Repeated Ct-based Hounsfield Unit Measurements as a Proxy Measure of Intercorporeal Bone Graft Remodelling Towards Spinal Fusion; a Feasibility Study.

JFH Reijmer

Rijnstate Hospital

LD Jong

Rijnstate Hospital

M. C. Kruyt

University Medical Center Utrecht

MJ van Gorp

Rijnstate Hospital

JLC van Susante (✉ JvanSusante@Rijnstate.nl)

Rijnstate Hospital

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Abstract

Background: There is a lack of knowledge about the biological process of intercorporeal bone graft remodelling towards successful lumbar spine fusion with bridging vital bone between two adjacent vertebrae. Hounsfield Units (HU) highly correlate with Bone Mineral Density (BMD) and changes in HU may be valuable as proxy measure to monitor ongoing fusion. The aims of this study were to explore the feasibility to quantify BMD changes in the intercorporeal bone graft after spinal fusion on consecutive CT-scans, and to explore whether trends in the individual changes in HU over time may serve as a proxy measure for successful fusion or non-fusion.

Methods: A retrospective case series was conducted using available one-year and two-year CT-data from patients after posterior lumbar interbody fusion surgery. First, a standardized measuring procedure was developed, incorporating internal phantomless calibration, to establish the HU values of the grafted region of interest using consecutive CT-slices. Subsequently, changes in the participants' bone graft HU over time between their first and second year after surgery were explored.

Results: Between one and two years after surgery, seven out of nine (78%) participants showed an increase in their bone grafts' HU, ranging from 3% to 41%. In two participants HU-values decreased 14% and 32%, respectively. The intraobserver reliability of the HU measuring procedure was excellent (ICC 0.93 (95% confidence interval 0.91 to 0.95)).

Conclusion: The majority (78%) of participants in the current study showed increases in their bone graft HU, which suggests ongoing bone graft remodelling towards lumbar fusion. This result corresponds with the established percentages of achieved rigid bony fusion after lumbar spinal fusion surgery reported in the literature. Thus, prospective follow-up of CT-based HU measurements may have potential as diagnostic measure to monitor bone graft remodelling in time and trends may predict successful fusion or non-fusion. The measurement procedure developed in this study, using internal phantomless calibration, showed excellent intraobserver reliability and merits further study in larger patient numbers.

Introduction

Lumbar spinal fusion is a surgical procedure that is widely used for the treatment of a variety of spinal disorders (1). The use of this procedure has increased in many Western countries (2, 3). For example, the incidence of spine fusion surgery in the United States has increased with 32% between 2004 and 2015 (4). Surgical techniques to achieve fusion differ and consensus regarding a superior technique is lacking (5–7). To date, posterior lumbar interbody fusion (PLIF) is the most frequently used technique for spinal fusion (8). This technique uses a dorsal approach to remove the intervertebral disc, to insert a intervertebral cage for stability purposes and to impact autologous decompressive bone behind this cage (8). Over time, the non-vital bone graft is expected to remodel towards new vital bone, thereby creating a sustainable fusion between two lumbar vertebral bodies. Ideally, this ultimately results in solid bridging of the bone graft and a corresponding rise in Bone Mineral Density (BMD). When bone remodelling and

subsequent fusion fail to establish, pseudoarthrosis will occur. This important and well-known complication occurs in 5-35% of patients treated with spinal fusion, which can lead to complaints of pain and a decrease in functional status (9). Subsequent revision surgery for symptomatic pseudoarthrosis is performed in up to 24% of patients (10).

In daily clinical practice, many orthopaedic surgeons and radiologists use their patients' computed tomography (CT) scan images to assess whether bone graft remodeling and sustainable spinal fusion have occurred. In general, solid interbody bony bridging between vertebrae takes approximately one to two years. However, objectively assessing bone remodelling and true fusion remains a challenge (11–15) and the use of several different fusion criteria in studies (12, 16) is not conducive to draw unequivocal conclusions about these patients' outcomes. For example, the most commonly used assessment methods for this purpose, such as the Bridwell or the Brantigan-Steffee criteria (17–19), have questionable reliability as well as questionable validity because of the discrepancy between radiological assessment and surgical exploration (12, 20, 21). Because of these limitations, less subjective and more valid and reliable quantitative methods to assess either intercorporate bone remodeling and sustainable fusion are needed.

One way to obtain quantitative information about changes in remodeling of bone is to establish the bone grafts' Hounsfield Units (HU) repeatedly. HU are derived from CT-imaging attenuation and measuring HU offers a promising method to objectively quantify bone expansion or resorption in e.g. instrumented areas in the spine. As such, changes in HU over time may be interpreted as a proxy measure for the process and quality of interbody bone remodelling over time (17, 22). For example, a downward trend in HU over time could be used as an early indicator of bone resorption, potential failure to achieve intercorporate bony fusion and possibly the development of pseudoarthrosis. Consequently, the orthopaedic surgeon can use this information to tailor the patients' treatment plan. The use of HU as a means to assess biological activity and increased bone mineral content after lumbar fusion surgery was first described in the early 2000's (23, 24). Unfortunately, these studies did not provide information about individual patient trends in bone remodelling over time because the bone grafts' HU were only established once. Other studies have only described bone remodelling processes qualitatively or in general terms of radiological graft changes around the bone fusion site (25, 26). The varying limitations of the studies described above, and the advances in medical imaging since the previous studies were published (27), led us to explore whether it was feasible to assess individual intercorporate bone graft remodelling on repeated CT-based Hounsfield Units after lumbar spondylodesis, and to explore changes in HU between one and two years after surgery.

Methods

Aims

The aims of this study were to explore whether it was feasible to assess intercorporate bone graft remodelling by determining CT-based values of HU after lumbar spondylodesis, and to explore trends in

the individual changes in HU over time as a proxy measure of the bone graft remodelling process towards intercorporal fusion or non-fusion.

Design and participants

We conducted a retrospective analysis of a subsample of available data from a previous fusion trial (28). The current study included patients from one of the participating centres with a one-year and two-year lumbar CT-scan and who were treated with a single-level Posterior Lumbar Interbody Fusion (PLIF) including insertion of a polyetheretherketone (PEEK) cage. At the time of surgery, a bilateral partial facetectomy for decompression was performed and the harvested decompressive bone was used as an autologous bone graft for impaction in the disc space behind the cage. Only participants with 'doubtful fusion' or 'non-union' one year after their PLIF (as judged on CT-scans (12, 29)) had a second CT-scan at 2 year follow-up and could thus be included in this study.

CT-scanning procedure

Participants were scanned on one of three different scanners (Philips iCT 256, Philips Brilliance 40, Siemens Emotion 16) using different kernels (HNP/Myelo and Trauma protocols), kilovoltage peaks (ranging between 100-140) and filter types (A or D). CT-scanner quality control was performed weekly by using air calibration and image quality checks.

Hounsfield Unit measurement procedure

First, using the dynamic oblique multiplanar reformatting option of the Sectra IDS7 software program, each participant's CT-scan was positioned with the lower endplate of the vertebrae above, and the upper endplate below the grafted area aligned as horizontally as possible. Each image was saved in a 1mm slice thickness setting and then viewed using the Sectra UniView medical image viewer with the dorsal structures displayed on the right. Subsequently, the observer scrolled through the different sagittal CT-slices to judge in which of these the largest and most hyperintense region of bone graft was visible. This slice was chosen as the primary slice of interest (pSOI) and used as the starting point for all subsequent HU measurements. To ensure that the exact same pSOI could be localised for the intraobserver reliability measurements, as well as for the two-year follow-up CT-scans, the observer scrolled through the sagittal CT-slices from the pSOI until the first available cage marker was visible. This cage marker was used as the reference slice to re-identify the pSOI.

Second, using the software program's freehand drawing option, in the pSOI a region of interest (ROI) was demarcated around the visible area of the bone graft, resulting in an automatically calculated HU value (see Figure 1). Care was taken that the ROI did not include the adjacent lumbar body endplates nor the cage. The latter was ensured by consistently demarcating the ROI posterior to the reference cage marker in all CT-slices used. This exact same procedure was repeated using five adjacent CT-slices to the participant's right and four to the participant's left of the pSOI, respectively. Subsequently, the resulting HU values from all CT-slices were summed and divided by the number of each participant's available CT-

slices (typically ten) to obtain a standardised estimate (mean) of the bone graft's HU both for the one-year and two-year CT-scan slices.

Calibration correction factor

Eight of the nine participants included in the current study had their baseline and follow-up CT-scans taken using different CT-scanners and scanner settings. Because these differences can potentially influence the HU measurement values (30–32) (see Figure 2A and 2B), establishing an internal correction factor was deemed necessary to mutually calibrate the patients' one-year and two-year CT-scans.

Previous research has shown that aortic blood and the psoas major muscle can be used as substitutes for phantomless calibration of HU to BMD on CT-imaging (33–36) since these tissues have stable HU values over time. Therefore, we first established the HU of these tissues at the one-year and two-year follow-up timepoints for each participant. The procedure used for this was similar to the one used to establish the ROIs in the bone grafts. The only difference was that the software program's circular shape drawing function was used on axial CT-scans of ten consecutive 1mm CT-slices of aortic blood and the left and right psoas muscle at the same vertebral level of instrumentation. Care was taken that the ROIs did not include visible areas of atherosclerosis and fatty muscle (see Figure 2). Resulting HU values of the 10 consecutive CT-scan slices of each of the three different tissues (right psoas muscle, left psoas muscle and aortic blood) were summed and divided by 10 to obtain a standardised estimate of each tissue's HU. This was done for the one-year and two-year CT-scans. The averaged baseline and follow-up HU values were then used to calculate each patient's specific 'internal correction factor' (ICF).

For calibration purposes the two-year mean HU values were multiplied by the ICF. The ICF was calculated using the following formula:

$$(((PrT1/PrT2) + (PIT1/PIT2)) / 2 + (AbT1/AbT2)) / 2.$$

First the right psoas muscle HU-value at one year (PrT1) was divided by its two-year HU-value (PrT2). The same calculation was used for the left psoas muscles (PIT1 and PIT2). Because both these values represent similar muscle tissue, they were added and divided by two. Then the aortic blood HU-value at one year (AbT1) was divided by its two-year HU-value (AbT2). Finally, the resulting HU-values of muscle tissue and aortic blood were added and divided by two. A correction factor of 1 was defined as there being no difference in HU between the two CT images with one-year interval. Each participant's bone graft mean HU value at two years was multiplied by the correction factor.

Reliability of bone graft measurement protocol

After development of the HU measurement procedure, a pretest was conducted to establish the method's intraobserver reliability. For this pretest, one observer (JFHR) established the values of the bone grafts' HU using each patient's available one-year postoperative CT-scan slices and repeated the same procedure two weeks later. The same procedure was repeated using the two-year follow-up CT-scan slices.

Statistical analysis

Participant characteristics were summarized descriptively. The participants' standardised estimate of the bone graft's HU established using the one- and two-year CT-scans were summarized descriptively using means (standard deviations). The change in the overall mean bone graft HU values from one to two years after surgery was also expressed as a percentage.

Intraclass correlation coefficients (ICC) estimates and their 95% confidence intervals (CI) were calculated based on a single-rater, consistency, two-way mixed-effects model for both the one- and two-year CT-scan slice measurements. All data were analysed using IBM SPSS Statistics for Windows (Version 25.0; IBM Corp, Armonk, NY).

Results

Patient characteristics

The patient group consisted of six (66%) male and three (33%) female participants. The mean age was 56 years (range 47 to 70 years). The fused segments were L4-L5 (33%) and L5-S1 (67%).

Bone graft measurements

The participants' change in bone graft HU values at one-year and two-years are presented in Figure 3A and their changes over time are visualized in Figure 3B. Seven participants showed an increase in their HU over time, representing a change between 3–41%. The two participants who had a decrease in their overall HU showed a change of -14% and -32%, respectively. The internal correction factors ranged between 0.66 and 1.49. One participant was scanned on the same scanner with identical setup at both one- and two-years postoperatively. The corresponding internal correction factor of this patient was 0.95.

Intraobserver reliability

In total, one observer assessed 174 CT-slices of the nine participants using their one-year, and another 174 CT-slices using their two-year CT scans. The resulting ICC was 0.93 (95% CI 0.91 to 0.95).

Discussion

The aims of this study were to explore whether it was feasible to assess intercorporal bone graft remodelling in time by determining the bone grafts' CT-based HU after lumbar spondylodesis, and to explore whether trends in the individual changes in HU over time may serve as a proxy measure to predict fusion or non-fusion. The results of this retrospective case series showed that the developed HU measurement procedure was feasible in terms that the observer could consistently demarcate the same region of interest on CT-scan slices. The resulting excellent intraobserver reliability of the measurements (ICC 0.93)(37) suggests that our HU measurement procedure can be highly reproducible on an individual observer's basis, and this gave us the confidence to subsequently explore the participants' intercorporal bone graft remodelling using the CT-based values of HU and their changes over time. The latter analysis

showed that 7 out of 9 participants showed increased HU over time from one to two years after their PLIF surgery, which corresponds with recognized successful fusion rates from literature.

To our knowledge, only two previous studies have investigated changes in HU over time as a proxy measure of the bone graft remodelling process after spondylodesis. One of these studies (23), published almost 20 years ago, revealed an increase of 23% in HU of the autografts inside fusion cages one year after surgery. Subsequently, a decrease in HU of 6% was detected at two years. However, comparison of these results with our study is hindered by the fact that patient data were pooled while individual trends are presented in the current study. In addition, in the previous study HU were assessed in bone graft placed within versus behind cages. This fact, in combination with the use of early generation CT scanners, may have introduced susceptibility to artefact influence and bias from limitations in calibration. A second study also reported a positive trend, i.e. increasing HU-values in individual patients' intercorporate bone grafts after spondylodesis up to two years after spinal fusion surgery (24). However, in this study single measurements of participants' bone graft HU-values were used for pooled trend analysis. Also, both available studies did not include validation of the HU measurement procedures using internal or external calibration methods. For this reason, we chose to develop a CT-based HU measurement procedure using modern CT and software applications, test its intraobserver reliability and subsequently explore individual patients' bone graft HU both at one year and two years after surgery.

Given the positive association between HU and BMD (38, 39), the increases in HU values of seven of our participants suggests that their bone was still remodelling up to two years after surgery. Intuitively, this increasing bone density may reflect ongoing fusion but this relation remains uncertain. Conversely, in the two participants (22%) that showed a decrease in their HU, this may indicate bone resorption which could lead to fusion failure and pseudoarthrosis. This latter finding is in line with research showing that 5–35% of patients develop pseudoarthrosis after spine fusion surgery (9).

The goal of lumbar interbody fusion surgery is to create rigid bony fusion between lumbar vertebral bodies through intercorporate bone graft remodelling between two adjacent vertebrae (40). However, current imaging techniques cannot reliably detect or quantify ongoing fusion (failure). Different radiographic scoring criteria are used (18, 41, 42). However, since these scoring criteria use semi-subjective non-quantitative assessments (17–19), and a questionable reliability (16, 43) and validity (20, 21), research into more objective, reliable and valid measures is warranted. We argue that assessing patients' intercorporate bone grafts using CT-based HU after lumbar spondylodesis could be a valuable and reliable adjunct to, and a proxy measure of, bone remodelling towards intercorporate fusion or non-fusion. Monitoring patients' HU-values over time after surgery could assist orthopaedic surgeons in gauging whether bone is remodelling toward fusion, non-fusion or whether the process of bone remodelling has stabilised. Future research could explore whether HU can be used to assess actual fusion between vertebrae. For example, monitoring the development of the grafts' HU over time repeatedly until a stable HU-value over the full range of the grafted area from the upper to the lower vertebral endplate has been achieved, combined with no signs of instability or radiolucency around the graft (17, 22, 44) could

assist in determining actual bony fusion between vertebrae, or whether longer follow-up is needed to determine fusion status.

This study has several limitations. First, the sample size was small, which hinders generalizability of the results. Still with this exploratory study we aim to present a validated concept which can be used in future studies to monitor ongoing bone remodelling towards fusion or non-fusion in-vivo. This may provide important new information about the biological process of bone graft remodelling towards solid bridging viable bone in successful spinal fusion. Another important limitation of the study is the absence of postoperative CT-images made during the first weeks after surgery. This limits insight into the development of HU-values and thus the process of bone graft remodelling from the start. In future studies we aim to incorporate a baseline CT. It is also of note that the HU measurement procedure we developed has some limitations that may have impacted on its validity and interobserver reliability. For example, although we took steps to mitigate the problem that different CT-scanners with different setups have been used between patients and between follow-up scans by introducing an HU internal correction factor, it is not clear whether this led us to the true two-year HU-values. In doing so we assumed that no significant changes in the participants' internal tissues had occurred over time, thereby not influencing the resulting HU values considerably. However, it could be possible that atherosclerosis or fatty muscle tissue was inadvertently included in the ROI. This might explain why the only participant who was scanned on identical scanners at one and two years after surgery had an internal correction factor of 0.95 instead of 1. Consequently, the changes in HU-values over time may have been slightly overestimated or underestimated. Ideally, to compare individual HU-values, identical CT-scanners with identical setups are used during follow-up. When this is not possible, HU-values need to be corrected to prevent scanner-related differences in these values. Although ideally a phantom model, with a constant density that allows for optimal calibration or calculating the most accurate correction factor, is scanned together with every patient, in daily practice this is not widely being used. One other downside of the assessment method used was that it required the observer to manually demarcate the ROI in the CT-scan slices. This may have introduced measurement bias. Future research could focus on finding a more objective assessment method, e.g. by using artificial intelligence to assess bone graft remodelling.

Conclusion

In this exploratory study repeated CT-based HU measurements in the intercorpal bone graft after lumbar fusion revealed increasing trends in 7 out of 9 patients versus a decrease in HU measurements in 2 out of 9. These prospective HU measurements may prove valuable as a proxy measure to diagnose development of successful fusion versus non-union in vivo. To date there is no reliable radiographic tool to discriminate fusion from non-union and as such the presented approach may prove to have clinical importance for spine surgery. The measuring procedure developed to quantify the participants' intercorpal bone graft HU showed excellent intraobserver reliability and may be used in necessary future studies.

Abbreviations

BMD, bone mineral density; CI, confidence interval; CT, Computed Tomography; HU, Hounsfield Units; ICC, intraclass correlation coefficient; ICF, internal correction factor; PEEK, polyetheretherketone; PLIF, posterolateral interbody fusion; pSOL: primary slice of interest; ROI, region of interest.

Declarations

Ethics approval and consent to participate

The trial that we used the subsample of was approved by the Medical Ethics Review Committee of the University Medical Center Utrecht and local Institutional Review Boards, it was in accordance with the principles of the Declaration of Helsinki (version October 2008) and the Medical Research Involving Human Subjects Act. Furthermore, approval of this study was also granted by Rijnstate Hospital's institutional research ethics review board (Rijnstate Lokale Haalbaarheids Commissie, study number 2020-1663) which granted a waiver of informed consent because non-identifiable patient data was used.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study are available and freely accessible at Mendeley Data, doi: 10.17632/632dx4vb96.1.

Competing interests

The authors declare that they have no competing interests

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There was no funding associated with this research.

Authors' contributions

JFHR designed the study, collected, analysed and interpreted the data and was a major contributor in writing the manuscript. LDdJ assisted in interpreting the data, performed the statistical analyses and was a major contributor in writing the manuscript. MCK advised with substantive analysis of the manuscript and performed reviewing before submission. MJvG advised with technical aspects and interpretation of radiological images. JLCvS was the originator of the research concept, assisted in interpreting the data, was a major contributor in writing the manuscript and performed final reviewing before submission. All authors read and approved the final manuscript.

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Figures

Figure 1 Free-hand drawn regions of interest (ROI) including intercorporeal bone graft at one (A) and two (B) years after surgery.

Note: The (0.5mm) cage markers, which acted as reference points beyond which the ROI was demarcated (posteriorly), are clearly visible on both scans. In this example HU increased from 488 HU to 536 HU over time.

Figure 1

Please See image above for figure legend.

Figure 2 Measurements from internal tissues with a one-year interval. Note: similar HU values when identical scanner and protocols were used (C&D) versus different values on different scanners (A&B) enabling calculation of the ICF

Figure 2

Please See image above for figure legend.

Figure 3 Change in bone graft HU over time using internal phantomless calibration. The change in HU from one- to two-years postoperative (A) and the percentage change, with the first year being the starting point (B). Each line represents a unique patient.

Figure 3

Please See image above for figure legend.