics of the linear correlation between SUVmean and age in the spine.

Region	Coefficient of Determination	P Value
Cervical	0.004	0.69
Thoracic	0.013	0.47
Lumbar	0.017	0.41

Increased ^{18}F-FDG activity has been previously observed in the cervical spine [45, 46] and has been popularly attributed to elevated grey matter in the spinal cord from C4-C8 [45, 47]. Further, there is spinal cord enlargement from C3 to T2 which increases the propensity for greater ^{18}F-FDG uptake in the cervical spine. Given the inclusion of the spinal cord in the global assessment methodology, such anatomical reasoning may explain the increased average SUVmean in the cervical spine (cervical>thoracic/lumbar, P<0.0001/<0.0001).
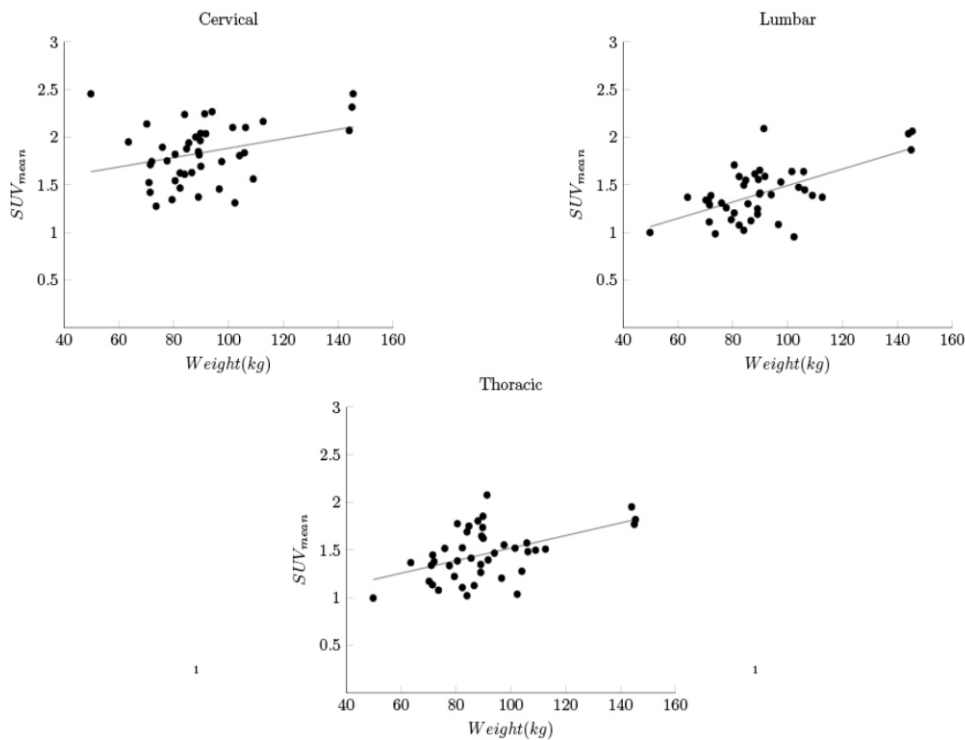
Figure 5. The plots above illustrate the relationships between weight and uptake in each region of the spine (LaTeX).

The relatively minimal influence of the spinal cord in the lumbar and thoracic spine may explain the lesser average SUVmean.

Our study did not observe any significant correlation between SUVmean and age, across all regions of the spine. The process of aging is accompanied by a loss of red bone marrow via a conversion to yellow marrow, a form of adipose tissue [48]. Further, red bone marrow volume [49, 50] and activity [51] decreases with age. The sum processes in marrow would hamper red bone marrow activity and reduce ^{18}F-FDG uptake; such was observed by Fan et al. (2007) [21]. Alternatively, increased inflammation has been associated with age in both osseous tissues [43, 52] and intervertebral discs [52, 53]. Processes regarding bone marrow and inflammation would be counteractive in assessing SUVmean with age given the non-specificity of ^{18}F-FDG. Such counteraction may explain the absence of correlation between age and SUVmean. This explanation is supported by Aliyev et al. (2012) observation of increased age-related inflammation (via ^{18}F-FDG uptake) by structures that lack bone marrow [52]. Additionally, weight was the preferred measure of vertebral load, as BMI normalization with height fails to account for the surface area to volume relationship between bone and body weight [32]; similar reasoning accounts for the use of SUVmean as opposed to alternative measures SUVbsa or SUL.

There are potential limitations to this study. The subjects of this study were limited to the male sex. Females often suffer from more severe osteoporosis and relevant complications which are heavily influenced by menopause. As such, the variable nature of menopausal onset [54] could contaminate the observation of a uniform aging process in the spine and potentially weight related matters as well. While the alignment of our study's results with epidemiological findings of back pain suggests that inflammation may offer a partial etiology for weight related non-specific back pain, there was no information as to whether subjects suffered from any spine related pain; therefore, such results cannot yet be deemed directly determinative of pain. Accordingly, a larger PET study of subjects with non-specific back pain is required to fully elucidate the implications of these findings.

In conclusion, this study has illustrated the potential of ^{18}F-FDG PET in assessing metabolic processes in the spine. While the non-specificity of ^{18}F-FDG complicated the global assessment of age related inflammation, this study provided likely evidence of weight dependent inflammation in the thoracic and lumbar spines. Our study provides a metabolic understanding of the spine with age and weight; accordingly, this study offers a precedent which should be expanded upon by further PET studies in populations affected by back pain.

The authors declare that they have no conflicts of interest.

Bibliography

1. Gerhardt A, Hartmann M, Blumenstiel K et al. The Prevalence Rate and the Role of the Spatial Extent of Pain in Nonspecific Chronic Back Pain-A Population-Based Study in the South-West of Germany. *Pain Medicine* 2014; 15(7): 1200-10.
2. Rosario-MEDERI B, do Maranhão SL, de Oncologia M, Garcia J. Prevalence of low back pain in Latin America: a systematic literature review. *Pain Physician* 2014; 17: 379-91.
3. Buchbinder R, Blyth FM, March LM et al. Placing the global burden of low back pain in context. *Best Practice & Res Clin Rheumatol* 2013; 27(5): 575-89.
4. Balagué F, Mannion AF, Pellisé F, Cedraschi C. Non-specific low back

pain. *The Lancet* 2012; 379(9814): 482-91.

5. Kuijer PPF, van der Molen HF, Schop A et al. Annual incidence of non-specific low back pain as an occupational disease attributed to whole-body vibration according to the National Dutch Register 2005–2012. *Ergonomics* 2015; 58(7): 1232-8.

6. Kleinman N, Patel AA, Benson C et al. Economic burden of back and neck pain: effect of a neuropathic component. *Population Health Management* 2014; 17(4): 224-32.

7. North RB, Shipley J, Wang H, Mekhail N. A review of economic factors related to the delivery of health care for chronic low back pain. *Neuromodulation: Technology at the Neural Interface* 2014; 17(S2): 69-76.

8. Friedly J, Standaert C, Chan L. Epidemiology of spine care: the back pain dilemma. *Phys Med and Rehabilitation Clinics of North Amer* 2010; 21(4): 659-77.

9. Häuser W, Schmutzer G, Brähler E et al. The impact of body weight and depression on low back pain in a representative population sample. *Pain Medicine* 2014; 15(8): 1316-27.

10. Walter B, Korecki C, Purmessur D et al. Complex loading affects intervertebral disc mechanics and biology. *Osteoarthritis and Cartilage* 2011; 19(8): 1011-8.

11. Shiri R, Karppinen J, Leino-Arjas P et al. The association between obesity and low back pain: a meta-analysis. *Amer J Epidemiol* 2009; 171(2): 135-54.

12. Hershkovich O, Friedlander A, Gordon B et al. Associations of body mass index and body height with low back pain in 829,791 adolescents. *Amer J Epidemiol* 2013; 178(4): 603-9.

13. Lidar Z, Behrbalk E, Regev GJ et al. Intervertebral disc height changes after weight reduction in morbidly obese patients and its effect on quality of life and radicular and low back pain. *Spine* 2012; 37(23): 1947-52.

14. Wiebe LI. FDG Metabolism: Quaecumque Sunt Vera…. *J Nucl Med* 2001; 42(11): 1679-81.

15. Kurdziel KA, Shih JH, Apolo AB et al. The kinetics and reproducibility of ^{18}F-sodium fluoride for oncology using current PET camera technology. *J Nucl Med* 2012; 53(8): 1175-84.

16. Zhuang H, Codreanu I. Growing applications of FDG PET-CT imaging in non-oncologic conditions. *J Biomed Res* 2015; 29(3): 189.

17. Glaudemans AW, de Vries EF, Galli F et al. The Use of F-FDG-PET/CT for diagnosis and treatment monitoring of inflammatory and infectious diseases. *Clin Developm Immunol* 2013; 2013.

18. Daley J, Shearer J, Mastrofrancesco B, Caldwell M. Glucose metabolism in injured tissue: a longitudinal study. *Surgery* 1990; 107(2): 187-92.

19. Yamada S, Kubota K, Kubota R et al. High accumulation of fluorine-18-fluorodeoxyglucose in turpentine-induced inflammatory tissue. *J Nucl Med* 1995; 36(7): 1301-6.

20. Plantade A, Montravers F, Selle F et al. Diffusely increased F-18 FDG uptake in bone marrow in a patient with acute anemia and recent erythropoietin therapy. *Clin Nucl Med* 2003; 28(9): 771-2.

21. Fan C, Hernandez-Pampaloni M, Houseni M et al. Age-related changes in the metabolic activity and distribution of the red marrow as demonstrated by 2-deoxy-2-[F-18] fluoro-D-glucose-positron emission tomography. *Mol Imag Biol* 2007; 9(5): 300.

22. Murata Y, Kubota K, Yukihiro M et al. Correlations between ^{18}F-FDG uptake by bone marrow and hematological parameters: measurements by PET/CT. *Nucl Med Biol* 2006; 33(8): 999-1004.

23. Salaun PY, Gastinne T, Bodet-Milin C et al. Analysis of ^{18}F-FDG PET diffuse bone marrow uptake and splenic uptake in staging of Hodgkin's lymphoma: a reflection of disease infiltration or just inflammation? *Europ J Nucl Med Mol Imag* 2009; 36(11): 1813-21.

24. Peter J, Houshmand S, Werner TJ et al. Novel assessment of global metabolism by ^{18}F-FDG-PET for localizing affected lobe in temporal lobe epilepsy. *Nucl Med Comm* 2016; 37(8): 882-7.

25. Al-Nabhani KZ, Syed R, Michopoulou S et al. Qualitative and quantitative comparison of PET/CT and PET/MR imaging in clinical practice. *J Nucl Med* 2014; 55(1): 88-94.

26. Basu S, Zaidi H, Houseni M et al. Novel quantitative techniques for assessing regional and global function and structure based on modern imaging modalities: implications for normal variation, aging and diseased states. *Sem Nucl Med* 2007: Elsevier.

27. Sadıç M, Houshmand S, Alavi A. Quantitative Global Disease Assessment of FDG-PET/CT Yeni Bir Teknik: FDG-PET/CT ile Quantitative Global Hastalık Degerlendirme. *J Clin Anal Med* 2015;6(3):-doi:10.4328/MJCAM.3573

28. Blomberg BA, Thomassen A, Takx RA et al. Delayed ^{18}F-fluorodeoxyglucose PET/CT imaging improves quantitation of atherosclerotic plaque inflammation: results from the CAMONA study. *J Nucl Cardiol* 2014; 21(3): 588-97.

29. Blomberg BA, Thomassen A, Takx RA et al. Delayed sodium ^{18}F-fluoride PET/CT imaging does not improve quantification of vascular calcification metabolism: results from the CAMONA study. *J Nucl Cardiol* 2014; 21(2): 293-304.

30. Blomberg BA, de Jong PA, Thomassen A et al. Thoracic aorta calcification but not inflammation is associated with increased cardiovascular disease risk: results of the CAMONA study. *Europ J Nucl Med Mol Imag* 2017; 44(2): 249-58.

31. Pal G, Routal R. A study of weight transmission through the cervical and upper thoracic regions of the vertebral column in man. *J Anat* 1986; 148: 245.

32. Haldane JBS. On being the right size: na; 1928.

33. Huang H, Kamm RD, Lee RT. Cell mechanics and mechanotransduction: pathways, probes, and physiology. *Amer J Physiol-Cell Physiol* 2004; 287(1): C1-C11.

34. Kobayashi N, Inaba Y, Tateishi U et al. New application of ^{18}F-fluoride PET for the detection of bone remodeling in early-stage osteoarthritis of the hip. *Clin Nucl Med* 2013; 38(10): e379-e83.

35. Knapik DM, Perera P, Nam J et al. Mechanosignaling in bone health, trauma and inflammation. *Antioxidants & Redox Signaling* 2014; 20(6): 970-85.

36. Guri AJ, Bassaganya-Riera J. Systemic Effects of White Adipose Tissue Dysregulation and Obesity-Related Inflammation. *Obesity* 2011; 19(4): 689-700.

37. Jilka RL, Hangoc G, Girasole G et al. Increased osteoclast development after estrogen loss: mediation by interleukin-6. *Science* 1992; 257(5066): 88-91.

38. Mundy GR. Osteoporosis and inflammation. *Nutrition reviews* 2007; 65(suppl 3): S147-S51.

39. Bertolini DR, Nedwin GE, Bringman TS et al. Stimulation of bone resorption and inhibition of bone formation in vitro by human tumour necrosis factors. *Nature* 1986; 319(6053): 516-8.

40. Tanaka S, Kuroda T, Saito M, Shiraki M. Overweight/obesity and underweight are both risk factors for osteoporotic fractures at different sites in Japanese postmenopausal women. *Osteopor Intern* 2013; 24(1): 69-76.

41. Crönlein M, Rauscher I, Beer AJ et al. Visualization of stress fractures of the foot using PET-MRI: a feasibility study. *Europ J Medic Res* 2015; 20(1): 99.

42. Schmitz A, Risse J, Textor J et al. FDG-PET findings of vertebral compression fractures in osteoporosis: preliminary results. *Osteopor Intern* 2002; 13(9): 755-61.

43. Jakab L. Bone tissue: rebuilding and inflammation. *Orvosi hetilap* 2014; 155(40): 1575-83.

44. Rosen RS, Fayad L, Wahl RL. Increased ^{18}F-FDG uptake in degenerative disease of the spine: characterization with ^{18}F-FDG PET/CT. *J Nucl Med* 2006; 47(8): 1274-80.

45. Do BH, Mari C, Tseng JR et al. Pattern of ^{18}F-FDG uptake in the spinal cord in patients with non-central nervous system malignancy. *Spine* 2011; 36(21): E1395-E401.

46. McCarville MB, Monu N, Smeltzer MP et al. PET-CT of the normal spinal cord in children. *Academic Radiol* 2009; 16(7): 881-5.

47. Kameyama T, Hashizume Y, Sobue G. Morphologic features of the normal human cadaveric spinal cord. *Spine* 1996; 21(11): 1285-90.

48. Takeshita S, Fumoto T, Naoe Y, Ikeda K. Age-related marrow adipogenesis is linked to increased expression of RANKL. *J Biol Chem* 2014; 289(24): 16699-710.

49. Herrmann J, Krstin N, Schoennagel BP et al. Age-related distribution of vertebral bone-marrow diffusivity. *Europ J Radiol* 2012; 81(12): 4046-9.

50. Jie H, Hao F, Na LX. Vertebral bone marrow diffusivity in healthy adults at 3T diffusion-weighted imaging. *Acta Radiol* 2016; 57(10): 1238-43.

51. Huovinen V, Saunavaara V, Kiviranta R et al. Vertebral bone marrow glucose uptake is inversely associated with bone marrow fat in diabetic and healthy pigs: [^{18}F] FDG-PET and MRI study. *Bone* 2014; 61: 33-8.

52. Aliyev A, Saboury B, Kwee TC et al. Age-related inflammatory changes in the spine as demonstrated by ^{18}F-FDG-PET: observation and insight into degenerative spinal changes. *Hell J Nucl Med* 2012; 15(3): 197-201.

53. Molinos M, Almeida CR, Caldeira J et al. Inflammation in intervertebral disc degeneration and regeneration. *J Royal Soc Interf* 2015; 12(104): 20141191.

54. Georgakis MK, Thomopoulos TP, Diamantaras A-A et al. Association of age at menopause and duration of reproductive period with depression after menopause: a systematic review and meta-analysis. *JAMA psychiatry* 2016; 73(2): 139-49.