Review

Adult Deformity

Yetişkin Deformite

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ABSTRACT

Adult deformity, which occurs with degeneration of the spine, is a pathology that has been seen usually in the older population. The patients with adult deformity have a pain and disability that develops within time. Adult deformity is different from adolescence idiopathic scoliosis because of its features. Primary degenerative scoliosis is the most common situation in adult deformities. Posterior dynamic stabilization systems can be used at the beginning period of progressive adult deformity. The treatment of adult deformity and scoliosis in advanced cases includes fusion along with osteotomies and instrumentations. Adult deformity has also high rates of both morbidity and complication.

KEYWORDS: Spinal deformity, Adult degenerative scoliosis, Fusion, Osteotomies

ÖZ

Yetişkin deformite omurganın dejenerasyonu sonucunda oluşan ve genellikle ileri yaşlarda karşımıza çıkan bir patolojidir. Yetişkin deformitede ağrı ve zamanla gelişen fonksiyon kaybı ön plandadır. Yetişkin deformite bu özellikleri ile idiopatik adelosan skolyozdan ayrılır. Primer dejeneratif skolyoz yetişkin deformiteler içinde en çok karşılaştığımız bir durumdur. İlerleyen yetişkin deformitenin başlangıç döneminde posterior dinamik stabilizasyon sistemleri kullanılabilir. İlerlemiş erişkin skolyoz ve deformite tedavisi osteotomileri içeren füzyon ve enstrümantasyonu içerir. Erişkin deformite cerrahileri yüksek morbidite ve komplikasyon oranlarına sahiptir.

ANAHTAR SÖZCÜKLER: Omurga deformitesi, Yetişkin dejeneratif skolyoz, Füzyon, Osteotomiler

INTRODUCTION

Adult deformity is a kind of deformity that progresses slowly and occurs in the elder population, and differs from idiopathic deformity with its radiological and clinical features, forming mechanism and treatment. Surgery indications, surgery strategies and medical treatments differ for idiopathic scoliosis.

Spinal canal stenosis, spondylolisthesis, rotational subluxation, lumbar hyperlordosis and rigid deformities occur with adult deformities. As a result, we cannot use adolescent idiopathic deformity criteria for thet treatment of adult deformities.

CLASSIFICATION

Classification of most common pathologies is important. The classification maintains a unique language to understand the problem and creates a protocol for treatment. The surgeon can understand the problem without seeing the radiologic imaging and can decide on the treatment promptly if he/she knows the classification.

King and Moe (19) have managed to classify deformity in 1983 after attempts from the beginning of last century. This classification is important for thoracic deformity treatment (Table I). The authors have shown appropriate fusion levels and places of distraction instrumentation. This system has caused a decrease in the rates of late decompensation and revision surgery. There are two important deficits at this classification; It is not appropriate for newer segmental instrumentation systems (28) and does not include lumbar deformities (11). There was also no information about sagittal plan deformities in this classification (7,8,14).

The Lenke Classification that came afterwards includes all curve types, and detailed information about curves and sagittal plan deformities that are of the highest importance for this classification (22). This classification is commonly used (Table II). The importance of this classification is to be standard of fusion levels (23,24). We also know that there are some arguments about deformity levels (21).

We expressed that adult deformity differs from idiopathic adolescent deformity. Especially in adult cases, the deformity is at the lumbar region. Lumbar lordosis, oliolisthesis and end-plate obliquity are important as radiological parameters in adult deformities (33). Degenerative parameters like lumbar stenosis, rotational subluxation and spondylolisthesis as well as sagittal imbalance play an important role at adult deformity classification (12). At first, Schwab made a classification which included these parameters (30). After that there were a lot of classifications. Nowadays we use the Schwab-SRS classification that is most popular and accepted (31). We disregard the other classifications to avoid confusion. Before making the last classification, firstly Jacson (16) then

Roussoly (27) and Lafage (20) explained the importance of the pelvis which ensures a correlation between vertebra and lower extremities and provides sagittal balance. The last classification includes this knowledge. If an adult deformity would be classified, sagittal vertical axis (SVA), pelvic tilt (PT) and pelvic incidence (PI) and known PI-LL and lumbar lordosis (LL) must be included. These parameters that are related with pain and disability are very important at reconstruction surgery (20, 29). Schwab classification, which is the last accepted and corrected classification, includes these pelvic parameters. We have to remember this classification when trying to treat adult deformities.

In this classification basic curves are (34);

Curve type T;

If thoracic major curve is more than 30 degrees, the apical vertebra is T9 and higher.

Table I: King and Moe Classification

Location	Type	Description
Thoracic	I	Principal lumbar, secondary thoracic curve
	II	Principal thoracic, secondary lumbar curve
	III	Thoracic curve only (apex ≥T10)
	IV	Long thoracic curve (extends to L4)
	V	Double thoracic curve
Double major		Equally structural thoracic & lumbar curves
Lumbar		Apex in lumbar spine
Thoracolumbar		Apex at thoracolumbar junction

Table II: Lenke Classification

Type	Proximal thoracic	Main thoracic	Thoracolumbar/lumbar	Curve type
1	Non-Structural	Structural (Major*)	Non-Structural	Main Thoracic (MT)
2	Structural	Structural (Major*)	Non-Structural	Double Thoracic (DT)
3	Non-Structural	Structural (Major*)	Structural	Double Major (DM)
4	Structural	Structural (Major*)	Structural	Triple Major (TM)
5	Non-Structural	Non-Structural	Structural (Major*)	Thoracolumbar / Lumbar (TL/L)
6	Non-Structural	Structural	Structural (Major*)	Thoracolumbar / Lumbar-Main Thoracic (TL/L-MT)

STRUCTURAL CRITERIA
(Minor Curves)

Proximal Thoracic: - Side Bending Cobb ≥25°
- T2-T5 Kyphosis ≥+20°

Main Thoracic: - Side Bending Cobb ≥25°
- T10-L2 Kyphosis ≥+20°

Thoracolumbar/Lumbar: - Side Bending Cobb ≥25°
- T10-L2 Kyphosis ≥+20°

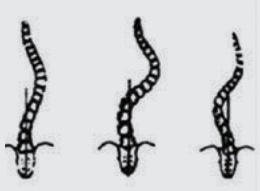
*Major = Largest Cobb Measurement, always structural
Minor = all other curves with structural criteria applied

LOCATION OF APEX
(SRS definition)

CURVE	**APEX**
THORACIC	T2 - T11 - T12 DISC
THORACOLUMBAR	T12 - L1
LUMBAR	L1-2 DISC - L4

Modifiers

Lumbar Spine Modifier	
A	CSVL Between Pedicles
B	CSVL Touches Apical Body(ies)
C	CSVL Completely Medial



Thoracic Sagittal Profile T5 - T12	
- (Hypo)	<10°
N (Normal)	10° - 40°
+ (Hyper)	>40°

Curve type L;

If lumbar and thoracic major curves are more than 30 degrees, the apical vertebra is T10 or lower.

Curve type D;

There is a double major curve and each curve much more than 30 degrees.

Curve type N; Coroner curve or curves are not much more than 30 degrees. There is no major coronal deformity.

Sagittal's modifiers are PI-LL, PT, SVA (Figure 1).

The first modifier is the difference between the PI and LL curve. It shows the proportional relation between PI and LL.

If the LL curve is lower than the PI curve you have to plan for performing an osteotomy or osteotomies. That is the importance of this knowledge .

Pİ; pelvic tilt + sacral slope

A line is drawn from the center of the S1 end-plate to the center of the femoral head and a second line is drawn perpendicular to line drawn along S1 endplate. The angle between the two lines is the pelvic incidence.

LL; It is estimated like the sagittal Cobb curve. The LL curve is intersected by the L1 upper end-plate target line and S1 lower target line.

The modifier is accepted as zero if the curve difference between PI and LL is lower than 10 degree.

If this curve is from 10 to 20 degrees, modifier is accepted as +. If it is more than 20 degrees, the modifier is accepted as ++.

PT is an important parameter in evaluation of spinal deformities. High PT is a sign of increased pelvic retroversion, and low PT curve means inadequate pelvic retroversion and compensation. Sagittal balance deteriorates more quickly (20). This parameter is related closely with pain and disability. It is also important for surgical strategy. In a recents study it is mentioned that patients who have got much more PT angle with same SVA need more osteotomies for providing stable instrumentation (32). Finally we can say that the PT curve is indicator of pelvis retroversion.

PT; a line is drawn from the center of the S1 endplate to the center of the femoral head. A second vertical line is drawn intersecting the center of the femoral head. The angle between the two lines is the pelvic tilt.

PT modifier is estimated as follows:

If the PT curve is lower than 20 degrees, it is accepted as zero. If it is between 20-30 degrees, it is accepted as '+', if the angle is much more than 30 degrees, it ıs accepted as '++'.

The last modifier is the Sagittal Vertical Axis (SVA). This is also a modifier closely related with pain and disability. SVA is the distance between plumb line and the sacrum posterior superior end.

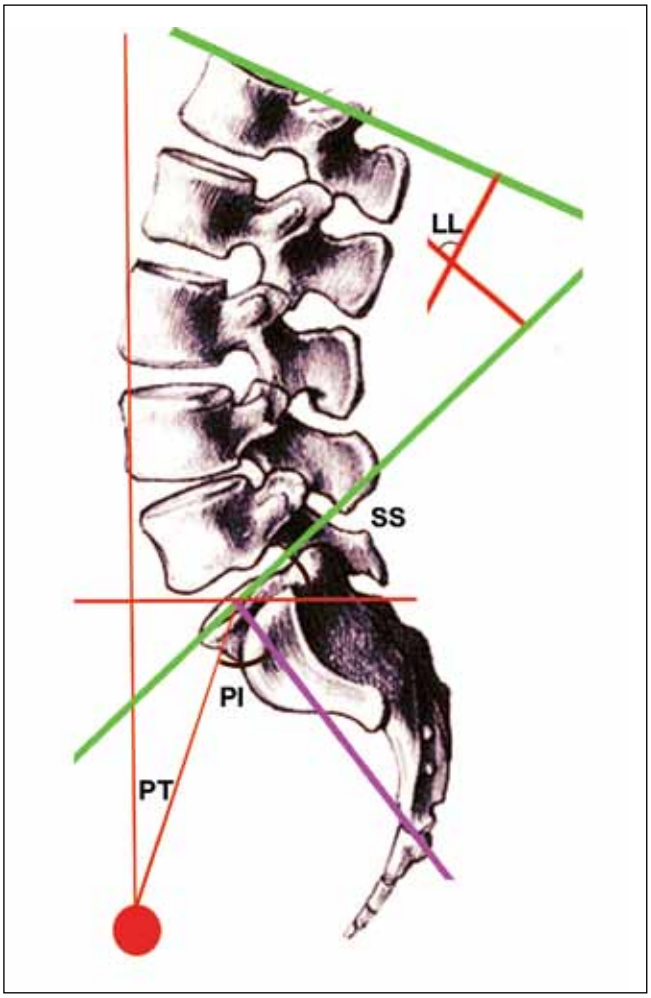


Figure 1: Sagittal modifiers: PI-LL, PT and SVA.

If the distance is lower than 40 mm, the modifier is accepted as zero.

If the distance is between 40 mm and 95 mm, the modifier is accepted as '+'.

If the distance is much more than 95 mm, the modifier is accepted as '++'.

A case is used to present this classification more clearly. (Figure 2A,B).

Aebi (1) made a deformity classification for etiology. It is very important for understanding the adult deformity.

Type 1 Scoliosis; Primary degenerative scoliosis (de novo scoliosis) is usually seen at the thoracic and lower region in childhood (Figure 3A-E).

Type 2 Scoliosis; This is progression of adolescent thoracal, thoracolumbar and/or lower scoliosis.

Type 3 Scoliosis; secondary degenerative scoliosis;

a) The idiopathic or other type of scoliosis progress and form this type. Also asymmetry of leg length, pelvic pathology or

lumbosacral transitional anomaly cause this type of scoliosis which is usually at thoracolumbar, lumbar or lumbosacral regions.

b) Metabolic bone disease (osteoporosis) with asymmetric arthritis or/and vertebra fracture (Figure 4).

Type 1 scoliosis is most common. In this group patients start their lives with a healthy spine but the spine stars to curve at older ages. Degenerative pathology begins from the intervertebral disc. The asymmetric degenerations of the disc make asymmetric loadings. As a result, the region where degeneration started curves slowly its own. Lysis of spine and foramens compress the roots and thus symptoms occur.

The other important group is type 3 b. In developed countries, osteoporosis is serious problem especially for women who live longer. Osteoporosis is also one of the main problems of older ages. Degenerations reduce vertebral resistance and thus excessive loading occurs and can cause acute vertebral fracture or progressive loss of vertebra height. The spine starts to curve.

CLINIC

The beginning of deformity is quite insidious. The degeneration that starts the loss of vertebral disc height progresses very slowly, especially in primer degenerative scoliosis. Most patients go to the medical center for pain. They lose time at wrong physical treatment programs and medications because vertebral ossifications are thought to be the reason of this pain.

Actually this approach is not wrong but there is missing point. You have to obtain all spine X- rays imaging that includes both femur heads every year to understand deformity progression. If deformity is caught at the beginning, it could be solved by minimal invasive surgery. However if deformity progresses, osteotomies and fusion having of high mortality and morbidity rate have to be used for these elder patients. Pain and disabilities are the main problems for progressive deformities. Degenerations causes pain. The stenosis of the vertebral canal and foramina also causes sciatica. Patients get worse and cannot move because of pain which is very hard to solve the causes of and thus other medical problems occur.

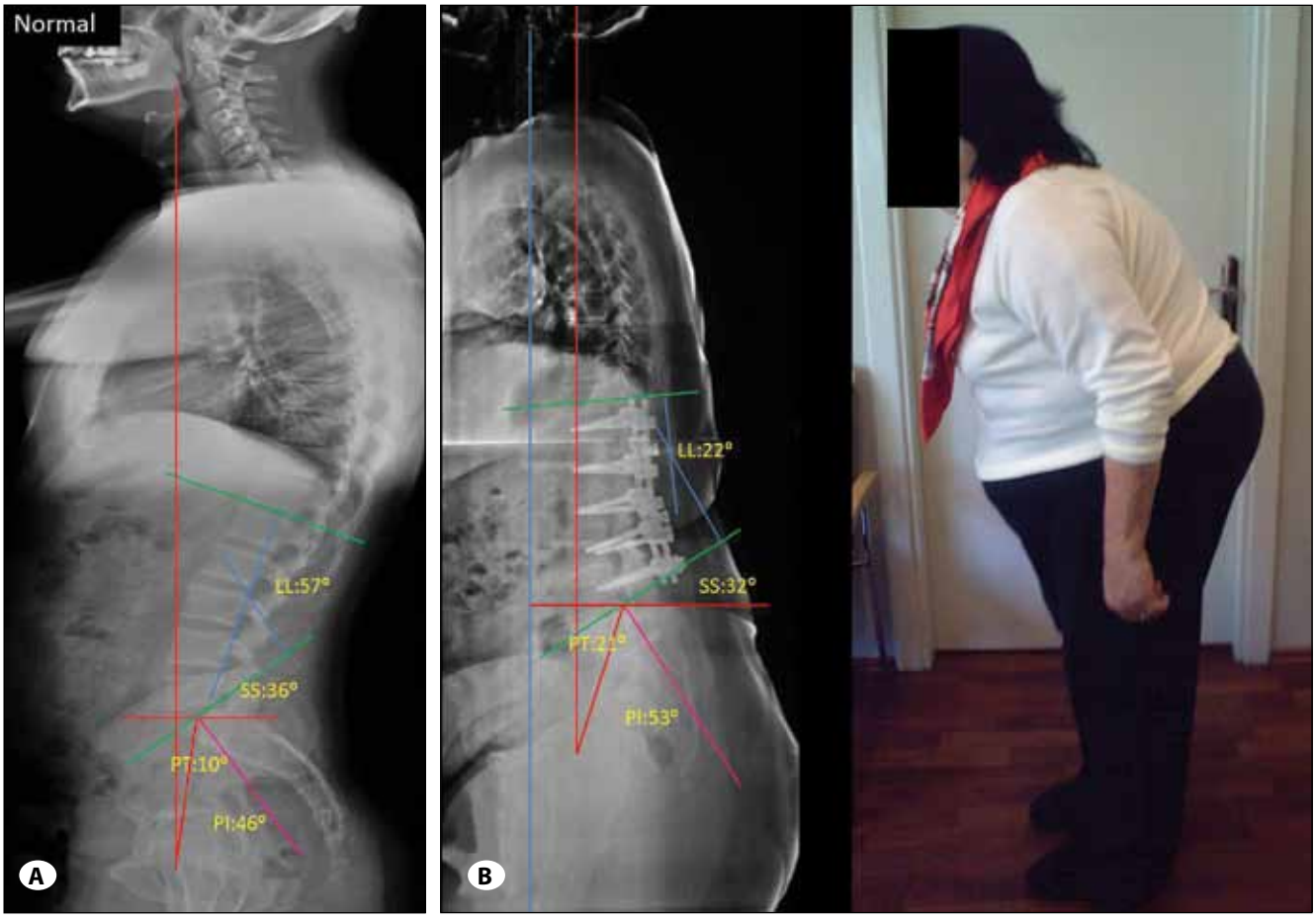


Figure 2: SVA is always gravity line or over and over ideally. At the beginning of deterioration of sagittal balance SVA becomes in front the gravity line. A 59-year-old female had got operated for degenerative disk disease. Flat back syndrome was formed by the operation. Plumb line had slided in front of the gravity line. Sacrum had got retroversion to the back and thus PI had increased. Patient tried to flex the legs because of trying to put head line into the pelvis. Nevertheless sagittal balance could not be corrected.

TREATMENT

Treatment is related with the degeneration stage. If it is at the beginning and not progressed, the combination of physical treatment, analgesics and anti-inflammatory drugs are beneficial.

You can use foraminal and spinal canal injection if there is minimal root compression. Deformity sometimes does not occur with any symptoms, You have to explain to patients that deformity could get worse and need surgical treatment. You can manage the deformity with more minimally invasive surgery at the beginning period while sagittal modifier (PI-LL, PT, SVA) and sagittal balance are normal. Therefore you can prevent the progression. We suggest dynamic stabilization at the beginning period of deformity similar to other authors (10,35,36). We can see this suggestion in various articles. Thus you can manage the problem without progression and you do not need to make massive osteotomies and fusion. In advanced cases you have to make fusion. We recommend a hybrid system for these (36) (Figure 5). The vertebra is a mobile system. If you make rigid stabilization at one region, you could face some problems at the other levels. The most important problem is proximal junctional kyphosis which is anterior angulation of the vertebra at the end of the stabilization system (18) (Figure 6). The other problem is to connect this rigid system to pelvis. Two sacral screws are

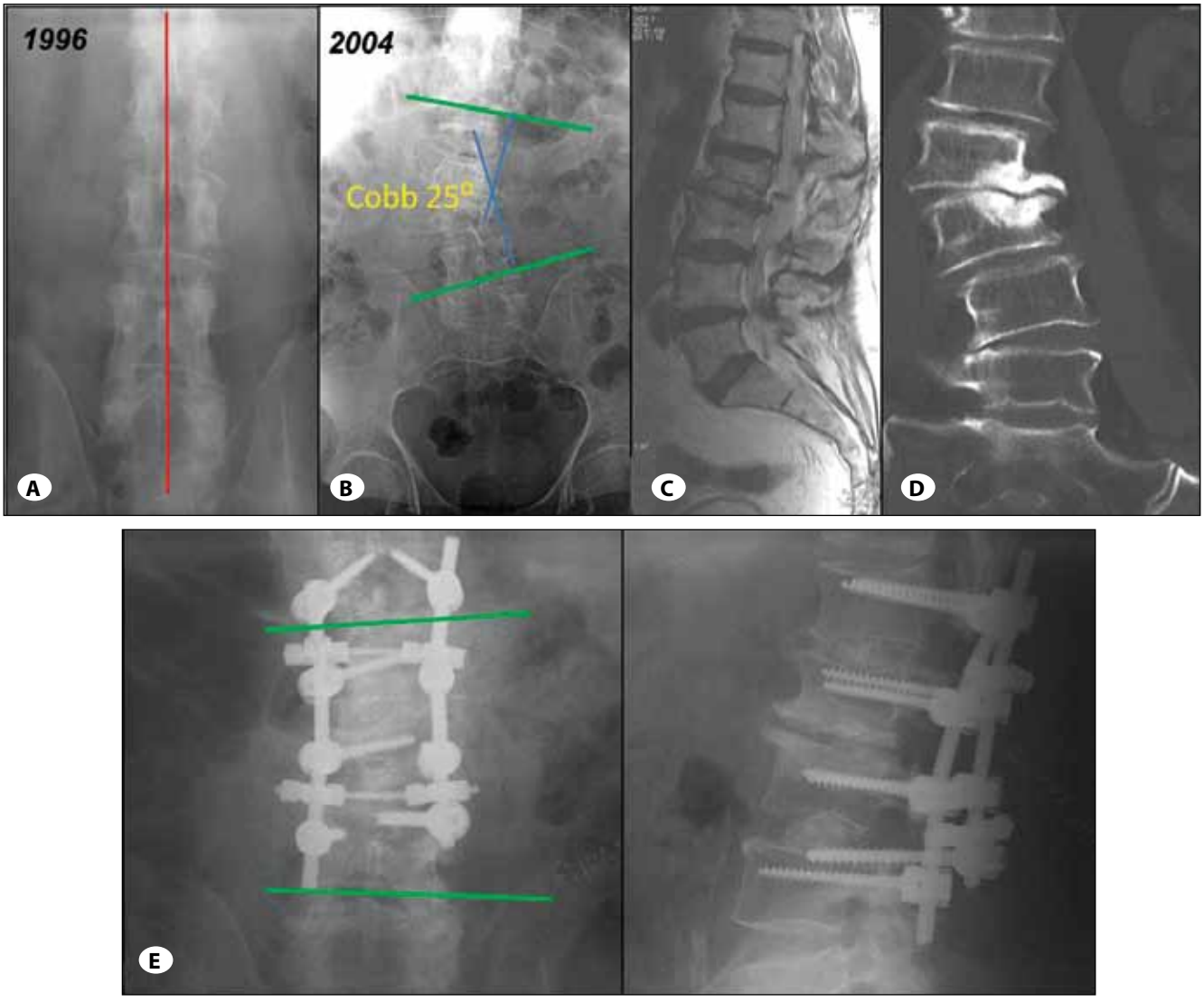


Figure 3: Primitive degenerative scoliosis makes up the bigger part of the adult deformities. Most of the patients have not got any problem at young ages. At elder ages the water ratio of the vertebral disc decreases and thus the height of the disc is decreased. Asymmetry of disc height, degeneration of facet joints, sliding of the spine in the front and back, and formation of osteophytes follow the degeneration mechanism. We see the 75-year-old female patient's X-ray imaging. **A)** we can see the major pathology on X ray imaging from at 67-years-old patient. **B,C,D)** we see prominent degeneration and scoliotic deformity on a 75-year- old patient 's X ray imaging. **E)** We see the spine corrected by fusion and instrumentation.

usually not enough for this. Anterior or posterior fusion must be done at the L5-S1 level. You can also use iliac screw or iliac instrumentation for providing a rigid system (2,9,13,39). It is a massive surgery and causes much blood loss In advanced deformity surgeries you have to think of the pelvic parameters, coronal and sagittal balance for inhibiting to loose instrumentation and pseudoarthrosis. High mortality, morbidity, risks, massive blood loss are serious problem for these patients (3). Bono and Lee (5) found good result in 82%, fusion rate of 87 %, complication rate of 55 % in their review. This means that there is a lot of trouble at operation like bleeding and infection. The amount of blood loss changes from 360 ml to 7000 ml, and the average is 1500ml. This causes a serious cardiovascular problem and 70% of the these patients suffer complications (4,15,25). Serious blood loss that causes pulmonary, cardiac, renal problems could result in DIC and increased infection (6,26,38). Long hospitalization time also triggers psychological problems and increases the mortality risk (17,37). Knowing BMI is important because obese patients are much more under risk for complications (40).

We have to check the comorbidities of these patients to avoid complications. The real problem is to manage the deformity surgery. We are trying to establish a standard for how to do the deformity surgery. How can a person who suffered from deformity deal with deformity surgery? We do not know whether or not a patient get away pain and his/her problem related deformity. This decision of surgery belongs to the surgeon.

Figure 4: Osteoporosis and deformities related with osteoporosis form the major part of adult deformities. We see thoracic kyphotic deformity because of thoracic osteoporotic fracture and lumbar scoliotic deformity because of lumbar osteoporotic fracture in a 79-year-old male.

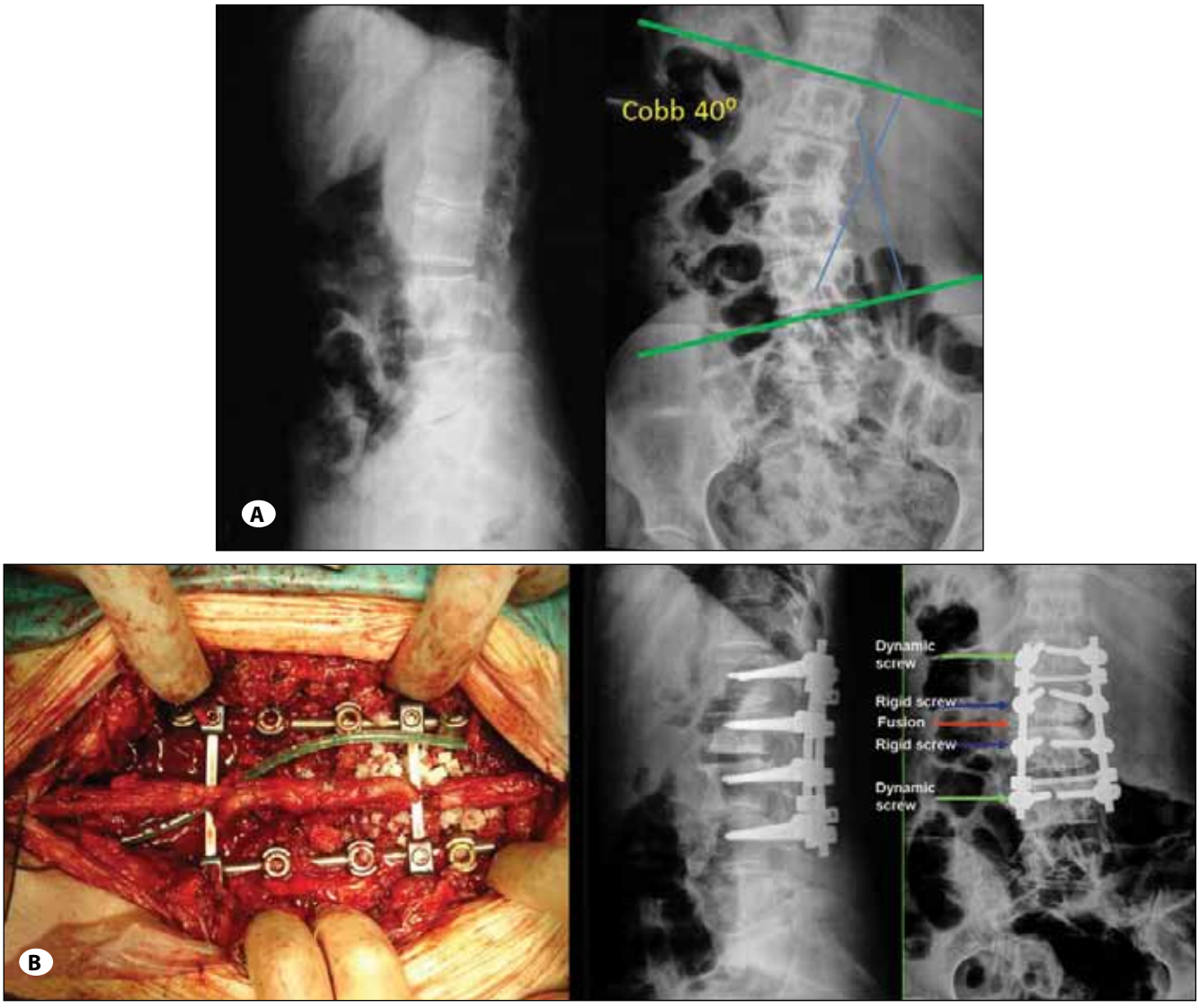


Figure 5: 56 years old female had suffered from back pain while walking and standing and need sitting. At neurological examination there is no pathology. 40 degree lumbar deformity had occurred. Laminar , vertebral fusion was made by instrumentation at L2-L3 vertebra segment. Dynamic screws were put in L1 and L4 vertebrae for not forming fusion.

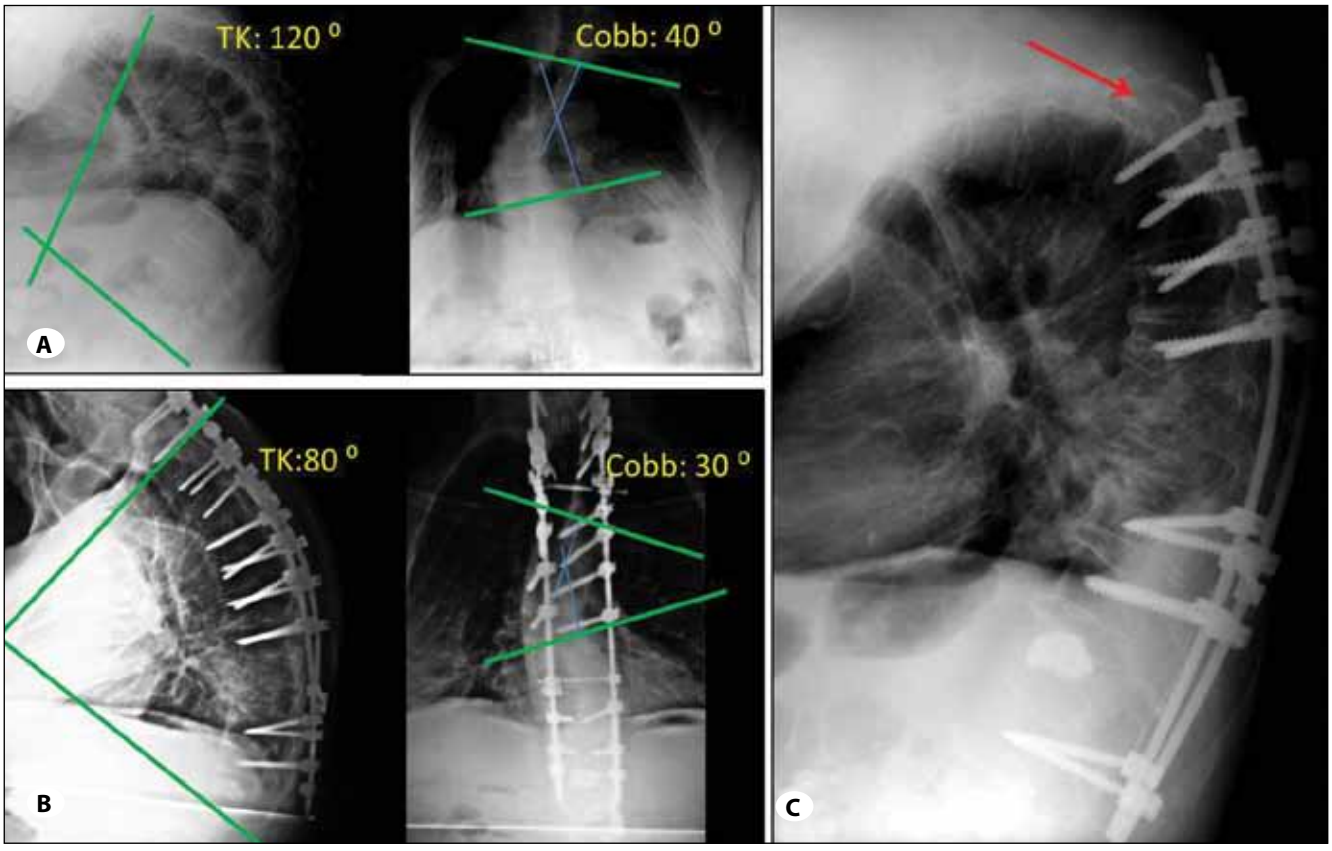


Figure 6: A) 63 years old male patient with thoracal adult deformity (kyphosis and scoliosis) applied with some complaints which are dyspnea, fallen head to front and difficulty of walking. **B)** Kyphotic and scoliotic deformities were improved with fusion and instrumentation. **C)** Loosened screws due to proximal junctional kyphosis in thoracal area were removed.

REFERENCES

1. Aebi M: The adult scoliosis. Eur Spine J 14: 925–948, 2005
2. Allen BL Jr, Ferguson RL: The Galveston technique of pelvic fixation with L-rod instrumentation of the spine. Spine (Phila Pa 1976) 9(4):388-394, 2005
3. Anand N, Baron EM, Thaiyananthan G, et al: Minimally invasive multilevel percutaneous correction and fusion for adult lumbar degenerative scoliosis: A technique and feasibility study. J Spinal Disord Tech 21:459-467, 2008
4. Baron EM, Albert TJ: Medical complications of surgical treatment of adult spinal deformity and how to avoid them. Spine 31:S106-118, 2006
5. Bono CM, Lee CK: The influence of subdiagnosis on radiographic and clinical outcomes after lumbar fusion for degenerative disc disorders: An analysis of the literature from two decades. Spine 30:227-234, 2005
6. Carson JL, Altman DG, Duff A, Noveck H, Weinstein MP, Sonnenberg FA, Hudson JI, Provenzano G: Risk of bacterial infection associated with allogeneic blood transfusion among patients undergoing hip fracture repair. Transfusion 39(7):694-700, 1999
7. Coonrad R, Murrell G, Motley G, et al: A logical coronal pattern classification of 2,000 consecutive idiopathic scoliosis cases based on the Scoliosis Research Society-defined apical vertebra. Spine 23:1380–1391, 1998
8. Cruickshank JL, Koike M, Dickson RA: Curve patterns in idiopathic scoliosis: A clinical and radiographic study. J Bone Joint Surg Br 71: 259–263, 1989
9. Dalbayrak S, Yilmaz M, Kaner T, Gokdag M, Yilmaz T, Sasani M, Oktenoglu T, Ozer AF: Lumbosacral stabilization using iliac wings: A new surgical technique. Spine (Phila Pa 1976) 36(10):E673-677, 2011
10. Di Silvestre M, Lolli F, Greggi T, Vommaro F, Baioni A: Adult's degenerative scoliosis: Midterm results of dynamic stabilization without fusion in elderly patients-is it effective? Adv Orthop 2013:365059, 2013
11. Garbuz DS, Masri BS, Esdaile J, et al: Classification systems in orthopaedics. J Am Acad Orthop Surg 10:290–297, 2002
12. Glassman SD, Berven S, Bridwell KH, et al: Correlation of radiographic parameters and clinical symptoms in adult scoliosis. Spine 30:682–688, 2005
13. Grob D, Scheier HJ, Dvorak J, Siegrist H, Rubeli M, Joller R: Circumferential fusion of the lumbar and lumbosacral spine. Arch Orthop Trauma Surg 111(1):20-25, 1991
14. Halm H, Castro WH, Jerosch J, et al: Sagittal plane correction in 'Kingclassified' idiopathic scoliosis patients treated with Cotrel-Dubousset instrumentation. Acta Orthop Belg 61: 294–301, 1995

15. Herkowitz HN, Sidhu KS: Lumbar spine fusion in the treatment of degenerative conditions: Current ındications and recommendations. J Am Acad Orthop Surg 3:123-135, 1995
16. Jackson RP, Peterson MD, McManus AC, Hales C: Compensatory spinopelvic balance over the hip axis and better reliability in measuring lordosis to the pelvic radius on standing lateral radiographs of adult volunteers and patients Spine (Phila Pa 1976) 23(16):1750-1767,1998
17. Kawaguchi Y, Kanamori M, Ishihara H, Abe Y, Nobukiyo M, Sigeta T, Hori T, Kimura T: Postoperative delirium in spine surgery. Spine J 6(2):164-169, 2006
18. Kim HJ, Bridwell KH, Lenke LG, Park MS, Ahmad A, Song KS, Piyaskulkaew C, Hershman S, Fogelson J, Mesfin A: Proximal junctional kyphosis results in inferior SRS pain subscores in adult deformity patients. Spine (Phila Pa 1976) 38(11): 896-901, 2013
19. King H, Moe J, Bradford DS, et al: The selection of fusion levels in thoracic idiopathic scoliosis. J Bone Joint Surg Am 65:1302–1313, 1983
20. Lafage V, Schwab F, Patel A, et al: Pelvic tilt and truncal inclination: Two key radiographic parameters in the setting of adults with spinal deformity. Spine (Phila Pa 1976) 34: E599-606, 2009
21. Lenke LG, Betz RR, Haher TR, et al: Multisurgeon assessment of surgical decision-making in adolescent idiopathic scoliosis: Curve classification, operative approach, and fusion levels. Spine 26:2347–2353, 2001
22. Lenke LG, Betz RR, Harms J, et al: Adolescent idiopathic scoliosis: A new classification to determine extent of spinal arthrodesis. J Bone Joint Surg 83:1169–1181, 2001
23. Lenke LG, Edwards CC, Bridwell KH: The lenke classification of adolescent idiopathic scoliosis: How it organizes curve patterns as a template to perform selective fusions of the spine. Spine 28(suppl):199–207, 2003
24. Lenke LG: Lenke Classification System of Adolescent Idiopathic Scoliosis: Treatment recommendations. AAOS Instructional Course Lectures 54:537–542, 2005
25. Möller H, Hedlund R: Instrumented and noninstrumented posterolateral fusion in adult spondylolisthesis--a prospective randomized study: Part 2. Spine (Phila Pa 1976) 25(13): 1716-1721, 2000
26. Murphy P, Heal JM, Blumberg N: Infection or suspected infection after hip replacement surgery with autologous or homologous blood transfusions. Transfusion 31(3):212-217, 1991
27. Roussouly P, Gollogly S, Berthonnaud E, Labelle H, Weidenbaum M: Sagittal alignment of the spine and pelvis in the presence of L5-s1 isthmic lysis and low-grade spondylolisthesis. Spine (Phila Pa 1976) 31(21):2484-2490, 2006
28. Roye DP, Farcy JP, Ricjert JB, et al: Results of spinal instrumentation of adolescent idiopathic scoliosis by King type. Spine 17(suppl 8): 270–273, 1992
29. Schwab F, Bess S, Blondel B, et al: Combined Assessment of Pelvic Tilt, Pelvic Incidence/Lumbar Lordosis Mismatch and Sagittal Vertical Axis Predicts Disability in Adult Spinal Deformity: A Prospective Analysis. Louisville, KY: Scoliosis Research Society; 2011
30. Schwab F, Farcy JP, Bridwell K, Berven S, Glassman S, Harrast J, Horton W: A clinical impact classification of scoliosis in the adult. Spine (Phila Pa 1976) 31(18):2109-2114, 2006
31. Schwab F, Lafage V, Boyce R, Skalli W, Farcy JP: Gravity line analysis in adult volunteers: Age-related correlation with spinal parameters, pelvic parameters and foot position. Spine 31(25):959-967, 2006
32. Schwab F, Lafage V, Shaffrey C, et al: Pre-operative pelvic parameters must be considered to achieve adequate sagittal balance after lumbar osteotomy. Vienna: IMAST, 2009
33. Schwab F, Smith V, Biserni M, et al: Adult scoliosis: A quantitative radiographic and clinical analysis. Spine 27:387–392, 2002
34. Schwab F, Ungar B, Blondel B, Buchowski J, Coe J, Deinlein D, DeWald C, Mehdian H, Shaffrey C, Tribus C, Lafage V: Scoliosis Research Society-Schwab adult spinal deformity classification: A validation study. Spine (Phila Pa 1976) 37(12):1077-1082, 2012
35. Schwarzenbach O, Berlemann U: Dynamic posterior stabilization with the pedicle screw system DYNESYS®. Oper Orthop Traumatol 22(5-6):545-557, 2010
36. Schwarzenbach O, Rohrbach N, Berlemann U: Segment-by-segment stabilization for degenerative disc disease: A hybrid technique. Eur Spine J 19(6):1010-1020, 2010
37. Thomason JW, Shintani A, Peterson JF, Pun BT, Jackson JC, Ely EW: Intensive care unit delirium is an independent predictor of longer hospital stay: A prospective analysis of 261 non-ventilated patients. Crit Care 9(4):R375-81, 2005
38. Triulzi DJ, Vanek K, Ryan DH, Blumberg N: A clinical and immunologic study of blood transfusion and postoperative bacterial infection in spinal surgery. Transfusion 32(6):517-524, 1992
39. Tsuchiya K, Bridwell KH, Kuklo TR, Lenke LG, Baldus C: Minimum 5-year analysis of L5-S1 fusion using sacropelvic fixation (bilateral S1 and iliac screws) for spinal deformity. Spine (Phila Pa 1976) 31(3):303-308, 2006
40. Yagi M, Patel R, Boachie-Adjei O: Complications and unfavorable clinical outcomes in obese and overweight patients treated for adult lumbar or thoracolumbar scoliosis with combined anterior/posterior surgery. J Spinal Disord Tech 2013 [Epub ahead of print]