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Perioperative bleeding, bone mineral density and health-related quality of life related to spinal fusion

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To my family

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ABSTRACT

Neuromuscular scoliosis (NMS), the three-dimensional deformity of the spine, has neurologic or muscular origin. Conservative treatment offers limited possibilities for severe deformities in NMS, hence surgical treatment is often ultimately necessary. Fusion surgery is a difficult procedure for the patient and carries substantial risks. In NMS, the surgical risks and complications are considerably higher than in patients with Adolescent idiopathic scoliosis (AIS). The aim of this dissertation was to investigate the characteristics associated with spinal fusion surgery in NMS patients in terms of perioperative bleeding, health-related quality of life (HRQoL) and bone mineral density.

Studies I and II examined perioperative bleeding and its risk factors. Perioperative bleeding was significantly higher in NMS patients compared to AIS. The risk factor profile differed between the study groups. Increasing operative time was a risk factor for intraoperative and total bleeding, whereas extent of fusion correlated to amount of drainage bleeding.

Study III investigated health-related quality of life changes associated with spinal fusion. NMS patients showed a significant improvement in quality of life at post-operative two-year follow-up, and the improvement of HRQoL was not inferior in comparison to AIS patients.

In study IV, the bone mineral density (BMD) of spinal muscular atrophy patients was investigated from spinal CT-imaging taken prior to spinal fusion. Patients pre-treated with growth-friendly spinal implants had poorer bone mineral density in a comparison to patients followed prior fusion without surgical interventions. Bone quality was poorer in both groups in comparison to healthy controls.

This study suggests that there are higher risks associated in spinal fusion for neuromuscular scoliosis patients compared to surgical treatment of idiopathic scoliosis. Perioperative bleeding is more extensive, and previous operative treatment further compromises the poorer bone quality of patients with neuromuscular scoliosis. Importantly, despite the risks, quality of life appears to improve significantly after spinal fusion surgery.

KEYWORDS: neuromuscular scoliosis, spinal fusion, perioperative bleeding, health-related quality of life, bone mineral density

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TIIVISTELMÄ

Neuromuskulaariskolioosissa (NMS) selän kolmiulotteisen virheasennon taustalla on jokin lihas- tai hermosairaus. Konservatiiviset hoitovaihtoehdot tarjoavat rajoitetusti mahdollisuuksia neuromuskulaariskolioosipotilaiden vaikeiden virheasentojen korjauksessa, joten kirurgiset hoitokeinot ovat lopulta usein välttämättömiä. Luudutusleikkaus on potilaalle raskas toimenpide, johon liittyy monia riskejä. Neuromuskulaariskolioosissa leikkausriskit ja komplikaatiot ovat selvästi yleisempiä kuin idiopaattisen skolioosin (AIS) leikkaushoidossa. Tämän väitöskirjatutkimuksen tavoitteena oli selvittää NMS-potilaiden luudutusleikkauksiin liittyviä erityispiirteitä leikkauksenaikaisen verenvuodon, elämänlaadun muutoksen sekä leikkausta edeltävän luuntiheyden osalta.

Osatöissä I ja II tutkittiin leikkauksenaikaista verenvuotoa ja sen riskitekijöitä. Leikkausverenvuoto oli merkittävästi suurempaa NMS-potilailla AIS-potilaisiin verrattuna. Riskitekijäprofiili erosi tutkimusryhmien välillä. Leikkauksen kesto oli vuotoa lisäävä riskitekijä leikkauksenaikaiselle ja kokonaisverenvuodolle ja luudutuksen laajuus korreloi positiivisesti leikkauksen jälkeiseen verenvuotoon.

Osatyössä III selvitettiin luudutusleikkauksen aiheuttamaa elämänlaadun muutosta tapaus-verrokkitutkimusasetelmassa. NMS-potilaiden elämänlaatu parani merkittävästi kahden vuoden seurannassa luudutusleikkauksen jälkeen, eikä elämänlaadun paraneminen ollut AIS-potilaita heikompaa.

Osatyössä IV tutkittiin SMA (spinaalinen lihasatrofia) potilaiden luuntiheyttä luudutusleikkausta edeltävästi otetuista tietokonetomografiakuvista. Kasvuystävällisillä implanteilla hoidettujen potilaiden luuntiheys oli heikompaa ennen luudutusleikkausta verrattuna potilaisiin, joita ei ollut hoidettu operatiivisesti ennen luudutusleikkausta. Luunlaatu oli molemmissa ryhmissä tervettä verrokkiväestöä heikompaa.

Tämän tutkimuksen perusteella neuromuskulaariskolioosipotilaiden luudutusleikkauksiin liittyy suurempia riskejä verrattuna idiopaattisen skolioosin leikkaushoitoon. Perioperatiivinen verenvuoto on runsaampaa, ja aiempi operatiivinen hoito heikentää neuromuskulaaripotilaiden entisestään heikompaa luunlaatua. Huomattavaa on, että riskeistä huolimatta elämänlaatu vaikuttaa parantuvan merkittävästi luudutusleikkauksen jälkeen.

AVAINSANAT: Neuromuskulaariskolioosi, luudutusleikkaus, perioperatiivinen verenvuoto, elämänlaatu, luuntiheys

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Abbreviations

AIS	Adolescent idiopathic scoliosis
aPTT	Activated Partial Thromboplastin Clotting Time
BMD	Bone mineral density
BMI	Body mass index
DXA	Dual-energy-x-ray-absorptiometry
EBV	Estimated blood volume
EOS	Early Onset scoliosis
CK	Creatinine kinase
CNS	Central nervous system
CP	Cerebral Palsy
CT	Computer Tomography
DMD	Duchenne Muscular Dystrophy
GFSI	Growth friendly spinal implants
GMFCS	Gross motor function classification score
HCT	Hematocrit
Hb	Hemoglobin
HRQOL	Health-related quality of life
INR	International Standardized Ratio
MCGR	Magnetically controlled growing rod.
MCID	Minimum clinically important difference
MCV	Mean corpuscular volume.
MCH	Mean corpuscular hemoglobin
MMC	Myelomeningocele
mRNA	Messenger ribonucleic acid
NMS	Neuromuscular scoliosis
QCT	Quantitative computer tomography
ROI	Range of interest
SMA	Spinal muscular atrophy
SS	Syndromic scoliosis
TGR	Traditional growing rods
TXA	Tranexamic acid

TYKS	Turku University Central Hospital
UMG	Universitätsmedizin Göttingen
vBMD	Volumetric bone mineral density
VEPTR	Vertical expandable prosthetic titanium rib

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Venla Soini, Arimatias Raitio, Ilkka Helenius, Linda Helenius, Johanna Syvänen. A retrospective cohort study of bleeding characteristics and hidden blood loss after segmental pedicle screw instrumentation in neuromuscular scoliosis as compared with adolescent idiopathic scoliosis. *North American Spine Society Journal*, 2022; 12: 100190.

II Venla Soini, Johanna Syvänen, Ilkka Helenius, Linda Helenius, Arimatias Raitio. Perioperative risk factors for bleeding in adolescents undergoing pedicle screw instrumentation for scoliosis. *Children,* 2023; 10(2):381

III Venla Soini, Johanna Syvänen, Linda Helenius, Arimatias Raitio, Ilkka Helenius. Health-related quality of life after segmental pedicle screw instrumentation in patients with neuromuscular scoliosis: Matched comparison to patients with adolescent idiopathic scoliosis. *Acta Orthopaedica*, 2023; 94:165-170

IV Venla Soini, Anna K. Hell, Luise Metzger, Katharina B. Jäckle, Lena Braunschweig, Katja A. Lüders, Heiko M. Lorenz, Konstantinos Tsaknakis. Scoliosis Treatment with Growth Friendly Spinal Implants (GFSI) relates to low Bone Mineral Mass in Children with Spinal Muscular Atrophy. *Journal of Pediatric Orthopaedics,* 2023 Apr 27. Online ahead of print.

1 Introduction

The first markings of scoliosis in the history of western medical literature date back to ancient Greece, as Hippocrates (460–377 BC) described abnormal spinal curvature on patients. Hippocrates used the Greek word ‘skolios’, meaning ‘bent’ to create the term of scoliosis, which he thought to be a result from bad posture. The treatment of choice in Ancient Greece was axial distraction on a mechanical apparatus, called Hippocratic board (Withington, 1928). Later, Claudius Galen (131–201 AD) recommended loud singing to exercise the rib cage to correct the thoracal abnormality (Galen, Huebert, 1967). The Middle Ages did not bring great advances in the treatment of scoliosis, as the bony deformities were mainly considered manifestations of sins (Gilchrist, 2012), but in the 16th century, the first metal braces for scoliosis were created. In the 19th century, rapid development began, as first surgical attempts to treat scoliosis and the invention of X-ray initiated a new era for scoliosis treatment. (Guérin, 1838, Huebert, 1967, Mould, 1995, Ogiliwie, 1995). Dr. Russel Hibbs performed the first spinal fusion procedure for scoliosis in 1911. (Hibbs, 2007)

Today, the treatment of scoliosis is multidisciplinary and individually planned. In addition to the patient and treating physicians, parents, physiotherapists, medical technicians, and specialists in many other fields are involved in the comprehensive treatment. The treatment plans consist of individual aids, conservative treatment (braces), and surgical procedures. (Vialle, et al., 2013)

There are multiple origins for scoliosis such as idiopathic, congenital, neuromuscular, and syndromic. This study concentrates on neuromuscular scoliosis, in which the deformity of spine originates as a consequence of a neuromuscular disease, such as cerebral palsy, or spinal muscular atrophy. The underlying condition can be neuropathic or myopathic. The neuromuscular scoliosis is characterized by an early onset, severe spinal deformity, and progression that is not limited to skeletal immaturity (Saito, et al., 1998). This often leads to necessity of an extensive spinal fusion, that as a major orthopedic surgery possesses great risk of perioperative bleeding. (Jain, et al., 2012, Shapiro and Sethna, 2004) To justify extensive surgical treatment it is important that the risks, benefits, and harms associated with it are as

widely understood as possible. Surgeons should do all possible means pre- and perioperatively to minimize the risk of bleeding.

The main focus of this thesis was to evaluate the characteristics and risk factors of perioperative bleeding related to spinal fusion in patients with neuromuscular scoliosis. The neuromuscular patients have been shown to have a greater risk to perioperative bleeding in comparison to adolescent idiopathic scoliosis, (Shapiro and Sethna, 2004) which makes it important to determine the risk factors and bleeding characters related to operation in question.

Patients with neuromuscular diseases, such as spinal muscular atrophy, already have compromised bone quality due to their underlying disease, and it is important to assess bone health when planning the final fusion surgery with multiple pedicle screws in order to prevent further implant-related complications and optimize the outcome. (Hensel, et al., 2020)

The debate on the benefits of the spinal fusion in patients with neuromuscular scoliosis continues and little is known about the impact of spinal fusion to quality of the life of the patients, therefore we sought to also address this question in this thesis.

2 Review of the Literature

2.1 Definition, diagnosis, and characteristics of scoliosis

Scoliosis is a lateral curvature of the spine. The definition requires a curvature greater than 10° in the coronal plane (Cobb, 1948). What is more, the deformity is three dimensional and therefore scoliosis contains a rotational component of vertebra in transverse plane. (El-Hawary and Chukwunyerenwa, 2014, Terminology Committee of the Scoliosis Research Society. A glossary of terms.)

The diagnosis of scoliosis is made by clinical examination including Adams forward bending test and the use of scoliometer (Figure 1.) followed by upright antero-posterior radiographs. EOS© -radiographs are commonly used in diagnostics and follow-ups of pediatric scoliosis patients. EOS imaging system is based on slot-scanning technology, that reduces radiation. With it biplanar views can be taken simultaneously. (Jarrett and Ecklund, 2021)

MRI is not routinely required for diagnosis, but in case of uncertainty or suspected medullary pathology, MRI should be obtained. (Vialle, et al., 2013)

The severity of scoliosis is determined by measuring the degree of curvature from a plain radiograph, posteroanterior view, preferably from an upright radiograph, taken standing or in a seated position. Cobb's technique is widely used for analyzing the magnitude of curvature (Figure 2). The vertebrae of maximal tilt are visually determined at both superior and inferior ends of the curvature, from where tangents are drawn following the furthermost endplate on both ends. The angle between the tangents is the sought Cobb's angle. (Cobb, 1948) The curves are also described by the direction of the convexity, as well as the location of the curve apex – the vertebra furthest way from the center of spine.

There might be multiple curves on one spine, and the term major curve refers to clinically the most important of the curves. The smaller curves are called minor curves and might be additionally indicated with terms as "lumbar" or "thoracal" depending on the curve location. A compensatory curve is a curvature beside the major curve, and has a tendency to correct the spinal alignment. (Sawin and Menezes, 1997)

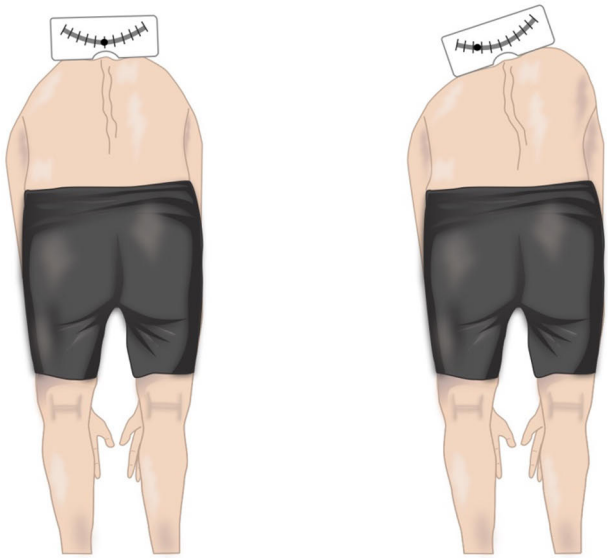

Figure 1. Adams forward bending test. On left side, bending test and measurement with scoliometer on a healthy patient. On right side, test performed on a scoliotic patient.

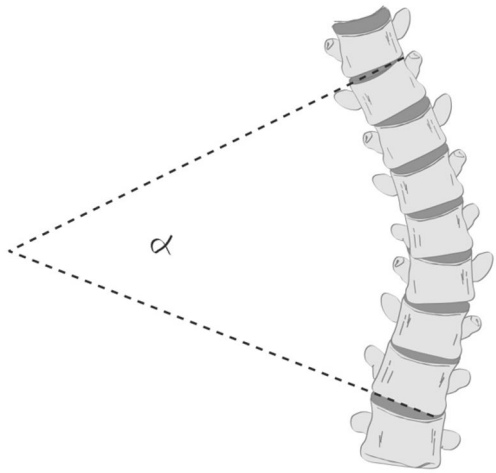

Figure 2. Measuring the scoliotic Cobb angle, anteroposterior view.

Several different types of scoliosis exist. Most common classification divides scoliosis into idiopathic, congenital, neuromuscular, and syndromic scoliosis (Williams, et al., 2014). Also, secondary scoliosis exists. Syndromic scoliosis is associated with an underlying disorder of the neuromuscular, skeletal, or connective tissue systems or other major medical conditions. Sometimes neuromuscular and syndromic scoliosis are classified together. (Karol, 2019)

Table 1. Classification of scoliosis.

Type of scoliosis	Origin	Characteristics	Prevalence
Idiopathic scoliosis	Unknown/idiopathic	Progression limited to growth period, can be treated with bracing	0.5–3% 60–80% of all scoliosis cases,
Congenital scoliosis	Congenital deficiency	Present already in early childhood, might progress	0.5–1 / 1000 births 10% of all scoliosis casees
Neuromuscular scoliosis	Any underlying neurological / muscular disease, such as Cerebral Palsy	Typically, more severe Progression is not limited to growth period Conservative treatment is often insufficient	25–100% depending on the neuromuscular disease
Syndromic scoliosis	Underlying disorder related to connective, skeletal or neuromuscular system, such as Down syndrome	Comorbidies make treatment more complicated	Depends on the syndrome
Secondary scoliosis	Caused by another condition, such as bone tumour, previous injury or operation.	Traumatic burns, or thoracotomies might cause secondary scoliosis	N/A

2.1.1 Idiopathic scoliosis

Idiopathic scoliosis, or IS, is the most common type of scoliosis, prevalence of which is 0.5–3% in pediatric population (Brooks, et al., 1975, Kesling and Reinker, 1997, Mackel, et al., 2018, Parent, et al., 2005, Willner and Uden, 1982). It covers 60 to 80% of all scoliosis cases (Lonstein, 1994, Rosenberg, 2011, Smith, et al., 2008, Terminology Committee of the Scoliosis Research Society. A glossary of terms.), and the pathophysiology behind remains unclear despite of the multiple suggestions. The current knowledge suggests IS to have a multifactorial background with underlying genetic susceptibility. (Do, et al., 2001, Wang, Qiu, et al., 2007)

The diagnosis of idiopathic scoliosis is done with exclusion: other underlying causes for scoliosis must be ruled out by history, clinical, and radiological examinations. There are three different onset times of idiopathic scoliosis, infantile includes patients aged 0-3, juvenile from 4 to 10 and adolescent patients > 10 years

(James, 1955) from which the two first can also be graded as early onset scoliosis, or EOS and the third to AIS (adolescent idiopathic scoliosis). The curve progression peaks during the growth spurt of adolescence and clearly slows down after the growth has ceased. (Charles, et al., 2006, Duval-Beaupere, 1970, Tan, et al., 2009, Weinstein and Ponseti, 1983)

Idiopathic scoliosis can be divided into treatment directed classes based on Lenke classification, that contains curve type, lumbar spine modifier (A, B, C) and sagittal thoracic modifiers (-, N, +). (Boachie-Adjei, et al., 2021). Treatment options include conservative treatment with bracing, and multiple operative options, in detail later. Spinal fusion is recommended for patients with curvature greater than 40–50°. (Weinstein and Ponseti, 1983). The most typical type of idiopathic scoliosis is thoracal dextroscoliosis, Figure 3.

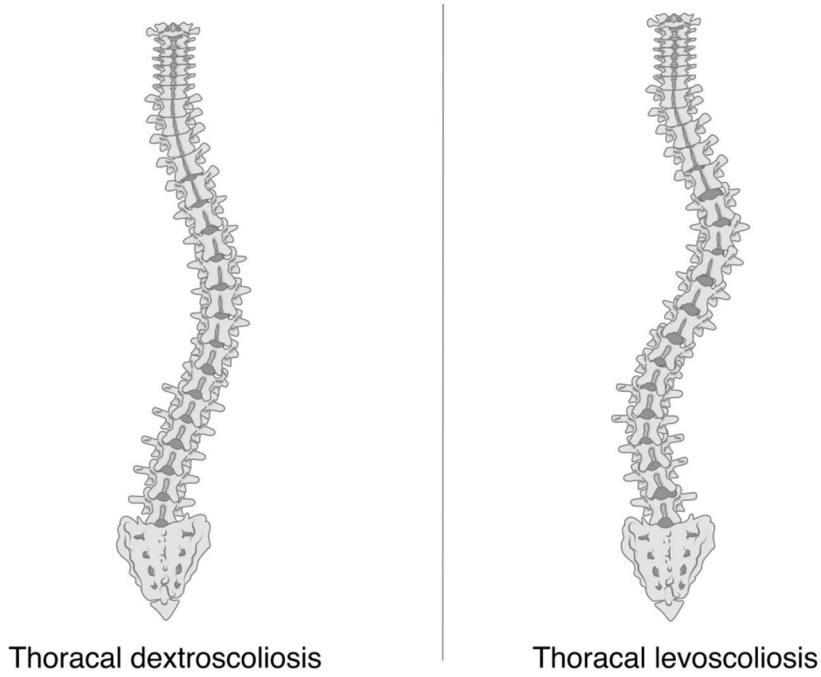

Figure 3. Anatomy of dextro- and levoscoliosis.

2.1.2 Congenital scoliosis

Congenital scoliosis is caused by congenital vertebral anomalies. Malformation might origin due to vertebral formation, segmentation or mixed defects. (McMaster and Ohtsuka, 1982) The estimated prevalence of vertebral abnormalities is approximately 0.5-1:1000 births that corresponds to approximately 10% of scoliotic

deformities (Wynne-Davies, 1975). In Finland, the prevalence has been estimated at 2.2 / 10000 births. (Heiskanen, et al., 2022) Maternal risk factors for congenital scoliosis include smoking, Diabetes Mellitus (hyperglycemia), systemic corticosteroids, and assisted reproductive technologies (Raitio, 2023) Congenital scoliosis is present already at birth, although a later change in severity might occur due to growth especially during rapid skeletal growth at puberty. (McMaster and Ohtsuka, 1982) It is also estimated that many anomalies are asymptomatic. (Giampietro, et al., 2009, Wynne-Davies, 1975) In 25% of the cases, there are multiple congenital curvature (Louis, et al., 2010, Shahcheraghi and Hobbi, 1999, Tsirikos and McMaster, 2005, Winter RB, et al.), and secondary curvature in response to the congenital abnormality also occur and can progress to more severe than the original anomaly (Louis, et al., 2010, McMaster and Ohtsuka, 1982). 30-60% of the patients also have other associated anomalies in skeletal and non-skeletal systems. (Beals, et al., 1993, Liu, et al., 2011, Louis, et al., 2010, Winter RB, et al.). If untreated, an evolution up to more than 40° curvature angle has been described in up to 75% of the cases. (McMaster and Ohtsuka, 1982, Shahcheraghi and Hobbi, 1999, Winter RB, et al.) The congenital scoliosis can be divided into subtypes regarding the type of defect, as visualized in Figure 3.

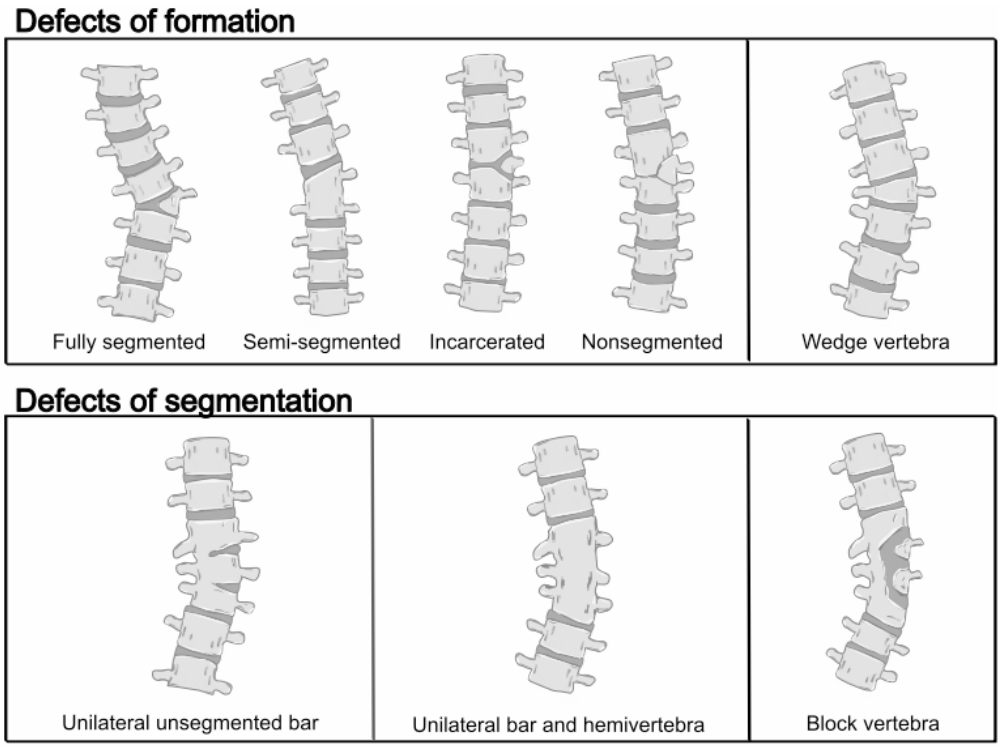

Figure 4. Deformity defects in congenital scoliosis.

2.1.3 Syndromic scoliosis

Syndromic scoliosis, or SS, includes scoliosis related to underlying systemic diseases. Chung et al. found out in their 12 year retrospective analysis, that Marfan syndrome (37%), Down syndrome (16%) and Prader-Willi syndrome (15%) were the most common underlying diagnoses for SS. (Chung, et al., 2019) Mental retardation and medical comorbidities are common in many of these syndromes which makes the treatment more complicated. The risk of complications included in the operative treatment have been found out to be significantly higher compared to idiopathic scoliosis, and comparable to neuromuscular scoliosis. (Chung, et al., 2019, Lerman, et al., 2003, Levy, et al., 2015, Milbrandt and Johnston, 2005)

2.1.4 Secondary scoliosis

Secondary scoliosis is caused due to another medical condition. Secondary scoliosis might happen for example due to bone tumor such as osteoblastoma (Lin, et al., 2008, Zhang, et al., 2016) or skin and/or soft tissue retraction due to injuries, such as severe trunk burn (Langlais, et al., 2020), or previous major operations, such as thoracotomy (Roclawski, et al., 2012).

2.2 Neuromuscular scoliosis

2.2.1 Clinical characteristics

Neuromuscular scoliosis (NMS) is a type of scoliosis with an underlying neuromuscular condition including myopathy and upper or lower motor neuron disease (Table 1). (El-Hawary and Chukwunyerenwa, 2014, Vialle, et al., 2013) (Sarwark and Sarwahi, 2007, Vialle, et al., 2013) Paraspinal muscles may be flaccid, spastic, or dyskinetic. (Bridwell, et al., 1999, Madigan and Wallace, 1981, Saito, et al., 1998)

As the group of neuromuscular scoliosis consists of various differing etiologies rather than a single pathophysiology, the classification of neuromuscular scoliosis is based on the etiology of the imbalance. Scoliosis Research Society classification divides neuromuscular scoliosis into two main categories, neuropathic and myopathic conditions. (Terminology Committee of the Scoliosis Research Society. A glossary of terms.) (Figure 4)

Regardless of the diagnosis, neuromuscular scoliosis is caused by impaired function such as flaccidity, spasticity or dyskinesia of the muscles around the spine leading to imbalance of the body. (Vialle, et al., 2013) Typically, the NMS comprises the entire thoracic and lumbar spine, including the pelvis, and results into oblique

pelvis. Thoracic hyperkyphosis is also frequently associated with neuromuscular scoliosis. (McCarthy, 1999)

As it progresses, neuromuscular scoliosis leads to difficult posture and movement difficulties, as well as difficulty in breathing by limiting chest volume. (Murphy and Mooney, 2019) On the other hand the lung function can be decreased also through the respiratory muscle dysfunction. (Newsom-Davis, 1980) In severe cases, lung impairment may be life threatening. (Roberts and Tsirikos, 2016, Wishart and Kivlehan, 2021) In addition, advanced scoliosis can be painful for the patients and cause troublesome skin problems. (Murphy and Mooney, 2019) Other associated conditions include heart problems such as cardiomyopathy, bladder dysfunction and gastrointestinal issues such as constipation and reflux. (Pruijs, et al., 2000)

The incidence of neuromuscular scoliosis varies with background diseases, and for example, CP has been associated in scoliosis incidence ranging from 25 to 90% in various studies, making neuromuscular scoliosis a significant clinical challenge for patients with neuromuscular diseases. (Sarwark and Sarwahi, 2007) The onset and progression of neuromuscular scoliosis is not limited to period of growth, but the condition may progress, or it may also occur after growth arrest for example after traumatic spinal cord injury. (McCarthy, 1999, Vialle, et al., 2013)

Table 2. Prevalence of etiological conditions and incidence of scoliosis. The references are specified in the text under each underlying disease.

	Global prevalence	**Incidence of scoliosis**
Cerebral palsy	2:1000–4:1000 (3–10 years)	15%–80%*
Duchenne muscular atrophy	1:3600 to 1:6300	97%
Poliomyelitis	N=6**	30%
Spinal muscular atrophy	1:6000–1:10000	80%
Myelomeningocele	0.1–13/1000	25–90% ***
Traumatic spinal cord injury	1.9/100000	67–100% ****

* Depending on number of limbs involved (2–4)
** 6 wildtype polio-cases in the whole World 2021
***Depending on myelomeningocele level
****Depending on injury age

I. Neuropathic

A) Upper motor neuron
- i. Cerebral palsy
- Ii. Spinocerebellar degeneration
  - a) Friedreich's ataxia
  - b) Charcot-Marie-Tooth disease
  - c) Roussy-Levy syndrome
- iii. Syringomyelia
- iv. Spinal cord tumour
- v. Spinal cord trauma

B) Lower motor neuron
- i. Poliomyelitis
- ii. Other viral myelitides
- Iii. Traumatic
- iv. Spinal muscular atrophy
- v. Werdnig-Hoffmann disease
  - a. Kugelberg—Welander disease

C) Dysautonomic disorders (Riley-Day syndrome)

II. Myopathic

A) Arthrogryposis

B) Muscular dystrophy
- i) Duchenne muscular dystrophy
- ii) Limb-girdle dystophy
- iii) Fascio-scapulo-humeral dystrophy

C) Fibre-type disproportion

D) Congenital hypotonia

E) Myotonia

Figure 5. Classification of neuromuscular scoliosis according to Scoliosis Research Society.

2.2.1.1 Deformity patterns

Coronal plane deformity is the dominant part of neuromuscular scoliosis. Literature states that C-typed scoliosis is the most common in neuromuscular disorders. (Loughenbury and Tsirikos, 2022)

Pelvic obliquity refers to coronal plane obliquity, angle value of ≥3° on upright radiographs. Pelvic obliquity is a common characteristic both in patients with adolescent idiopathic (Boulay, et al., 2006, Jung, et al., 2015, Ploumis, et al., 2018, Qiu, et al., 2012) and neuromuscular scoliosis (Berven and Bradford, 2002, Leong, et al., 1981). Pelvic obliquity in neuromuscular scoliosis is affected by the C-typed curvature that includes the pelvis, which is elevated on the concave side of the

curvature. The supra-or infra-pelvic contractures also interplay in the abnormal pelvic position. More prominent curves are associated with more pelvic obliquity. (Loughenbury and Tsirikos, 2022) Pelvic obliquity is to be considered during diagnosis and treatment planning.

Considering curve type, standardized classification systems, such as Lenke (Lenke, et al., 2003) for idiopathic scoliosis, are less common. Neuromuscular scoliosis can be classified by Lonstein and Akbarnia (1983) presented their classification of neuromuscular scoliosis in patients with cerebral palsy or mental retardation (Lonstein and Akbarnia, 1983). Figure 5. Group 1 consists of curves with compensated trunk, and Group 2. of decompensated trunk and pelvic obliquity.

Sagittal plane deformities in neuromuscular scoliosis are rarer compared to coronal plane, but still rather common. The poor muscle tone due to neuromuscular condition in lumbar level can lead pelvic retroversion and loss of lumbar lordosis, which affects the stability and compensatory mechanics of the whole spine and leads to (hyper)kyphosis. Kyphosis impairs the already compromised lung function by diminishing the thoracic height and affects the ability to maintain forward gaze. (Loughenbury and Tsirikos, 2022) Lumbar hyper-lordosis also exists in neuromuscular scoliosis, and the mechanism is related to pelvic anteversion and hip flexor contractures. (Karampalis and Tsirikos, 2014)

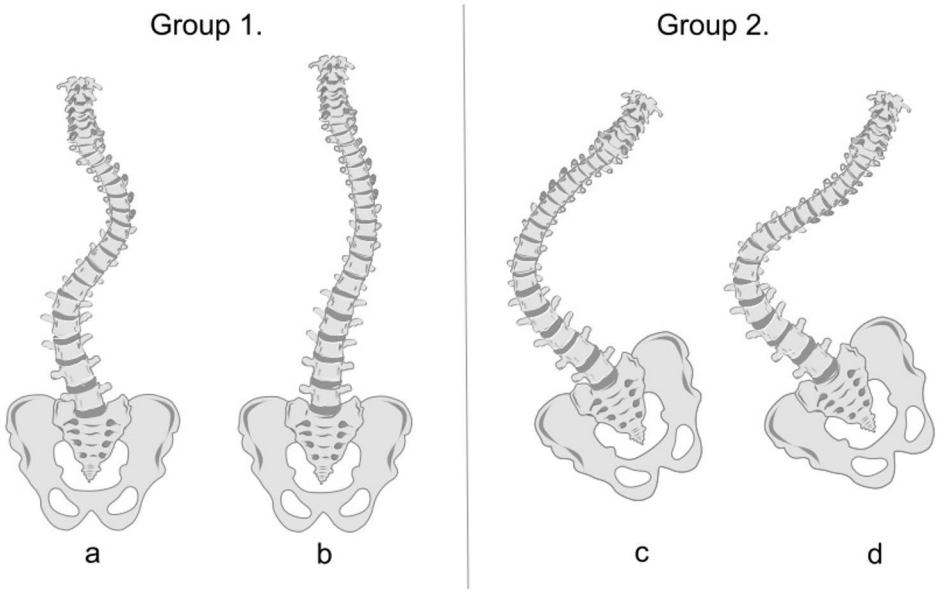

Figure 6. Classification for neuromuscular scoliosis in cerebral palsy. Adopted by Lonstein and Akbarnia. **a)** Compensated trunk, well balanced double curve. **b)** Compensated trunk, major thoracic curve, minor lumbar curve. **c)** Trunk decompensated, pelvic obliquity, small fractional caudal curve. **d)** Trunk decompensated, pelvic obliquity and main curve extending to sacrum.

2.2.2 Subgroups

2.2.2.1 Spinal Muscular Atrophy

Spinal Muscular Atrophy, or SMA, is a group of rare neuromuscular diseases that have autosomal recessive inheritance. SMN1-gene mutations or deletions cause changes in the Survival Motor Neuron (SMN1) gene, leading to a decrease in the number of lower motoneurons in the spinal cord and the nuclei of the brainstem. The chromosome 5q13 has two similar SMN genes; the telomeric SMN1 gene and centromeric SMN2 gene, which differ from each other by a single nucleotide that affects to splicing, and thereby the produced SMN protein is unstable and insufficient. (Vitte, et al., 2007) This leads to progressive symmetrical muscle weakness and atrophy. Patients also lose their respiratory function, which is the cause of major morbidity and mortality in SMA patients. (D'Amico, et al., 2011) Outbreak age and disease severity range widely from complete weakness and paraplegia in infancy to mild proximal weakness in adulthood. Severity correlates with the number of SMN2 gene copies. (Kolb and Kissel, 2015, Ross and Kwon, 2019)

SMA has four subtypes which correlate to the development of motor performance. Type 1 SMA (Werdnig-Hoffman disease) patients never sit independently, type 2 patients sit at some point in development independently but never walk and type 3 (Kugelberg-Welander disease) patients walk at least at some point in development independently. In patients with type 4 SMA, the disease does not appear until adulthood, and patients are able to walk. (Kolb and Kissel, 2015, Munsat and Davies, 1992) Incidence of SMA is approximately 1:6000 to 1:10000 births. (Ogino, et al., 2002, Prior, et al., 2010) The diagnosis is confirmed with genetic testing. (Rudnik-Schoneborn, et al., 2009, Wang, Finkel, et al., 2007)

The incidence of scoliosis in SMA patients is significant as almost all patients who do not move independently develop scoliosis. C-typed scoliosis with pelvic obliquity is the most common type in SMA children. The studies suggest the incidence in overall SMA to be around 80%. (Roberts and Tsirikos, 2016) If left untreated, scoliosis leads to thoracic deformities and restriction of respiratory function. The main principles in orthopedic treatment of SMA patients are posterior scoliosis instrumentation and contracture therapy. SMA 2 patients often end up being treated with growing rods or spinal fusion depending on the patient's age and stage of growth. SMA 1 patients are typically at lower risk for severe scoliosis, as the condition often results in death before the age of 2 years. (Finkel, et al., 2014, Mercuri, Finkel, et al., 2018, Neil and Bisaccia, 2019, Oskoui, et al., 2007, Parker, et al., 2008). Although the novel treatment options have improved survival and

thereby also the need for scoliosis surgery has increased in these patients in recent years. (Wijngaarde, et al., 2019)

In the past, treatment for SMA, especially in more severe subtypes, was largely supportive due to the poor prognosis of the disease, but since the launch of a new drug nusinersen (Spinraza®), the treatment plans have been expanded to include detailed recommendations for physiotherapy, rehabilitation, orthopedic treatment, nutrition, and respiratory treatment. (Neil and Bisaccia, 2019, Ross and Kwon, 2019)

In 2016, the first use of the drug, nusinersen, was approved. Nusinersen is an antisense oligonucleotide that modulates splicing of the SMN2 mRNA transcript, increasing including of exon 7 and the production of the full-length SMN protein. (Neil and Bisaccia, 2019) The drug is administered into the spinal canal (intrathecally). (Wurster, et al., 2019) The patient receives four doses in the first month of treatment and treatment is continued at a maintenance dose every four months. (Claborn, et al., 2019, Hoy, 2018) In scoliosis-operated patients especially infants, intrathecal administration can be challenging due to anatomy and requires laminectomy to enable the injections. (Khadilkar and Singh, 2020)

Nusinersen has been shown to improve both motor function and prevent death and final ventilator treatment. (Finkel, et al., 2017) Studies have shown that the earlier the treatment is started, the better the results. (Albrechtsen, et al., 2020, Finkel, et al., 2017) This applies even to the point that if treatment is started before the onset of clinical symptoms, the development of the disease can be prevented. (Khadilkar and Singh, 2020) The safety and tolerability of the medicine have been well studied in all age groups. (Neil and Bisaccia, 2019) The development of SMA after initiation of nusinersen therapy has so far been limitedly studied and no natural history remains unknown.

In 2020, another drug, Risdiplam®, was also approved for the treatment of SMA, the effect of which is based on the utilization of the SMN2 gene splicing and ending to the increasing the amount of full length SMN gene produced. It is administrated orally, which compared to nusinersen has been hypothesized to have an affect also in other tissues outside spinal canal. (Hamilton and Gillingwater, 2013, Messina and Sframeli, 2020, Yeo C.J.J. and B.T., 2020) In addition, direct adenoviral vector-mediated gene therapies have been studied. (Alexiades, et al., 2020, V and S., 2018), and the first of which, Onasemnogene abeparvovecene (Zolgensma®), has recently become available for SMA patients. This gene-replacement therapy with a one-time injection delivers the SMN1-gene to motor-neuron cells with promising clinical results. The criteria for gene therapy are limited as the costs remain tremendous. (Messina and Sframeli, 2020)

2.2.2.2 Cerebral Palsy

The concept of cerebral palsy (CP) includes several non-progressive conditions in which a disruption of the developing central nervous system (CNS) leads to the impairment of postural maintenance and motor function. Cerebral palsy is the most common cause of physical disability in childhood. (Kuban and Leviton, 1994) Globally, a prevalence of 2-4 cerebral palsy patients per 1000 children aged 3-10 years has been reported. (Balmer and MacEwen, 1970, Boyle, et al., 1996, Rumeau-Rouquette, et al., 1997)

Damage to the CNS leading to cerebral palsy can occur at different stages of neurological development: during the fetal period, at birth or during the first two years of life. (Surveillance of Cerebral Palsy in, 2000) The clinical characteristics depend strongly on the location, severity, and extent of the lesion. Typical features of CP patients include muscle weakness, spasticity, movement disorders, ataxia and rigidity and severity ranges from mild motor function impairment to an involvement of full body. (Kuban and Leviton, 1994, Paneth, 1986) Mental retardation and seizure disorders are also common in CP. (Balmer and MacEwen, 1970) In the treatment of CP patients, the individual characteristics, developmental status and age of the patient determine the overall treatment plan, which may include observation, physiotherapy, drug therapies such as spasmolytics, supportive devices and aids such as individual wheel chairs, parenteral therapy and orthopedic surgery. (Koman, et al., 2004)

Cerebral palsy is the most common neuromuscular diagnosis leading to NMS and scoliosis is the most common spinal deformity seen in CP (Lonstein, 1994, Murphy and Mooney, 2019).

Persson-Bunke et al. found out on their epidemiological total population study with prospective data collection that altogether approximately 15% of the cerebral palsy patients develop scoliosis with curvature angles greater than 10°, leading to diagnosis. They also found out that GMFCS (Gross motor function classification score) level IV and V and age increased the risk of scoliosis in patients with Cerebral Palsy. (Hagglund, et al., 2018, Persson-Bunke, et al., 2012) CP Patients with severe tetraparesis have also been studied and a scoliosis incidence of 67% were observed. (Madigan and Wallace, 1981)

The progression of scoliosis in CP has also been studied, and it seems to continue after skeletal maturity, most extreme of which in patients with more extensive involvement. (Thometz and Simon, 1988)

2.2.2.3 Duchenne muscular atrophy

Duchenne muscular dystrophy, or DMD, is a severe muscle disease, the most common muscular dystrophy and has a X-chromosome linked inheritance.(Moat, et

al., 2013) It is caused by mutations in dystrophin gene. (Hoffman, et al., 1987, Kunkel, et al., 1986) There are no signs of the disorder at birth as the first symptoms present in early childhood in boys between ages 3-5, with an incidence from 1:3600 to 1:6300 male births. (Chung, et al., 2016, Mendell, et al., 2012, Moat, et al., 2013) The prevalence in females is rare, and limited to chromosomal abnormalities, such as Turner syndrome. (Chelly, et al., 1986, Satre, et al., 2004, Takeshita, et al., 2017) The carrier females are usually asymptomatic or might represent with mild symptoms. (Ishizaki, et al., 2018) The clinical characteristics include progressive weakness in proximal lower limb and truncal muscles, elevated creatine kinase levels and additional calf hypertrophy. These lead to noticeable symptoms, such as gait abnormality, frequent falls, difficulty in rising from the ground and a gross motor delay. Sometimes a language or global development delay can be involved. (Aartsma-Rus, et al., 2019) Most patients initially gain gait function and strength until the age of 6, but after this, the strength gradually weakens again, and untreated DMD leads to the need of wheelchair by 12 years of age and to death due to cardiorespiratory complications by early adulthood. (Mercuri, et al., 2019)

DMD patients have problems with multiple organ systems, but the most common of these are cardiorespiratory conditions. Restrictive lung disease leading to secondary chronic respiratory insufficiency is prevalent. Vital capacity improves with growth until the age of 12, and after that decreases by ca. 5% per year. (Khirani, et al., 2014, Phillips, et al., 2001) Cardiac presentations include dilated cardiomyopathy, leading to chronic heart failure, cardiac insufficiency, and conduction disorders. A sudden death might occur due to arrythmias. (Kieny, et al., 2013, Passamano, et al., 2012)

Almost all the DMD patients not receiving corticosteroid therapy develop scoliosis. (Birnkrant, et al., 2018, Yilmaz, et al., 2004) Scoliosis further impairs the respiratory volume and thereby worsens the existing chronic respiratory insufficiency. In Duchenne muscular dystrophy an incidence of scoliosis of up to 97% has been described in the literature. (Shapiro, et al., 2014) The corticosteroid therapy has decreased the incidence of scoliosis dramatically, although scoliosis might still develop. (Birnkrant, et al., 2018, Yilmaz, et al., 2004) On the other hand the constant use of corticosteroids leads to impairment in bone marrow density, which is why increasing amount of vertebral and long bone compression fractures are observed. (King, et al., 2007)

Development in treatment options have shown clear and promising improvements to the patients' quality of life and life expectancy. Corticosteroids, spinal surgery, and artificial respirators have been proven beneficial in DMD patients. (Eagle, et al., 2002, Eagle, et al., 2007, Kieny, et al., 2013, Passamano, et al., 2012) Novel gene replacement therapy opportunities are also upcoming, yet until

further the more traditional treatment options are a golden standard of care for DMD. (Abreu and Waldrop, 2021)

2.2.2.4 Myelomeningocele

Myelomeningocele (meningomyelocele or spina bifida or MMC) is a neural tube defect, where spinal cord, meninges and vertebrae have not developed normally. It is caused by an incomplete closure of the neural tube during the fourth week of gestation, Figure 6. (Meuli, et al., 1997) Intrauterine trauma to the exposed spinal cord neurons occurs via prolonged exposure to amniotic fluid, that leads to motor and sensory deficit below the lesion, paralysis, urinal and/or fecal incontinence and cognitive disabilities. (Centers for Disease, 1989) Diagnosis is made prenatally in vast majority of cases, which allows the option to consider fetal intervention (Michejda, 1984, Nicolaides, et al., 1986, Palomaki, et al., 1999) termination of pregnancy. For children who survive to birth, lesion is surgically closed (if not closed antenatally), and any associated problems such as common hydrocephalus, tethered cord, hindbrain herniation (Chiari II malformation) and orthopedic abnormalities are appropriately treated. (Copp, et al., 2015)

It is traditionally recommended that MMC should be closed within the first 72 hours postnatally, as the risk of later complications increases when time passes, especially concerning CNS infections, shunt malfunction and neurogenic bladder prognosis. (Bowman, et al., 2001, McLone, 1998, Talamonti, et al., 2007, Tarcan, et al., 2006) As the prenatal diagnostics methods had improved and the damage to exposed spinal cord in uterus is known to be progressive, prenatal surgery options gained increasing interest. (Danzer, et al., 2012) In between the years 2003 to 2010 the National Institutes of Health (NIH) supported the Management of Myelomeningocele Study (MOMS) to evaluate the advances of prenatal intrauterine repair with promising results and since then prenatal repair has been available in specialized fetal surgery centers. Fetal surgical repair of MMC has been associated with improved early neurological outcomes compared with postnatal operation yet increased maternal risks. (Douglas Wilson, et al., 2021)

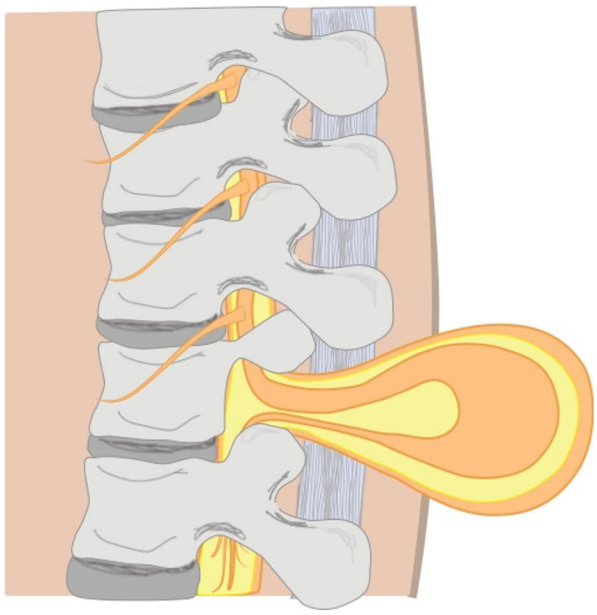

Figure 7. Anatomy of myelomeningocele.

The prevalence of MMC is from 0.1 to 13 per 1000 births globally, although there are large differences in prevalence between different areas (Januschek, et al., 2016, Li, et al., 2006, Oumer, et al., 2020, Spazzapan and Velnar, 2021). Maternal low folate level is the most strongly associated risk factor for MMC, others include but are not limited to alcohol usage, low dietary quality, and smoking. (Carmichael, et al., 2012, Grewal, et al., 2008, Hernandez, et al., 2022) From a scoliosis perspective, the condition is neuromuscular scoliosis due to flaccid paralysis, but with features of congenital scoliosis due to birth defects such as severe kyphosis (gibbus) making neonatal closure difficult (Crawford et al. Neonatal kyphectomy, Spine 2000).

Heyns et al. found a scoliosis prevalence of 78% and Trivedi et al. 52% in patients with MMC. (Heyns, et al., 2021, Trivedi, et al., 2002) The incidence correlated with the level of paralysis included in MMC, the higher the level, the higher the incidence, for example, 25% of those with L5 level and over 90% of those of MMC higher than L1. (Berven and Bradford, 2002, Muller and Nordwall, 1992)

The co-existing medical conditions in MMC, such as insensate of the skin, make it difficult to maintain brace treatment, and the pathophysiology of MMC itself complicates the surgical treatment options. (Loughenbury and Tsirikos, 2022)

2.2.2.5 Poliomyelitis

Poliomyelitis is a lower motor neuron condition, caused by poliovirus. Due to vaccination, polio outbreaks are rare in developed countries, yet the disease has not yet been eradicated globally.

In case of polio, the scoliosis can develop through three different reasons. Firstly, asymmetrical truncal paralysis leads to muscle imbalance. Secondly, the paralysis of truncal muscles can also be symmetrical, and when extensive enough, that also leads to scoliosis or other spinal deformities. The literature also describes poliomyelitic scoliosis on origin of lower limb paralysis. (Colonna, 1941, Leong, et al., 1981)

Most common curvature type in poliomyelitis is C-typed. The incidence of scoliosis associated with poliomyelitis is about 30%. (Colonna, 1941) The same treatment methods are used for polio, as for other neuromuscular conditions leading to scoliosis, but interestingly, many of the scoliosis treatments were invented during the previous polio epidemies. (Wishart and Kivlehan, 2021)

2.2.2.6 Spinal cord injury

Spinal cord injury (SCI) can occur through a traumatic or non-traumatic etiology and has been linked to late-onset neuromuscular scoliosis. In patients with non-traumatic SCI, the incidence is significantly larger than with traumatic etiology. (Kulshrestha, et al., 2020) Time of injury has been identified in multiple studies to play a major role in curvature progression. (Dearolf, et al., 1990, Lancourt, et al., 1981, Mayfield, et al., 1981, Mulcahey, et al., 2013)

The reported prevalence of spinal cord injuries in pediatric population has been estimated 1.99 to 100 000 children in United States population. Incidence is also linked to the time of injury. If a child suffers a spinal cord injury before the age of 10 years, the incidence has been reported to be as high as 100%, in comparison to 67% if the incidence occurs before the child achieves skeletal maturity. (Dearolf, et al., 1990, Parent, et al., 2010, Schottler, et al., 2012)

Impact of bracing in neuromuscular scoliosis due to spinal cord injury are inconclusive, and curvature progression delay might be achieved, yet the progression still leads eventually to spinal fusion. (Mehta, et al., 2004, Tsirikos, et al., 2008)

2.2.2.7 Other conditions

Other subtypes of neuromuscular scoliosis can be divided into neuropathic and myopathic conditions, and are listed in Table 4. (Terminology Committee of the Scoliosis Research Society. A glossary of terms.)

2.3 Treatment of scoliosis

2.3.1 General

In the general treatment guidelines of neuromuscular scoliosis, monitoring and bracing are the first line options, but their efficacy has proven to be limited. (Olafsson, et al., 1999, Saito, et al., 1998) Non-operative treatment also includes individually commissioned aids, repeated casting, and treatment of pre-existing underlying cause, such as treatment of Duchenne muscular dystrophy with steroids (Lebel, et al., 2013, Ward and Weber, 2019) and SMA treatment with nusinersen (Finkel, et al., 2017, Mercuri, Darras, et al., 2018).

2.3.1.1 Indications for treatment

The treatment of choice depends on the patient's situation and age, varying from growth-friendly management in early-onset scoliosis to definitive spinal fusion in adolescence. In neuromuscular scoliosis, conservative treatment is the recommended option when progression of the condition is limited, and the patient tolerates the conservative methods. Growth control methods should be considered when the patients can no longer tolerate the braces, or the braces do not control the curvature. (Cunin, 2015) The starting point for transition to surgical therapy in NMS patients is curvature progression, loss of back balance, and pelvic obliquity that affects sitting balance or posture. In non-ambulatory patient population, skin problems, ability to maintain adequate positioning and difficulty with hygiene maintenance might affect the decision-making. The average age and curve angle of growing rods has been estimated to be 5.7 years and 80° with a large deviation. (Akbarnia, et al., 2005, Cunin, 2015) The fundamental goal in fusion is to maintain upright posture. (Helenius, et al., 2020, Murphy, et al., 2006) Indications for surgical treatment vary from diagnosis to diagnosis. For example, in patients with Duchenne muscular dystrophy, the indications for surgical treatment often include sufficient thoracal growth (age) to maintain ventilatory flow in adulthood rather than curve progression. (Shapiro, et al., 2014)

2.3.2 Conservative treatment

Observation is the first-line treatment for patients with mild scoliosis. Regular follow-ups and upright radiographs are scheduled on an interval typically from 6-12 months, depending on the patients' age and growth. Bracing plays a major role in the treatment of idiopathic scoliosis. Studies have shown bracing to halt spinal curve progression in AIS patients and decrease the need for spinal fusion. The effect comes

in a dose dependent manner, the more time worn, the slower the curve progression.(Weinstein, et al., 2013) In NMS bracing mostly affects as an external support for posture in patients with remaining flexibility in their spine and has little or no effect on the curve progression. (Olafsson, et al., 1999, Saito, et al., 1998) However, bracing might still improve the patients quality of life, such as sitting balance or function. (Majd, et al., 1997) Customized wheelchair inserts are commonly used for posture improvement in NMS patients, head and neck support but their ability to halt the progression of curvature is rather limited. (Renshaw, et al., 1996)

In neuromuscular patients, poor adherence to treatment significantly reduces the effectiveness of brace therapy. Olafsson et al. found a positive response to bracing in small subset of ambulatory patients with muscle hypotonia, spasticity and short lumbar curvature (<40°). (Olafsson, et al., 1999)

Physiotherapy is a part of standard care of neuromuscular patients, but has shown no effects on preventing the progression or improving the existing scoliosis. (Ferrari, et al., 2010) Also, concerning physiotherapy the patient's diagnosis leading to neuromuscular scoliosis must be considered; in hypertonic conditions, patients might benefit from reflex-modulation techniques while in hypotonic syndromes, patients are often challenged by gravity and spinal collapse. (Matussek, et al., 2021)

2.3.3 Operative treatment

During growth period prior to final spinal fusion distraction or compression-based methods can be used temporarily, yet progression of neuromuscular scoliosis almost always leads to excessive spinal fusion.

2.3.3.1 Distraction methods

2.3.3.1.1 Traditional Growing Rods

In Traditional Growing Rods (TGR) method, the paired rods are placed posteriorly on each side of the spine. The rod is stabilized with pedicle screws at the top and bottom of the instrumentation. The bars have an extension area. Maintaining distraction allows normal spinal growth, and therefore instrumentation extension surgeries are performed at regular intervals, most typically every 6 months. (Akbarnia, 2007) The TGR method has been extensively studied and with TGR, patients can achieve a normal back growth and 40-50% of scoliosis can be corrected. The disadvantages of continuous surgery are a major problem. This includes a 50% risk of complications such as deep surgical site infection, implant failure such as rod

breakage, and instrumentation pull-out. (Akbarnia, 2007, Bess, et al., 2010, Kabirian, et al., 2014)

2.3.3.1.2 Magnetically controlled growing rod

Magnetically controlled growing rod (MCGR) system for the treatment of early scoliosis. After implantation, rod extension occurs non-invasively by placing an external magnetic extension machine on the patient's skin. This makes it possible to avoid repetitive surgeries and at the same time avoid the complications caused by surgeries.(Keskinen, et al., 2016, Kwan, et al., 2017) The MCGR method achieves a similar correction of scoliosis compared to the TGR method, with fewer wound complications, but on the other hand, spinal growth may be slightly less compared to the TGR method. (Calderaro, et al., 2020) Metallosis can develop in the surrounding of magnetic rods. (Teoh, et al., 2016)

The magnetic growing rods are commonly implanted with posterior pedicle screw instrumentation.(Akbarnia, et al., 2012, Cheung, et al., 2012, Lebon, et al., 2017) To avoid ossification and autofusion of the developing spine, an alternative subcutaneous technique to combine the traditional VEPTR-implant type costal to pelvis fixation has also been described in literature with promising results. (Hell, et al., 2018) (Figure 8).

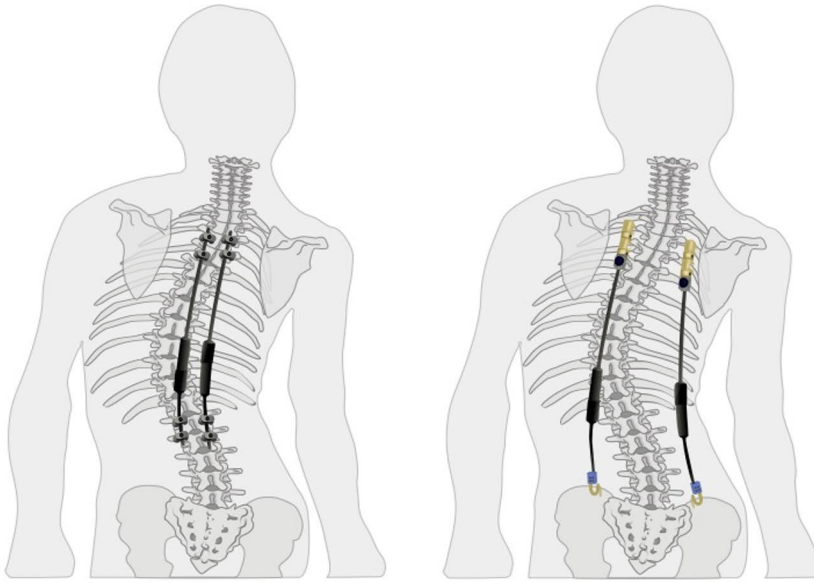

Figure 8. Positioning of MCGR implants: left side traditional technique with pedicle screw insertion, right side rib-to pelvis technique.

2.3.3.2 Growth Guidance methods

2.3.3.2.1 Shilla Growth Guidance

The Shilla method was developed to secure the possibility of growth without prolonging measures requiring repeated surgeries. The method is based on selective Apex fusion: stainless steel bars are placed on both sides of the spine posteriorly with pedicle screws, the screws in the middle of which are fixed to the bars, while the proximal and distal screws are sliding screws that move as the patient grows. This allows growth in both the cranial and caudal directions. (Luhmann and McCarthy, 2017, McCarthy and McCullough, 2015, Thompson, et al., 2005) The number of procedures required is reduced, so the risk of wound complications and surgical infections is reduced. Implant-related problems, on the other hand, are more common and often lead to reoperation.(Andras, et al., 2015, Zhang and Zhang, 2020) In addition, the spinal growth achieved was slightly less but the deformity correction was relatively similar than in the methods where bars are extended at intervals (TGR or MCGR). (Andras, et al., 2015)

2.3.3.2.2 Luque-Trolley

In the Luque-Trolley method two rods that slide against each other are placed on each side of the spine. The upper rod is attached to the spine cranially and the lower caudally. These are connected in the middle by a wire that allows them to remain in connection with each other. (Ouellet, 2011)

2.3.3.2.3 Vertical expandable prostetic titanium rib (VEPTR)

VEPTR was originally developed for the treatment of thoracic insufficiency syndrome but has also been used with successful results in the treatment of scoliosis. (Campbell and Hell-Vocke, 2003, Dede, et al., 2014, El-Hawary, et al., 2020, Emans, et al., 2005) The fixation depends on the type of scoliosis and surgeons' preference: the proximal hooks are placed typically around upper ribs such as T3-T4 with single or double rib cradle and the distal fixation can be placed either to lower rib cradle, to ileum with hooks, or to lumbar vertebral pedicles by pedicle screw instrumentation (Figure 8). (Parnell, et al., 2015)

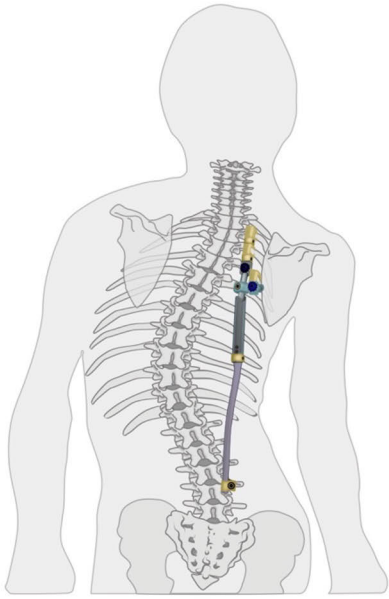

Figure 9. VEPTR implant with rib to lumbar insertion.

2.3.3.3 Compression methods

Compression methods have been studied mainly in idiopathic scoliosis, and their use in neuromuscular patients is rare.

2.3.3.3.1 Stapling

The anterior growth guiding metal rivets (hemiepiphysiodesis) are placed thoracoscopically and can achieve a good result of 70-80% in EOS with only moderate < 35° skew. The results are comparable to corset therapy. (Betz, et al., 2010)

2.3.3.3.2 Anterior vertebral body tethering

Anterior vertebral body tethering or spinal tethering is a method in which a bicortical screw is placed on each vertebra and a cable is tensioned between the screws (Newton, et al., 2018, Samdani, et al., 2014). The correction of scoliosis occurs in two stages. First, during surgery but also in the future with growth modulation because according to the Hueter-Volkmann principle as growth plate compression reduces growth and distraction increases. (Roaf, 1960, Sanders, et al., 2008) The anterolateral approach has been found to be more effective in deformation correction (Aubin, et al., 2018, Jain, et al., 2014) therefore tethering operations are performed thoracoscopically, mini-invasively or in an open surgery.

2.3.3.4 Fusion

After growth has ceased or when sufficient growth has been achieved to obtain sufficient lung volume (Karol, 2011), and other instrumentation methods have not been sufficient, a final fusion can be completed. The goal of spinal fusion in scoliosis generally, as in idiopathic and congenital scoliosis patients, is to achieve fixed ossification of the spine to prevent an increase in malalignment, correct the current misalignment in the spine and pelvis. However, as the most NMS patients are non-ambulatory, the main goal in NMS is often to restore balance while sitting or standing. (Murphy and Mooney, 2019) The extent of the merger and the method of surgery will be decided on an individual basis. However, in many NMS patients, the instrumentation is extended to the upper parts of the thoracic spine, thereby simultaneously correcting possible thoracic (hyper) kyphosis, which on the other hand could be a risk factor for surgical failure (Sink, et al., 2003). Distally, the length of the instrumentation is affected by the patient's ability to exercise, pelvic inclination, and whether the disease that caused the patient's scoliosis is spastic or non-spastic: the pelvic inclination that develops in spastic patients is often greater. (Takaso, et al., 2018) In NMS patients with preoperative sagittal or coronary imbalance, it is recommended to extend the operation distally to include pelvic fixation. (Tondevold, et al., 2020) Non-ambulatory neuromuscular patients typically undergo a spinal fusion extending from the upper thoracic spine all the way to pelvis. (El-Bromboly, et al., 2021, El-Hawary and Akbarnia, 2015, Tondevold, et al., 2020, Wishart and Kivlehan, 2021) Concerning pelvic fixation, obliquity of > 15° requires pelvic fixation. (Suresh, et al., 2021) The S2-Alar iliac method has been linked to less implant failure in comparison to standard iliac screw method. (Lee, et al., 2018)

In spinal fusion the desired vertebrae are ossified together by means of instrumentation. The traditional surgical technique has been to combine anterior diskectomy and ligament release to posterior instrumentation. (Drummond, 1996, Tokala, et al., 2007) During the last years, the most commonly used method for spinal fusion has been posterior spinal fusion with segmented posterior pedicle screw insertion (Hopf and Eysel, 2000), which give better correction of scoliosis and pelvic obliquity than hybrid constructs in patients with NMS (Mattila, et al., 2012). The operation is first initiated by exposing the posterior elements of the spine with electrocautery. When a total exposure has been reached, the surgeon proceeds to inserting posterior pedicle screws, typically with a free-hand technique (Helenius, et al., 2019, Kuklo, et al., 2005), combined to intraoperative c- or o-arm screw insertion verification (Saarinen, et al., 2022). Intraoperative navigation systems that are based on the preoperative computer tomography imaging and navigate through stereotactic intraoperative visual imaging can be used as support of the pedicle screw implantation. (Moore, et al., 2021) Correction of deformity is then continued using bilateral rods. Bony auto- (for AIS and NMS patients) and allograft (for NMS

patients) might be used to maximize the potential of posterior bony elements to obtain spinal fusion. In addition, osteotomies may be performed during surgery to facilitate spinal rigidity. (Ha, et al., 2020)

If the patient has a very large curvature of the spine, preoperative halo-gravity traction can be used in ward conditions (Sun, et al., 2020).

The debate about the need for GFSI treatment continues, and recently there has been a lot of discussion about the possibility of early fusion in 7–11-year-old EOS adolescents. Li et al. studied the same phenomenon in neuromuscular patients, and found early fusion to result in less spinal growth than GFSI, but GFSI patients had an 8 times higher risk of complications, and a 9 times higher risk of unplanned reoperation compared to the fusion group.(Li, et al., 2021) In a retrospective comparative study, Keil et al. found that GFSI treatment results in an average of 2 cm more chest height compared to early definitive fusion but suggested that this may often not be relevant to patient prognosis.(Keil, et al., 2021) When considering GFSI treatment, one should carefully weigh the harms and benefits and consider whether an increase in chest volume is beneficial for the patient in question.

2.3.4 Treatment results

Mean correction of 65% in spinal fusion has been reported previously. (Benson, et al., 1998, Gitelman, et al., 2008) Acceptable surgical outcome can be achieved with a screw density of 70%. (Wolfram, et al., 2022) Sarwahi et al. conducted a review of NMS and AIS patients undergoing spinal fusion and found out that the results from ambulatory NMS patients and AIS patients were statistically similar, whereas non-ambulatory NMS patients showed inferior results. (Sarwahi, et al., 2022)

2.3.5 Complications

Studies have shown that patients with neuromuscular scoliosis have a higher risk of intra- and postoperative complications associated with surgical treatment than patients with idiopathic scoliosis (Cognetti, et al., 2017, Reames, et al., 2011, Rumalla, et al., 2016, Toll, et al., 2018). Complication rate to up to 40% has been described in the literature. (Rumalla, et al., 2016) The most common postoperative complications in the treatment of NMS patients with spinal fusion are bleeding, infections, dyspnea, gastrointestinal issues (dysphagia, ileus), implant complications and death (Brooks and Sponseller, 2016). The incidence of complications in NMS patients has ranged from 6 to 40% in different studies (Cognetti, et al., 2017, Rumalla, et al., 2016, Toll, et al., 2018, Turturro, et al., 2017). In particular, the incidence of bleeding (Jain, et al., 2012) and infections has been studied from many perspectives. (Glotzbecker, et al., 2013)

The postoperative wound infection risk after spinal fusion in NMS patients is more than ten times higher compared to AIS. (Mackenzie, et al., 2013) Use of postoperative subfascial drain has been shown to be beneficial to wound healing and recovery and is commonly used in pediatric spinal surgery.(Blank, et al., 2003)

2.3.6 Perioperative bleeding

Spine surgery in NMS patients is associated with a risk of significant blood loss, due to the long dissection required for the fusion itself, in addition to the patient-related tendency to bleed more. (Jain, et al., 2012, Meert, et al., 2002) There are many operation-related reasons for profuse bleeding in posterior spinal fusion: high blood supply to the paraspinal muscles, epidural plexus bleeding, osteotomies in the posterior column and bleeding from the cancellous bone while inserting the pedicle screws in posterior pedicle screw technique might be causes for voluminous bleeding. (Miao, et al., 2015, Ogura, et al., 2019, Smorgick, et al., 2013) Total perioperative bleeding can be divided into intraoperative, drainage and hidden blood loss, out of which intraoperative and drainage bleeding are directly measurable, and hidden blood loss must be estimated. (Sehat, et al., 2000)

Shapiro et al. concluded that the neuromuscular diagnosis plays a role in more voluminous bleeding, and depicted that patients with Duchenne muscular dystrophy have a tendency for highest amounts of perioperative bleeding. (Shapiro and Sethna, 2004) Edler and al. stated in their retrospective review, that when taking into account the demographic differences and the differences in operation between AIS and NMS patients, NMS patients had still a 7-times higher risk for losing >50% estimated blood volume compared to idiopathic control patients. (Edler, et al., 2003)

Table 3. Risk factors for perioperative bleeding in spinal fusion in neuromuscular scoliosis.

Factors increasing bleeding	Factors reducing bleeding
Lower body weight	Anterior approach
Male sex	Use of plasma blade
Older age	Use of bipolar sealer device
Larger preoperative curvature angle	Wiltse approach
Extent of fusion (levels)	Use of Cell-saver
Number of osteotomies performed	Use of gelatin matric with human thrombin
Higher preoperative hematocrit	Perioperative tranexamic administration
Lower preoperative platelet count	Maintaining intraoperative hypotension
Diagnosis of Duchenne muscular dystrophy	Larger amount of transfused fresh frozen plasma

Concerning other patient related demographics, lower body weight, (Meert, et al., 2002) older age and male sex (Jia, et al., 2017, Toombs, et al., 2018) has been associated with larger blood loss.

Larger preoperative curvature angle, longer duration of the operation and the extent of the fusion level and number of osteotomies performed have been also linked to more voluminous bleeding in spinal fusion for NMS patients. (Li, et al., 2022, Shapiro and Sethna, 2004, Song, et al., 2021)

When it comes to operative techniques used, anterior approach, plasma blade usage, bipolar sealer devices and Wiltse approach have been found to have a beneficial influence on the total bleeding in spinal fusion surgeries. (Hardesty, et al., 2018, Kieser, et al., 2020, Piazzolla, et al., 2020, Shapiro and Sethna, 2004)

Tranexamic acid administration, fresh frozen plasma amounts, preoperative hematocrit and platelet levels have also been associated with the amount of bleeding in the fusion. (Hasan, et al., 2021, Lewen, et al., 2021, Sadacharam, et al., 2020) Cell-saver intraoperative blood salvage systems with autologous blood transfusions and the use of antifibrinolytic medications, such as Gelatin matrix with human thrombin, (Helenius, et al., 2016) have been found to be beneficial for NMS patients undergoing spinal fusion. (Michelet, et al., 2018, Thompson, et al., 2008) Maintaining intraoperative hypotension have also proved its efficacy in diminishing the intraoperative bleeding. (Michelet, et al., 2018)

Brenn et al. investigated. the clotting parameters of patients with neuromuscular scoliosis undergoing spinal fusion, found out that partial thromboplastin time and prothrombin time in neuromuscular patients were significantly lower in comparison to patients with idiopathic scoliosis, although both of these were within laboratory limits in both groups. (Brenn, et al., 2004) Other abnormalities in clotting parameters concerning patients with neuromuscular scoliosis have not been described in the literature.

2.3.6.1.1 Hidden blood loss

Sehat et al. introduced the concept of hidden blood loss in their publication of knee arthroplasty. (Sehat, et al., 2000) Hidden blood loss encompasses the blood accumulated perioperatively in the tissues surrounding and in the surgical area. (Kolz, 2022, Li, et al., 2022, Wang, et al., 2021) It is thought to be caused by mechanisms of hemolysis, extravasation and subfascial hemorrhage. (Miao, et al., 2015, Ogura, et al., 2019, Smorgick, et al., 2013)

The hidden blood loss can be estimated by using different formulas, for example the Gross formula (Figure 9). In Gross equation, the pre- and postoperative hematocrit levels are utilized to calculate the estimated total perioperative bleeding. (Gross, 1983) Hidden blood loss can then be calculated by adding the amount off

infused blood and subtracting the measured bleeding from the estimated total blood loss. (Bourke and Smith, 1974, Nadler, et al., 1962, Smorgick, et al., 2013, Wang, et al., 2021)

In spine surgery research, hidden blood loss has been described as notable part of the total blood loss.(Ogura, et al., 2019) Kolz et al. found out in their AIS patient cohort, that the hidden blood loss exceeded the intraoperative bleeding. (Kolz, 2022) Smorgick et al. reported hidden blood loss estimates of approximately 40% of the total blood loss. (Smorgick, et al., 2013) Hidden blood loss in NMS patients' spinal fusion has not been reported previously.

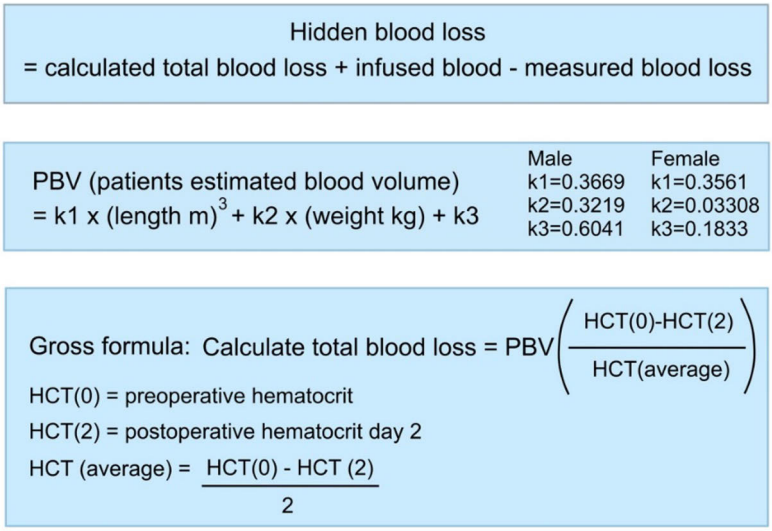

Figure 10. Calculation formula for hidden blood loss, adapted from Gross et al. (Gross, 1983) published in connection with Study I.

2.4 Health-related quality of life

The most frequently used questionnaire in spinal research is the Scoliosis Research Society-24 (SRS-24) outcome questionnaire. (Haher, et al., 1999) SRS-24 consists of 24 questions in seven categories: pain, general function, general self-image, general activity, satisfaction, postoperative function, and postoperative self-image. The questions are scaled from 1 to 5, 5 meaning the best possible outcome on quality of life and 1 meaning the worst possible outcome concerning quality of life. The maximum score for the questionnaire is 120, that is divided by the number of questions, higher score meaning better overall outcome. The score was originally developed for AIS patients, which might deteriorate the accuracy of the questionnaire in NMS patients. Preoperative quality of life can be assessed with the same questionnaire by leaving out the last 3 domains of questions 16-24 (satisfaction,

postoperative function, and postoperative self-image) and dividing the total score by 15.

Health-related quality of life after spinal fusion has been studied in adolescents with idiopathic scoliosis, and the current literature suggests that explicit improvements in health-related quality of life in AIS patients after spinal fusion have been observed compared to control group with observation. (Helenius, et al., 2019)

In papers reporting the health-related quality of life in NMS population, similar results have been reported. Some improvements in quality of life have been demonstrated in multiple papers (Miller, et al., 2020, Roberts and Tsirikos, 2016, Suk, et al., 2015), but the results are not directly comparable as there is a wide selection of questionnaires used.

Hsu et al. investigated the overall differences in HRQoL in different scoliosis types and a comparison to healthy children and found out that the quality of life of NMS patients was inferior to other types of scoliosis. Yet their analysis did not specify what phase of treatment was current. Also, the number of neuromuscular patients, N=15, remained small. (Hsu, et al., 2019)

Mercado et al. performed a systematic literature review to find out whether spinal fusion improved the quality of life in different types of neuromuscular patients. The conclusion states that based on their review, spinal fusion improves the quality of life in patients with Duchenne muscular dystrophy and cerebral palsy, yet not in myelomeningocele patients. (Mercado, et al., 2007)

In retrospective review of 150 EOS patients, Shaw et al. found a clear difference in health-related quality of life following surgical intervention between NMS and AIS/congenital scoliosis subgroups. (Shaw, et al., 2023)

Miller et al. studied the improvement in HRQoL in 157 CP children (under the age of 21) after spinal fusion and found out that meaningful improvement in HRQoL assessed by CPCHILD (Caregivers Priorities and Child Health Index of Life with Disabilities) scale was seen in a little over third of the patients, and it correlated with worse preoperative quality of life scores. (Miller, et al., 2020)

Suk et al. scoped the improvement of quality of life in neuromuscular scoliosis after spinal fusion and found a statistically significant improvement in body pain and social functioning domains, when using a SF-36 questionnaire. They stated that functional results do not necessarily correlate with the quality-of-life outcome. (Suk, et al., 2015)

Obid et al. reported an improvement of quality of life after spinal fusion in NMS population in their cohort study. (Obid, et al., 2013)

Ersberg et al. conducted a retrospective register study with SRS-22r questionnaire, an updated model from the traditional SRS-24 to compare the quality-of-life improvements between AIS and NMS patients. They did not find any

statistically significant differences between the groups, yet an improvement of function was noted in NMS group. (Ersberg and Gerdhem, 2013)

Table 4. Studies made of postoperative HRQoL after spinal fusion in NMS patients.

Authors	Questionnaire	Patients	Outcome
Miller et al.	CPCHILD (Caregivers Priorities and Child Health Index of Life with Disabilities)	N = 157 Age: Under 21 years Diagnosis: Cerebral Palsy	36% of the patients had meaningful improvement of HRQoL
Suk et al.	MDSQ (Muscular Dystrophy Spine Questionnaire) SF-36 (Short From 36)	N = 58 Age: 15 ± 4.1 years Diagnosis: Multiple	MDSQ: improved sitting balance SF-36: less pain and better social function
Obid et al.	PEDI (Pediatric disability inventory) GMFS(Gross motor function scale)	N = 46 Age: mean 12.7 Diagnosis: Multiple	Improvement in quality of life
Ersberg et al.	SRS-24 (Scoliosis Research Society 24 questionnaire)	N= 32 Age: 14.7 ± 2.8 Diagnosis: Multiple	Improvement in quality of life.

2.5 Bone health

2.5.1 Bone health in scoliosis

Multiple studies have shown the AIS patients to have lower bone mineral density (BMD) in comparison to healthy peers, and this might develop into osteopenia. (Cheng, et al., 1999, Cheng, et al., 2000) Yu et al. demonstrated the phenomenon in their study of 214 AIS girls, and in their study measurements of BMD were made with a high resolution peripheral quantitative computed tomography. (Yu, et al., 2014) The effect is significant centrally, such as in spine, but smaller differences have also been observed at peripheral skeletal sites. (Diarbakerli, et al., 2020) AIS has been linked to Vitamin-D deficiency, which plays a role in the low BMD levels observed. (Balioglu, et al., 2017) Bone health has also been linked to curve progression in AIS. (Hung, et al., 2005, Yip, et al., 2016)

As the first-line treatment for idiopathic scoliosis is bracing, the effect of bracing on BMD has been reported previously in various studies. The results are however somewhat contradictory. In a report from Cook et al., a significant reduction of spinal BMD in adolescents with bracing treatment was observed, while Thomas et al. did not observe any reduction of BMD after treatment of neither bracing nor surgery. (Cook, et al., 1987, Thomas, et al., 1992) Sun et al. assessed the BMD in bracing treated patients, and represented a comparison with reported normal values with no significant differences. (Sun, et al., 2006) Snyder et al. conducted two studies on the matter, and found no changes in BMD in study constructs of bracing versus observation group (Snyder, et al., 1995) and effects of bracing in a one-year follow up (Snyder, et al., 2005).

The vitamin-D status of the AIS patients undergoing spinal fusion should be examined and treated preoperatively, as low levels of vitamin-D lead to an increased risk of complications, such as fractures, instrumentation failure or increased postoperative back pain. (Adogwa O, 2018, Mabey, et al., 2016)

The bone health after spinal fusion was studied primarily in preclinical canine studies by McAfee and Dalenberg, and their studies demonstrate a reduction of BMD caused by rigid spinal implants. (Dalenberg, et al., 1993, McAfee, et al., 1989) In AIS, very long-term follow-ups after spinal fusion have also been conducted. Akazawa et al. studied the long-term postsurgical progression of BMD in adults 27 years after spinal fusion for idiopathic scoliosis and found out that 4.3 and 39.1% of the patients had osteoporosis or osteopenia respectively. (Akazawa, et al., 2017) Ohashi et al. found out that over 50% of their patients had osteoporosis or osteopenia in an average of 32 year follow up (Ohashi, et al., 2018). Watanabe et al. observed similar findings in their retrospective follow-up study. (Watanabe, et al., 2019)

2.5.2 Bone health in neuromuscular diseases

Low BMD-levels have a high prevalence in patients with neuromuscular diseases. (Ness and Apkon, 2014) Maturity stage, BMI and the level of mobility have been shown to have an independent influence on BMD levels. Ability to walk diminishes the risk of BMD decrease significantly. (Larson and Henderson, 2000, Razmdjou, et al., 2015) When measuring the BMD in neuromuscular patients from conventional x-ray absorptiometry imaging, the patient size should be taken in account in the analysis, as the patient age does not directly correlate to size in neuromuscular patients. (Crehua-Gaudiza, et al., 2019)

2.5.3 Bone health in SMA

Previous literature recognizes reduced BMD as a clinical issue in scoliotic SMA children. (Campbell, 1965, Granata, et al., 1991) The disease itself has been proven to play a major role in bone health, and the BMD of SMA patients is also inferior to patients with other types of neuromuscular diseases. (Khatri, et al., 2008) Also, the effect of muscle weakness also plays a role in bone health of SMA children. (Hensel, et al., 2020) Vermeren et al. found out in their mice model study that SMN-protein, the key pathophysiological factor in development associated with bone metabolism. (Vermeren, et al., 2017) Reduced BMD leads also to increased risk for fragility fractures. (Vestergaard, et al., 2001)

3 Aims of the Study

1. To compare the perioperative bleeding characteristics of NMS and AIS patients undergoing spinal fusion. (I)
2. To determine the bleeding characteristics for hidden blood loss in children with neuromuscular scoliosis undergoing spinal fusion. (I)
3. To examine the risk factors for bleeding in spinal fusion in NMS patients. (II)
4. To assess the impact of spinal fusion with segmental pedicle screw instrumentation on health-related quality of life of NMS patients. (III)
5. To evaluate the effect of growth-friendly instrumentation on bone health in SMA children. (IV)

4 Materials and Methods

4.1 Ethical aspects

The patient data used in the studies I-III origins from our institutional spine register in the pediatric orthopedics unit of University of Turku, that comprises the data of all operated spine patients willing to give their patient information for research use, since 2009 until present. The data of the register is prospectively updated when new patients enroll. For studies I-III the data was retrospectively collected from the patient register in question. Approval from the ethical committee was obtained for the studies I-III, (ETMK 96/1801/2020)

The study IV was conducted in the University Medical Center Göttingen, department of Pediatric Orthopedics and was approved by the institutional Ethics Committee of University Medical Center Göttingen (number 33/8/17).

4.2 Standardized perioperative protocol

The operations in question in studies I–III were performed at the University Hospital of Turku using a standardized protocol for perioperative care. The protocol consisted of anesthetic and surgical pre-, intra-, and postoperative components.

4.2.1 Surgical protocol

Preoperative surgical protocol included clinical examination, imaging with posteroanterior and lateral upright radiographs (sitting for NMS), and spine MRI imaging. Preoperative laboratory testing protocol consisted of blood count, coagulation profile (platelets, activated thromboplastin time, international normalized ratio, thrombin time), creatinine, c-reactive protein, creatinine kinase, procalcitonin and ferritin.

Abnormalities in preoperative testing were addressed individually for each patient. In cases of low ferritin, patients received an oral iron supplement preoperatively. Abnormalities in coagulation tests were responded to by consulting pediatric hematologists, who clarified the susceptibility to clotting with further test when necessary.

Additionally, consultations were made to other pediatric specialists based on individual patient characteristics, such as pulmonology concerning pulmonary

function and neurology concerning the continuities of epilepsy medication on perioperative period.

Preoperative surgical planning including the implant placement, the need of osteotomies and the extent of fusion level was performed based on the imaging. The guidelines for fusion level for NMS patients were T2/T3 to ileum for non-ambulatory patients. The distal level of L4 to L5 was planned for ambulatory patients without pelvic obliquity, and S2AI or iliac crews for ambulatory patients with pelvic obliquity.

Prophylaxis dose of antibiotics (Cefuroxime and Vancomycin) were infused at induction and continued 3 doses postoperatively.

The patients were placed in prone position with a careful layout to prevent pressure ulcer in long operation. After the incision, the posterior elements were exposed to subperiosteal level with monopolar electrocautery, and simultaneous hemostasis was performed with bipolar and temporary packing. Cell-saver device was used for intraoperative blood salvage in 86% of the patients.

Posterior pedicle screws (6.35 Legacy, Solera 6.0, Medtronics Spinal and Biologics, Memphis, Tennessee, USA; Mesa2, Stryker Spine, USA) were then placed bilaterally by a single experienced senior pediatric orthopedic surgeon with a free-hand technique, and the placement was confirmed with C-arm radiographs, until O-arm became available in our institute year 2016. (Helenius, et al., 2019, Kuklo, et al., 2005, Saarinen, et al., 2022) Scoliosis correction was implemented inserting dual titanium rods to pedicle screws. Direct translation and segmental compression or distraction were used to optimize the correction result, aiming at >70% correction of spinal deformity in both coronal and sagittal plane in both NMS and AIS and obtaining the horizontal pelvis in NMS.

A routine neurophysiological monitoring with motor evoked potentials, somatosensory evoked potentials and lumbar nerve root EMG was carried out at preset operational time points: incision, full exposure, pedicle screw insertion, correction and at the end of the operation, an in addition every 20 minutes intraoperatively.

In addition to the autograft received from the patient's own osteotomies and facetectomies NMS patients received a morselized femoral head allograft, which were applied on posterolateral bony elements to achieve spinal fusion. A routine use of gelatin matrix with human thrombin (2-4 x 5 mL Floseal, Baxter) was included in our surgical protocol to restrain the bleeding from pedicle screw channels, and cancellous bone as well as from the epidural space when performing osteotomies.

Wound closure was performed in multiple layers: running sutures in fascia (Vicryl 1), subcutaneous tissue (subdermal, Vicryl 2-0) and skin (intradermal, absorbable suture, Monocryl 3-0). The protocol included a closed suction subfascial drain, for the first 24-hours postoperatively (Hemovac 14, Zimmer Biomet, Warsae, Indiana, US), and drainage was only elided in case of special circumstances, such as

epidural bleed. Intraoperative bleeding was reported by measuring the amount of blood suctioned from the surgical site and absorbed into the drapes and subtracting that with the amount of fluid used for irrigation.

Postoperative care included a pediatric intensive unit follow up length of which depended on the individual condition, minimum of 24 hours.

4.2.2 Anesthetic protocol

Total intravenous anesthesia was performed for all operations. Propofol, remifentanil and dexmedetomidine were infused for sedation, anesthesia, and analgesia. Anesthetically the patients were kept normothermic, and a mean blood arterial blood pressure level of 65-75 mmHg was maintained throughout the operation, as well as 24 hours postoperatively. Vasopressors, such as norepinephrine were used, if necessary, to maintain the level. All patients received tranexamic acid (TXA) during the operation, a bolus dose of (30mg/kg maximum 1500mg) was given briefly before incision, and then continued as an infusion (10mg/kg/h), maximum 500mg/h throughout the operation.

The autologous blood collected intraoperatively with cell saver was returned to the patient. The hemoglobin threshold of 80g/L was used as a protocol for allogenic red blood cell transfusions. If the patient's blood loss exceeded 50% of the estimated blood volume, an infusion of fresh frozen plasma was given, and if the bleeding exceeded 100% of the EBV, platelets were also infused.

4.3 Study designs

4.3.1 Study I

The study I was a retrospective cohort study with consecutive NMS patients undergoing spinal fusion in Turku University hospital between the years 2009 and 2021. All the 81 available consecutive NMS patients were selected as cohort and 199 AIS patients as control group. During the patient record review, one patient was excluded from our cohort due to an operational complication that led to reoperation on the first postoperative day. The findings were compared to a control cohort undergoing similar operation during the same years. The intraoperative, drainage, hidden and total blood loss and transfusions given were used as markers for bleeding. Hidden blood loss was calculated using Gross formula according to the principles represented in the literature and visualized in our Figure 9. The primary analysis of differences in bleeding were made using bleeding amount in mL, but in order to remove the effect of patient size and extent of surgery, blood loss rates were standardized by patient weight and number of fusion levels for further analysis.

Table 5. Study designs.

STUDY	Design	Main focus	Patients (N)	Controls (N)	Age ± SD	Sex (% female)
STUDY I	Retrospective cohort Study	Bleeding characteristics	81	199 AIS patients	15.2 ± 3.4	45%
STUDY II	Retrospective cohort study	Risk factors for perioperative bleeding	81	199 AIS patients	15.2 ± 3.4	45%
STUDY III	Matched Case-control study	Health-related quality of life	60	120 AIS patients	18.1 ± 3.9*	55%
STUDY IV	Prospective cohort study	Bone mineral density	42	29 Healthy adolescents	13.0 ± 1.5	56%

* Age at final follow up

4.3.2 Study II

The study II was a retrospective cohort study on risk factors for perioperative bleeding in 81 NMS and 199 AIS patients. The cohort used in Study II is the same as described under study I. The risk factors included in the analysis were sex, age, Body Mass Index (BMI), angle of preoperative main curvature, fusion level, operation duration as posterior time, number of osteotomies performed and preoperative laboratory levels (leukocytes, erythrocytes, hemoglobin, hematocrit, MCV (mean corpuscular volume), MCH (mean corpuscular hemoglobin), Platelets, Ferritin, aPTT (activated partial thromboplastin time), Thrombin time TT, International Normalized Ratio INR, C-reactive protein CRP, creatinine, potassium (K), magnesium (Mg), sodium (Na), and procalcitonin.

4.3.3 Study III

The study III was a retrospective case-control study, assessing the health-related quality of life in children with neuromuscular scoliosis undergoing spinal fusion with posterior pedicle screw instrumentation. The operations were performed between the years 2009 to 2020 in the University Hospital of Turku. All the NMS patients with available existing HRQoL data were enrolled in the study, N=60. A control group of adolescent idiopathic scoliosis patients undergoing similar spinal fusion was chosen, and gender and age (at the last follow up ±3.5 years) matching for control group of patients was performed in a 2:1 ratio (N=120). The minimal follow-up time was 2 years for all patients.

The SRS-24 questionnaire was used to assess the health-related quality of life, and the participants were requested to fill the questionnaire at three timepoints: preoperatively, 6 and 24 months after the operation. As the questionnaire consists of

seven domains of which 3 (and 9 questions) assess the postoperative situation, and 4 both, the patients were instructed to answer only the 15 first questions preoperatively. If the patient was incapable of filling in the questionnaire themselves, due to a disability or other reason, the form was filled out by a caregiver.

The clinical relevancy of HRQoL improvements were tested against predetermined levels of minimum clinically important difference (MCID). (Adindu, et al., 2023) As there are no available predetermined MCID values for SRS-24 score, the nearest alternative of MCID for SRS-22R scale was used to estimate the clinical relevancy. MCID for SRS-22R after surgical correction was defined by Carreon et al. MCID thresholds of 0.2 for pain, 0.08 for activity and 0.98 for appearance were used in our study. (Carreon, et al., 2010).

4.3.4 Study IV

The study IV was a prospective cohort study on volumetric bone mineral density (vBMD) of adolescents with spinal muscular atrophy. The study was conducted in the department of pediatric orthopedics in the University Clinic of Göttingen, Germany. In total 42 adolescents with SMA undergoing spinal fusion for scoliosis between the study enrollment time in years 2017 to 2022 were included in the analysis.

17 of our cohort patients had been pre-treated with GFSI – growth friendly spinal implants with bilateral rib-to-pelvis implantation prior to the preoperative planning of spinal fusion. 15 patients had had MCGR implants, and 2 patients had had originally VEPTR implants and a later conversion to MCGR. 25 patients presented to the preoperative examination without prior surgical treatment. Demographical data and imaging results were reviewed and collected from the institutional database.

An additional age- and sex-matched control group of 29 otherwise completely healthy adolescents undergoing computer tomograph imaging for other reasons was selected for the two study groups. The indications for imaging included but were not limited to trauma and spondylolisthesis. Out of the control group, 10 patients underwent native computer tomography imaging and 19 were examined with contrast enhanced (Imeron 350, iodine concentration of 350mg/ml, [Bracco imaging, Deutschland GmbH, Konstanz, Germany]) CT imaging. Scans with maximal slice of 0.6 to 0.75 mm were included, and all patients with spinal abnormalities were excluded from the study. The vBMD values of contrast enhanced images were converted according to Bauer equation (2007) to adjust for artificially higher measurements caused by the contrast agent (Bauer, et al., 2007), $BMD_{converted} = 0.96 \times BMD_{measured} - 20.9$ mg/mL.

All patients were examined to assess the health, individual spinal deformity characteristics and suitability for operation prior to the spinal fusion. Computer images of the spine with a slice thickness of 0.6 mm (Somatom Definition AS;

Siemens, Erlangen, Germany) were performed routinely as a part of standardized preoperative evaluation for all patients. No additional radiographs were obtained for research purposes.

QCTpro® version 6.1. (Mindways Software Inc., Austin, TX, USA) was used for analyzing the CT images. Measurements included aligning each vertebra in different projections, defining a range of interest (ROI) for these projections, and obtaining vBMD values from the software. (Figure 10) The spinal deformities of the patients were so complex that the software itself could not correctly align the measurements, but these were done manually for all the patients' measurements separately for each vertebra individually by two physicians. The average of these measurements for each vertebra was included in the analysis, and if there was a > 5% deviation in accuracy between the two measurements, the measurement was repeated by a third measurer. Out of 748 measurements per examiner, 266 (35.6%) of the measurements were revised. The differences in results of the two measurers were due to the non-trabecular structures in the ROI area (neurovascular, cortical bone structures) as well as error to the alignment or to level definition of the segments.

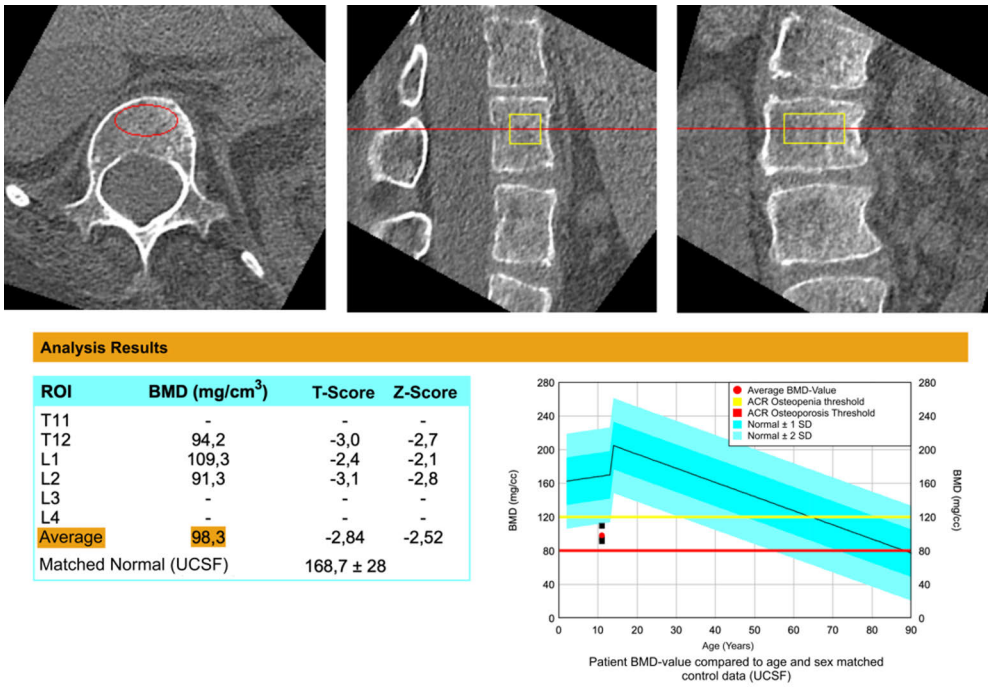

Figure 11. BMD measuring with QCT software. Defined ROI areas defined in red and yellow on CT images. Published in study IV.

4.4 Study hypotheses and outcome measures

The primary hypothesis of study I was that postoperative drainage bleeding and hidden blood loss would be significantly larger in NMS patients in comparison to AIS patients. Our primary outcome measure in study I was total blood loss. It included intraoperative, 24-hour drainage, and calculate hidden blood loss. Secondary outcome measures included the need and amount of autologous (Cell-Saver) and allogenic transfusions (red blood cell, fresh frozen plasma, and platelets).

The hypothesis in study II stated that preoperative hematocrit and platelet values would be an independent risk factors for perioperative bleeding in NMS. Main outcome measure in study II was drainage and hidden blood loss (mL) in spinal fusion. Secondary outcome measures included intraoperative and total blood loss.

In study III we hypothesized that the health-related quality of life of NMS patients undergoing spinal fusion would be superior to their own preoperative HRQoL levels, yet inferior compared to AIS control patients. Postoperative mean differences in HRQoL domains were our primary outcome measures, and additionally change of means inside and between the groups and comparison to patient related demographic factors such as curvature angle and fusion level were at our secondary interest.

In Study IV, the hypothesis was that patients treated with GFSI implant prior to spinal fusion would have lower levels of vBMD in comparison to SMA patients treated without GFSI. We assumed that the vBMD of all SMA patients would be inferior to control patients. BMD values of each vertebra was our primary outcome measure, and the secondary outcome measure was the Z-value.

4.5 Statistics

All the analyses for studies I-III were performed with JMP Pro 16.2. for Macintosh (SAS-institute in USA 1989-2023) Normal assumption was tested statistically and visually. For continuous variables, linear fit and Mann-Whitney-U test was used to perform statistical comparisons, and x^2-test test was used for categorical variables. Continuous variables were expressed as mean ± standard deviation. Wilcoxon rank sum test was used for nonparametric data. The statistical significance threshold was set at $p<0.05$. A limited multivariable regression analysis with risk factors was performed for study I, and diagnosis, sex, age, and preoperative major curvature angle were included as factors in the analysis against bleeding in mL/kg/levels of fusion.

In study II the possible risk factors were determined for each group (NMS and AIS) by bivariate analysis visually and statistically, with Fisher's exact test for categorical data and one-way analysis of variance ANOVA for continuous variables. Wilcoxon rank sum test was used for non-parametric data. The Statistically

significant risk factors ($p<0.05$) for each type of bleeding in mL in bivariate analysis were forced into the multivariable regression analysis. The correlation coefficients were identified for each factor. The factors represented with less than 10 observations were left out from further analysis, despite the possible statistical significance.

In study III, mean changes of health-related quality of life between preoperative and postoperative follow up points were analyzed with matched pairs t-test.

For Study IV, the statistical analysis was performed with GraphPad Prism® and Excel® (Microsoft Corporations, Redmond, USA). BMD values of SMA patients in treatment groups were compared individually concerning each vertebra. Additionally, Z-scores were calculated to each vertebra and compared to threshold Z-scores below 120mg/mL for low bone mass and 80mg/mL for very low bone mass. (ACR-SPR-SSR practice guideline for the performance of quantitative computed tomography (QCT) bone, 2018). As the measuring software already takes into account all three dimensions, the size of the patients no longer needed to be considered in comparison of the Z-values, as in dual-energy-x-ray-absorptiometry. (Zemel, et al., 2010) The following formulas were used to calculate the threshold Z-scores from the average vBMD for each vertebra in the control group, $Z_1 = (120 – BMD_{control}) / SD_{control}$, and $Z_2 = (80 – BMD_{control}) / SD_{control}$.

In statistical analysis, the normal distribution assumption was verified, and unpaired t-test was used to compare BMD of each vertebra between treatment groups, and between different SMA groups and controls. For non-categorical variables one-way ANOVA was utilized.

The statistical analyses of studies I-III were carried out entirely by the doctoral candidate herself. For Study IV, the statistical analyses were carried out in collaboration with a clinical research associate (KL).

5 Results

5.1 Studies I and II

Eighty-one consecutive NMS patients undergoing spinal fusion with posterior pedicle screw instrumentation were included in our cohort. The control group consisted of 199 AIS patients. The same cohort was used for both studies I and II.

5.1.1 Patient demographics

The mean age of NMS patients was 15.2 ± 3.4 with no significant difference to AIS group, 15.6 ± 2.1. In NMS group, both genders were almost evenly represented, as 54% of the patients were male, whereas in AIS, only 28% of the patients were male, difference of which was statistically significant, $p<0.001$. The preoperative major curvature angles in NMS group were greater in comparison to AIS group, 72 ± 18 and 52 ± 8 respectively, $p<0.001$. The difference decreased in operation leading to postoperative major curvature angles of 20° ± 12° for NMS patients, and 12° ± 5° for AIS, $p<0.001$. Curve correction percentage was lower in NMS 73% in comparison to AIS 76%, which was statistically significant, $p=0.0426$. Osteotomies were performed for 48% of the NMS patients, with a mean number of 3.49 ± 0.25. Although in AIS group osteotomies were performed for only 25% of the patients, with a mean of 2.95 ± 0.22, the difference did not show a statistical significance, $p=0.1920$. (Table 5.)

The amount intraoperative bleeding was 1085 ± 1049 mL for NMS and 554 ± 349 mL for AIS respectively. This difference was statistically significant, $p<0.001$. Similar mean differences were also observed in drain output, 566 ± 209 mL in NMS group and 489 ± 188 mL in AIS group, $p=0.0294$, and in hidden blood loss, with means of 566 ± 533 mL in NMS patients, and 398 ± 411 in AIS patients, $p=0.0332$. The total measured bleeding and total bleeding markers to integrate the above showed reportedly also significant differences, $p<0.001$ for both. There was also a significant difference in operation times, means of 4.2 ± 0.13 hours in NMS and 3.08 ± 0.07 hours in AIS, respectively, $p<0.001$. (Figure 12)

Table 6. Clinical characteristics of the study groups. Adapted from Study I published in NASSJ (Soini, et al., 2022) Values are mean ± SD for continuous variables and numbers (percentages) for categorical variables.

	NMS	AIS	P-VALUE
N	81	199	
AGE	15.2 ± 3.4	15.6 ± 2.1	p = 0.201
GENDER(M/F)	44 / 37	56 / 143	p<0.001
MAJOR CURVE, degrees			
Preoperatively	72 ± 18	52 ± 8	p<0.001
Postoperatively	20 ± 12	12 ± 5	p<0.001
CURVE CORRECTION (%)	73% ± 0.01	76% ± 0.00	p=0.0426
FUSED LEVELS (N)	16.6 ± 1.4	11.2 ± 1.8	p<0.001
PELVIC INSTRUMENTATION, n (%)	63 (77)%	0/0	
OSTEOTOMIES, n (%), mean ± SD	39 (48%), 3.49 ± 0.25	49 (25%), 2.96 ± 0.22	p=0.1920
INTRAOPERATIVE BLEEDING (mL)	1085 ± 1049	554 ± 349	p< 0.001
DRAIN OUTPUT (mL)	566 ± 208	489 ± 188	p=0.0294
HIDDEN BLOOD LOSS (mL)	566 ± 533	398 ± 411	p=0.0332
TOTAL MEASURED BLEEDING (mL)	1348 ± 1066	965 ± 453	p <0.001
TOTAL BLEEDING (mL)	1914 ± 1006	1358 ± 544	p < 0.001
OPERATION TIME (h)	4.2 ± 0.13	3.08 ± 0.07	p < 0.001

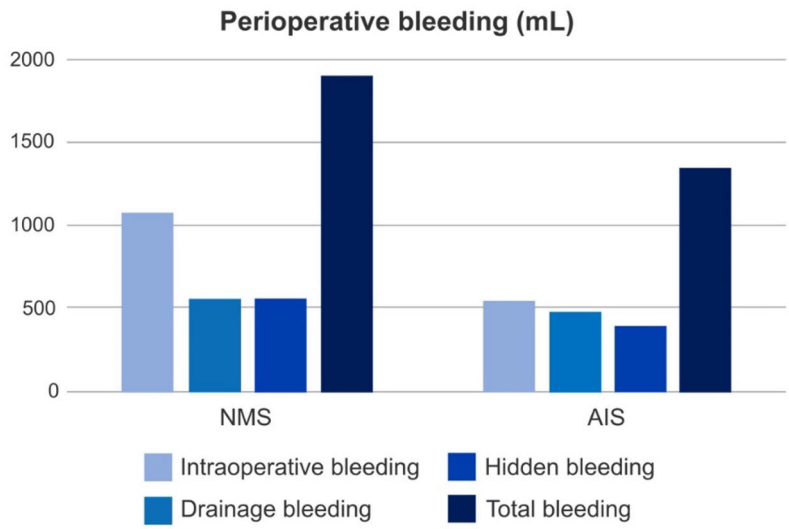

Figure 12. Perioperative bleeding (mL) in spinal fusion for AIS and NMS.

5.1.2 Study I

In comparison for each bleeding standardized by ml/kg/fusion level between AIS and NMS, a significant difference was found concerning intraoperative bleeding, means of 1.79 vs. 0.87 ml/kg/levels fused, p<0.001. A similar tendency was seen in drainage bleeding without statistical significance (0.87±0.36 mL/kg/fused level vs. 0.78±0.35 mL/kg/fused level, p=0.1645), and in hidden blood loss with borderline significance (1.00 ml/kg/levels fused vs. 0.65 ml/kg/fused levels, p=0.053).

Concerning variables explaining bleeding characteristics male sex was found to have an influence on greater hidden blood loss in NMS patients (mean 1.13 ± 0.17 ml/kg/level, 0.84 ± 0.19 ml/kg/level, respectively, p=0.0429) and on intraoperative blood loss in AIS group, p= 0.014. Longer operative time showed a correlation to larger intraoperative bleeding in both NMS and AIS, p<0.001. Preoperative main curvature angle had a positive influence on total bleeding in NMS patients, p=0.0473. Age and number of osteotomies performed showed no correlations to bleeding in ml/kg/level analysis and weight and fusion level were excluded from the analysis, as already considered in standardizing the bleeding amounts.

Multivariable regression analysis for bleeding in ml/kg/levels fused was conducted in order to control the demographic features differing between the NMS and AIS groups. Preoperative major curve degree was a significant risk factor for intraoperative, total measured and total bleeding, p<0.001. NMS diagnosis was an independent risk factor for more hidden blood loss, p=0.0011. We could not find any significant risk factors for drainage bleeding in ml/kg/levels fused. (Table 6.)

Table 7. Regression analysis, risk factors for bleeding in ml/kg/fusion level, p-values, correlation coefficients for continuous variables, published in connection with study I.

BLEEDING ml/kg/level	NMS vs. AIS	SEX	AGE	MAIN CURVE	MULTIVARIABLE ANALYSIS
INTRAOPERATIVE BLOOD LOSS	p<0.001	p=0.006	-	0.2934 p<0.001	-0.9703, Main curve p<0.001
DRAINAGE BLEEDING	-		-	-	-
TOTAL MEASURED BLEEDING	p=0.0395	p=0.0565		0.3273 p<0.001	-0.9699, Main curve p<0.001
HIDDEN BLOOD LOSS	p=0.0524	-	-	-	-0.4848, NMS vs AIS p=0.0011
TOTAL BLOOD LOSS	p<0.001	p=0.0171	-	0.3246 p<0.001	-0.9701, Main curve p<0.001

5.1.2.1 Use of blood products

There was a significant difference in need for blood products concerning or transfusion substances. In NMS group, 73% of the patients received allogenic red blood cells, whereas in AIS only 14% of the patients required a RBC transfusion. Concerning platelets, this difference was smaller but significant, 9% of NMS and none of AIS received allogenic platelets. Fifty-two percent of NMS patients needed fresh frozen plasma, in comparison to AIS group, out of which only 16% required a plasma transfusion. In 86% of the operations for NMS an autologous RBC infusion was received, compared to AIS, where 47% of the patients received an autologous RBC transfusion. All of the differences were considered statistically significant, both for number of patients receiving transfusion and also for the ml/kg adjusted transfusion amount, $p<0.01$. (Table 7)

Table 8. Need for blood transfusion amounts in the study groups.

	NMS (N=81)	AIS (N=199)	P-VALUE
ALLOGENIC RBC N (%) **ml/kg**	59 (73%) 18.2 ± 21.2	27 (14%) 9.1 ± 7.1	p < 0.001 p = 0.002
PLATELETS N (%) **ml/kg**	7 (9%) 23.9 ± 22.8	0 (0%)	p < 0.001 p < 0.001
FRESH FROZEN PLASMA N (%) **ml/kg**	42 (52%) 15.4 ± 13.7	31 (16%) 7.0 ± 3.47	p < 0.001 p <0.001
AUTOLOGOUS RBC N (%) **ml/kg**	55 (86%) 5.5 ± 6.9	86 (47%) 2.8 ± 1.6	p < 0.001 p < 0.001

5.1.3 Study II

In comparison of preoperative laboratory levels, significant differences between NMS and AIS groups were found concerning creatinine levels, 38 ± 18 μmol in NMS and 66 ± 23 μmol in AIS groups. Significant differences between NMS and AIS were also observed regarding sodium and CRP levels, $p=0.0156$ and $p<0.001$ respectively. (Table 8.)

Table 9. Preoperative laboratory levels. Adapted from Study II.

LABORATORY LEVELS	NMS	AIS	P-VALUE
LEUKOCYTES	6.60 ± 2.04	6.33 ± 1.84	0.3855
ERYTHROCYTES x10E12/l)	4.8 ± 0.4	4.78 ± 0.41	0.9864
HEMOGLOBIN (g/l)	138 ± 14	138 ± 11	0.9060
HEMATOCRIT (HCT)	0.41 ± 0.04	0.41 ± 0.03	0.6689
MVC (fl)	86 ± 6	86 ± 3	0.6781
MCH (pg)	29 ± 3	29 ± 1	0.6778
PLATELETS (x10E9/l)	273 ± 87	268 ± 57	0.8273
FERRITIN (μg/l)	48 ± 43	38 ± 26	0.1546
aPTT (s)	28 ± 6.6	29.0 ± 3.9	0.8531
TT	86.6 ± 22.7	86.8 ± 19.3	0.0936
INR	1.04 ± 0.20	1.07 ± 0.09	0.37171
CREATININE (μmol)	38 ± 18	66 ± 23	<0.0001
POTASSIUM (K) mmol/l	3.9 ± 0.3	4.1 ± 0.3	0.0843
SODIUM (Na)	139.6 ± 3.5	142.1 ± 2.3	0.0156
MAGNESIUM (Mg) (mmol/l)	0.82 ± 0.08	0.89 ± 0.12	0.3486
CRP (C-reactive protein)	2.0 ± 5.4	0.31 ±1.28	<0.001
PCT (procalcitonin)	0.05 ± 0.03	0.05 ± 0.01	0.4863

5.1.3.1 Risk factors for intraoperative blood loss

In bivariate analysis for intraoperative bleeding, age (correlation coefficient of 0.38, p=0.0013 and ferritin level (0.40, p=0.002) could be determined as possible preoperative risk factors. Operative time was the only perioperative risk factor to correlate with intraoperative bleeding, 0.67, p<0.001. Ferritin (0.0714, p=0.0165) and operative time (0.9305, p<0.001) were also independent risk factors in multivariable regression analysis.

In our control group of AIS, male sex (0.3992, p=0.0044), increasing fusion level (0.8373, <0.001) and longer operative time (0.2425, <0.001) were determined as independent risk factors for more voluminous intraoperative bleeding. (Tables 9 and 10)

5.1.3.2 Risk factors for drainage blood loss

A correlation in bivariate analysis to drainage bleeding was observed between age (0.38, p=0.0294) and preoperative magnesium levels, 0.43, p=0.022, when analyzing the preoperative risk factors. Additionally, from perioperative factors, fusion level correlated to drainage bleeding, 0.42, p=0.0018. In multivariable regression analysis

fusion level could be stated as an independent risk factor, with correlation of 0.9305, p<0.001. Concerning AIS group, male sex (0.2440, 0.0227) and the number of osteotomies (0.9118, 0.0231) correlated significantly to drainage bleeding in multivariable regression analysis. (Tables 9 and 10)

5.1.3.3 Risk factors for hidden blood loss

Male sex was the only factor to correlate to hidden blood loss (p=0.0463) in NMS group, and this significance was not observed in multivariable regression analysis. MCV levels (0.9909, 0.0391) and operative time (0.2211, 0.0038) were determined as risk factors in AIS patient group. (Tables 9 and 10)

5.1.3.4 Risk factors for total blood loss

From preoperative risk factors, older age (0.42, p<0.001), male sex (p=0.0127), higher hemoglobin (0.29, p=0.0142), MCV (0.35, p=0.003), MCH (0.25, p=0.036), hematocrit (0.32, p=0.0066), ferritin (0.36, 0.006), and potassium (0.39, p=0.047) levels, correlated in bivariate analysis with total bleeding. Perioperative factor of operative time, 0.66, p<0.001 was also determined as an influencing factor. Out of these factors, preoperative MCV levels (0.9807, p<0.001) and operative time (0.2227, <0.001) could be identified as independent risk factors also in multivariable analysis. Preoperative factors of male sex (0.3530, <0.001), and larger BMI (0.5254, <0.001), and perioperative factors of longer operative time (0.6884, <0.001) and more numbers of levels fused (0.1806, <0.001) were configured as risk factors for total blood loss in spinal fusion for AIS. (Tables 9 and 10)

Table 10. Risk factors for bleeding in NMS: Correlation coefficients for linear data in bivariate analysis, statistical significance ($p<0.05$) is indicated with (*).

	IBL	DBL	HBL	TBL
PREOPERATIVE FACTORS				
AGE	**0.38***	**0.38***	0.04	**0.42***
MAJOR CURVATURE ANGLE	0.21	0.15	-0.07	0.177
BMI	0.06	0.01	-0.11	-0.01
PREOPERATIVE LABORATORY LEVELS				
LEUKOCYTES	-0.11	-0.03	0.11	-0.10
ERYTHROCYTES	0.01	0.03	0.06	0.07
HEMOGLOBIN, Hb	0.14	0.23	0.11	**0.29***
HEMATOCRIT, HCT	0.15	0.19	0.17	**0.32***
MCV	0.19	0.30	0.15	**0.35***
MCH	0.12	0.24	0.06	**0.25***
PLATELETS	0.08	-0.032	-0.10	-0.00
aPTT	0.05	0.08	-0.27	-0.01
TT	0.01	-0.21	-0.05	-0.05
INR	0.05	0.28	0.16	0.09
FERRITIN	**0.40***	-0.16	0.14	**0.36***
CRP	0.17	-0.20	0.07	0.19
PCT	-0.05	0.11	-0.32	-0.15
CREATININE	-0.15	0.09	-0.16	0.06
POTASSIUM, K	0.35	0.15	-0.15	**0.39***
SODIUM (Na)	0.012	0.08	-0.20	0.00
MAGNESIUM, Mg	-0.01	**0.43***	-0.24	-0.21
PERIOPERATIVE FACTORS				
FUSION LEVEL	-0.13	**0.42***	0.19	0.01
OPERATIVE TIME	**0.67***	0.30	-0.11	**0.61***
OSTEOTOMIES	0.22	-0.11	-0.25	0.03

Table 11. Significant risk factors for bleeding in NMS and AIS: Correlation coefficients and p-values for linear data in multivariate analysis. Adapted from Study II.

RISK FACTORS	NMS			AIS				
	IBL	DBL	HBL	TBL	IIBL	DBL	HBL	TBL
PREOPERATIVE FACTORS								
SEX					0.3992, 0.0044	0.2440, 0.0277		0.3530, <0.001
BMI								0.5254, 0.0391
MCV				0.9807, <0.001			0.9909, 0.0391	
FERRITIN	0.9305, <0.001							
PERIOPERATIVE FACTORS								
FUSION LEVEL		0.9971, 0.0019			0.8373, <0.001			0.1806, <0.001
OPERATIVE TIME	0.9305, <0.001			0.2227, <0.001	0.2425, <0.001		0.2211, 0.0038	0.6884, <0.001
OSTEOTOMIES						0.9118, 0.0231		

5.2 Study III

In Study III, NMS group consisted of 60 patients undergoing spinal fusion. AIS control group consisted of 120 age-and sex matched controls.

Table 12. Clinical characteristics of the study groups. Values are Mean (SD). Adapted from Study III.

	NMS	AIS	P-VALUE
N	60	120	
AGE (at final follow-up)	18.14 (0.39)	17.59 (2.55)	p=0.4454
GENDER, females (%)	33 (55%)	66 (55%)	
MEAN MAJOR CURVE ANGLE			
Preoperative	69.0° (18)	52.1° (8)	p<0.001
Postoperative	18.5° (11)	13.0° (5)	p = 0.0016
Correction	51° (15)	39° (9)	p<0.001
2 years follow-up	19.4° (12.4)	12.6° (6)	p=0.0176
BLOOD LOSS, mean ml	1084 (1175)	580 (366)	p<0.001
OPERATION TIME, hours mean	4.14 (1.28)	3.21 (0.92)	p<0.001
NUMBER OF LEVELS FUSED	16.3 (1.6)	11.4 (1.7)	p<0.001
ILIAC SCREWS	24	0	
S2AI SCREWS	12	0	

5.2.1 Patient demographics

Age at final follow up was 18.14 ± 0.39 in NMS group and 17.59 ± 2.55 in AIS patients respectively. Fifty-five percent of the patients were female. Several different etiological causes of scoliosis were represented in the neuromuscular group, cerebral palsy being the most common. Other included but not limited to were Duchenne muscular dystrophy, spinal muscular atrophy, myelomeningocele, and congenital myopathies. Preoperative major curvature angles of 69 ± 18 degrees were measured in NMS with a curvature correction mean of 51° ± 15°, in comparison to AIS group, in which the means for major curvature angle were 52.1° ± 8° preoperatively and correction of 39° ± 9° was achieved, p<0,001 for both comparisons. (Table 8.)

Mean blood loss was 1084±1175 ml in NMS group and 580 ml in AIS group, NMS patients bled significantly more, p<0.001. Operation time means of 4.14 ± 1.28 hours for NMS and 3.21 ± 0.92 hours for AIS were recorded, the difference of which was statistically significant, p<0.001. The number of fused levels was greater in NMS with a mean of 16.3 ± 1.28 in comparison to AIS, 3.21 ± 0.92, p<0.001. 24 of the 60 NMS patients were fused distally with iliac screws, and 12 with S2AI screws.

5.2.2 Health-related quality of life

In study III, we analyzed both the preoperative to postoperative improvement of HRQoL within NMS and AIS groups, as well as comparison of HRQoL scores between NMS and AIS groups in different time points and of overall change.

5.2.2.1 Change in HRQoL scores within groups

HRQoL improved significantly in NMS groups from pre- to postoperative evaluation. Concerning total-SRS score mean, a significant increase of 0.31 was seen at two-year follow-up. An improvement of statistical significance was also seen in individual domain means of pain, 0.55, $p<0.001$; function 0.29, $p=0.043$; general self-image 0.46, $p=0.0146$ and general activity, 0.29, $p=0.0469$. In comparison similar statistically significant improvements were evaluated in pain (0.87), general self-image (0.42) and function (0.15) domains in AIS group. (Table 9.)

5.2.2.2 Comparison of HRQoL between groups

Comparison between NMS and AIS HRQoL scores was made at 3 follow-up points (preoperative, 6-months postoperative and 2-years postoperative) and concerning overall change of domains. Preoperative HRQoL scores of Total-SRS, general function and general activity were significantly lower in NMS group compared to AIS group, p-values of 0.0190, 0.005, and <0.001 respectively. On contrary, pain score was higher in NMS patients, $p<0.001$.

Six months postoperatively the preoperative differences were no longer observed, yet postoperative function scores were significantly better in the NMS group compared to AIS patients, (2.67 ± 1.39 vs. 2.11 ± 0.99, $p<0.0288$).

At our study's final follow up at 2-years postoperatively, the total SRS-scores of NMS and AIS groups were almost similar, with no significant differences, $p=0.2715$. The general activity and function scores were superior in AIS group compared to NMS, p-values of <0.001 and 0.0017 respectively. On the contrary, NMS patient group showed a significantly better postoperative self-image score than AIS patient group, $p=0.0133$.

Regarding the differences in changes of individual domain scores between study groups, the improvement of total SRS-score was more prominent in NMS group, $p=0.0204$. On the other hand, pain score improvement was smaller in NMS group than in AIS group, $p=0.0378$. (Table 9.)

5.2.2.3 Predictive factors

In bivariate analysis for influencing factors for SRS domain scores at 2-year follow-up, more extensive spinal fusion (levels fused) showed a correlation to pain scores (lower scores – more pain, correlation coefficient -0.35, $p<0.0485$) and total SRS-scores (lower scores – worse outcome, -0.40, $p=0.0222$) in NMS group. Similar findings were not found in AIS.

Neither curve correction nor residual curve showed any significant influences on HRQoL in NMS, yet in AIS patients, negative impact on total SRS-score (-0.43, $p=0.0010$), pain (-0.29, $p=0.0316$), general activity (-0.40, $p=0.0022$), and satisfaction (-0.30, $p=0.0265$) domains were observed by residual curve. Correspondingly, correction percentage led to improved total SRS-score, 0.31 $p=0.0083$.

The distal fusion insertion showed a correlation to HRQoL. In NMS patients without pelvic fixation the postoperative function domain was superior to the patient with pelvic fixation (S2 alar iliac or iliac screws, mean 3.27 (1.1) vs 1.88 (1.13) $p=0.0192$). In comparison between S2 AI screw insertion to iliac insertion, the patients with iliac insertion represented with higher function domain scores than the ones with S2AI implantation, mean 3.21 (1.13) vs 1.88 (1.13) $p=0.014$.

Table 13. Health-related quality of life.

	NMS PREOP.	NMS 2-YR	NMS CHANGE, 95% CI, p-value	AIS PREOP.	AIS 2-YR	AIS CHANGE, 95% CI-, p-value	NMS vs AIS POSTOP., p-value	NMS vs AIS CHANGE p-value
TOTAL SCORE	3.8 (0.6)	4.1 (0.58)	0.31 (0.05-0.58), 0.0228	4.1 (0.5)	4.1 (0.4)	0.01 (-0.10-0.12), 0.83	0.2715	0.0204
PAIN	3.9 (0.70)	4.4 (0.48)	0.55 (0.27–0.81), 0.0008	3.5 (0.6)	4.3 (0.6)	0.87 (0.72-1.0),<0.001	0.7170	0.0378
GENERAL SELF-IMAGE	3.8 (0.80)	4.2 (0.67)	0.46 (0.10–0.83), 0.0146,	3.7 (0.7)	4.1 (0.7)	0.42 (0.25-0.59),<0.001	0.8131	0.8
FUNCTION	3.6 (0.80)	3.9 (0.6)	0.29 (-0.02-0.61) 0.0433	4.0 (0.5)	4.2 (0.4)	0.15 (0.01-0.29), 0.0302	0.0017	0.36
GENERAL ACTIVITY	3.7 (1.1)	4.0 (0.8)	0.29 (-0.13-0.71) 0.0469	4.5 (0.7)	4.7 (0.6)	0.12 (-0.04-0.28), 0.1309	0.001	0.37
POSTOPERATIVE SELF-IMAGE	N/A	3.6 (0.6)		N/A	3.3 (0.5)		0.0133	
POSTOPERATIVE FUNCTION	N/A	3.0 (1.2)		N/A	2.8 (0.9)		0.3236	
SATISFACTION	N/A	4.3 (0.6)		N/A	4.3 (0.6)		0.6780	

5.3 Study IV

5.3.1 Patient demographics

A total of 71 adolescents were included in the analysis, 17 SMA children with prior GFSI treatment, 25 SMA children without prior treatment, and 29 healthy controls. The mean age of GFSI-group was 13.2 ± 1.2 years, 12.9 ± 1.7 of non-GFSI-group and 13.3 ± 2.0 of control group. (Table 10). 8 patients in the non-GFSI, 15 patients in the GFSI and 17 patients in the control group were female. Most of the patients had SMA type 2; 16, 94% in the GFSI-group and 18, 72% in the non-GFSI-group. All patients in GFSI-group and 23/25 patients in the non-GFSI group were non-ambulatory, and the 2 patients were minimal ambulatory, able to walk some steps with walking aids. There were no significant differences concerning BMI between the non-GFSI and the GFSI groups (BMI means of 18.34±4.77 in the GFSI group and 18.94 ± 5.41 in the non-GFSI group). The preoperative scoliosis angle degrees were significantly smaller in pre-treated GFSI group (72.3°±23.9°) compared to non-GFSI, (96.8°±30.7°); p=0.0123. Postoperative angles did not show significant differences. (Table 10)

5.3.2 Comparison of BMD and Z-scores

The GFSI treated group showed a significantly lower average vBMD values for the whole spine compared to non GFSI treated patients, 82.1 ± 8.4 mg/cm^3 and 108.0 ± 6.8 mg/cm^3 respectively, p =0.0014. The values were gradually decreasing from upper thoracic T2 (125 ± 29 mg/cm^3 for GFSI and 134 ± 38 mg/cm^3 for non-GFSI) to lower lumbar vertebrae L4 (45 ± 37 mg/cm^3 for GFSI and 71 ± 44 mg/cm^3 for non-GFSI group). Statistical significance in differences between the groups was observed in vertebrae T7 to L3. (Figure 12A)

Both SMA treatment groups showed significantly lower vBMD values for all vertebrae when compared to the control group of healthy adolescents, $p<0.05$ for all comparisons. (Figure 13).

When comparing the calculated Z-value, the observed difference is accentuated. In the upper parts of the thoracic spine at the levels T1-T4, the bone mineral density between the two treatment groups does not differ much. From vertebrae T5 onwards, a significant difference is observed in the decrease in Z-values, in the GFSI group, this decreases sharply, while in the non-GFSI group the decrease is less prominent. The Z-score of the GFSI group drops below 80 mg/cm^3 threshold at vertebrae T9 and remains approximately at -3.0 level thereafter, while in the non-GFSI group the

corresponding drop is only observed at level of L2, and even below this level, the Z-value remains between -2.0 and -2.5. (Figure 12B)

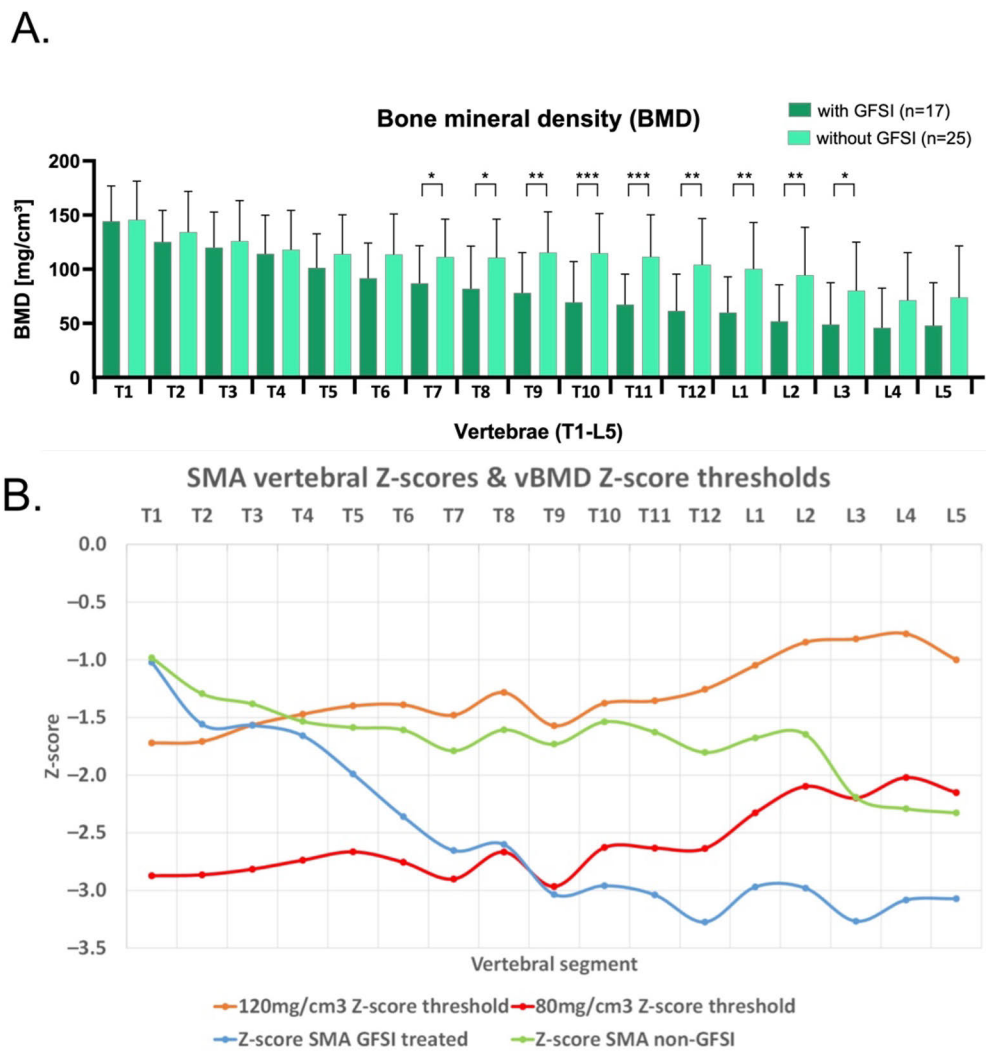

Figure 13. BMD in SMA children, comparison between GFSI and non-GFSI treatment groups. Published in connection with Study IV. **A:** Statistical significance in BMD concerning vertebrae T7 to L3. **B:** Z-scores in comparison to vBMD thresholds. A clear difference in BMD is observed from T 4 downward, with values gradually deteriorating in GFSI treatment group, while in non-GFSI group the decrease is more limited.

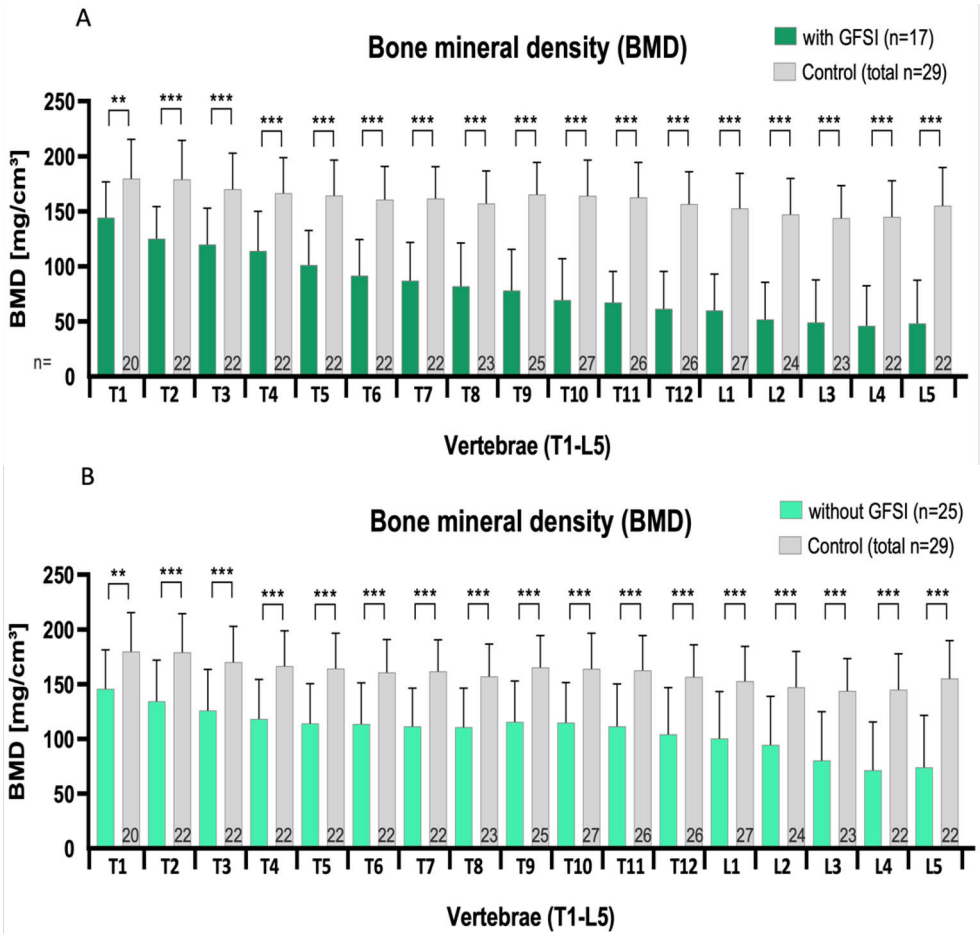

Figure 14. BMD comparison of SMA children to healthy controls. Published in connection with Study IV. **A:** GFSI pre-treated patients. **B:** Patients without pre-treatment.

5.3.3 Influencing factors

Influencing factors for BMD were searched by analyzing the effect of demographic data. Patient size (BMI), preoperative scoliosis curvature characteristics, ventilation status, or presence of gastrostomy tube showed no influence on BMD values in SMA children. A trend towards the severity of the SMA disease (types I-III) was observed, yet this could not be proven statistically. (Figure 14A) A similar trend was found comparing the effect of SMN2-gene copy count to the BMD. In non-GFSI children, who had previously been experiencing extremity fractures, the BMD was significantly smaller than in children without any previous fractures. (Figure 14B). Almost all of the patients (80%) received Vitamin D (1000 IU) as a supplementary therapy, so we were not able to analyze the effects of Vitamin-D Status on BMD in

scoliotic SMA children. 62% of SMA patients received intrathecal nursinersen treatment with a mean duration of 1.7 ± 0.96 years prior to CT imaging in the GFSI group, and 3.0 ± 1.5 in non-GFSI group. This did not influence the BMD. However, different treatment times might influence these results. In our cohort, the number of patients receiving other kinds of pharmaceutical therapy was low (risdiplam n=3, and onasemnogen abeparvovec n=0) and we could not study the effect of these drugs on BMD.

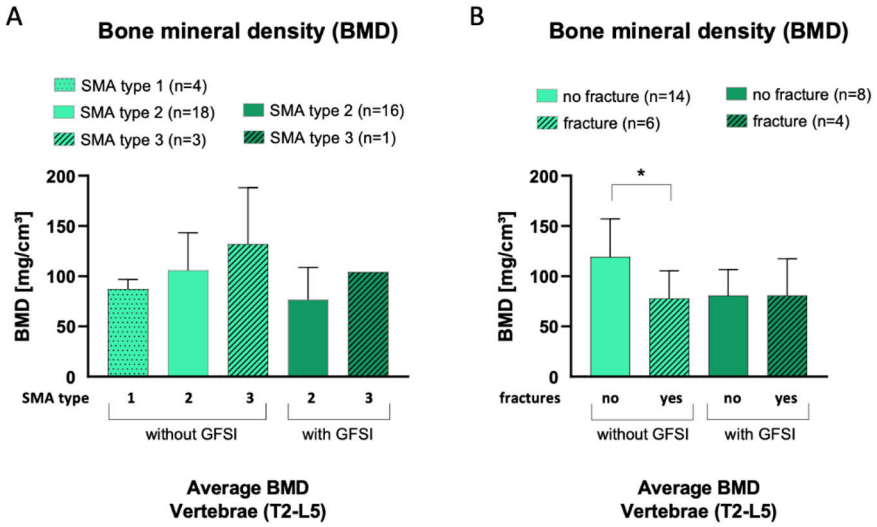

Figure 15. BMD and influencing factors. Published in connection with Study IV. **A:** Visual difference in BMD is observed between SMA types, yet no statistical significance could be found. **B:** Association of previous fractures to BMD in SMA children.

Table 14. Patient demographics, and p-values of difference between with and without GFSI treated patients. Adapted from table published in connection with Study IV.

	with GFSI	without GFSI	p-value	healthy controls
N	17	25		29
AGE AT CT (years)	13.2 ± 1.2	12.9 ± 1.7		13.3 ± 2.0
SEX, n (%)				
female	8 (47%)	15 (60%)		17 (58%)
male	9 (53%)	10 (40%)		12 (42%)
HEIGHT (cm)	145 ± 11	148 ± 6		-
WEIGHT (kg)	40.3 ± 13.2	40.5 ± 11.3		-
PREOPERATIVE SCOLIOTIC ANGLE	72.3° ± 23.9°	96.8° ± 30.7°	p=0.0123	-
POSTOPERATIVE SCOLIOTIC ANGLE	36.7° ± 15.9°	38.2 ± 24.0°		-
SMA TYPE, n (%)				
SMA 1	0	4 (16%)		-
SMA 2	16 (94%)	18 (72%)		
SMA 3	1 (6%)	3 (12%)		
AMBULATORY (few steps) (%)	0/17 (0%)	2/25 (8%)		-
MECHANICAL VENTILATION				
No	4	12		-
Non-invasive	11	12		-
Continuous	1	1		-
PERCUTANEOUS ENDOSCOPIC GASTROSTOMY TUBE (%)	9/17 (53%)	1/25 (4%)		
VITAMINE D SUPPLEMENT (%)	12/15 (80%)	21/25 (84%)		-
PREVIOUS FRACTURES				
No (52%)	8	14		-
Yes (24%)	4	6		-
TIME WITH GFSI (years)	4.9 ± 1.8	-		-
GFSI TYPE				
MCGR	15	-		-
VEPTR -> MCGR*	2			
PHARMACEUTICAL THERAPY PRIOR CT				
Nusinersen (>1 year) (%)	8/17 (47%)	15/25 (60%)		

*Initiating the GFSI treatment with VEPTR, later transitioning to MCGR.

6 Discussion

6.1 Strengths and limitations

Both studies evaluating the postoperative bleeding (I and II) and study III to evaluate the HRQoL have relatively large numbers of patients and show a comparison to otherwise healthy AIS controls who have undergone similar but more limited surgery. Our pediatric spine register with its standardized surgical and especially anesthetic protocols increase the reliability of these studies. Prospective data collection used for the register further increases the value of our data. All of our operations had the same experienced pediatric spine surgeon as main surgeon which diminishes the possibility for bias. The main limitation of the studies I-III is their retrospective setting based on the prospective spine register.

6.1.1 Studies I–II

Study I is the largest study cohort published with a standardized anesthetic and surgical protocol from a single center to assess the bleeding characteristics of NMS patients, and the first paper to report hidden blood loss in neuromuscular patients. The cohort in studies I and II was reasonable, with 81 NMS and 199 AIS patients.

Study II is the first study to investigate the risk factors related to hidden blood loss after spinal fusion in neuromuscular patients. It provides additional information about risk factors for other types of bleeding and for the control group of AIS patients.

In studies I and II, drainage tubes left in the surgical site postoperatively were routinely removed at 24 hours, as previous studies have found bacterial drainage contamination in up to 18% of cases where drenches were left in place for longer periods. (Drinkwater and Neil, 1995) There is a possibility, that the amount of drainage bleeding could have resulted higher in case of the drain would have been in the patient for longer period, but to minimize the possibility of ignoring this amount of leakage, we decided to estimate the amount of hidden bleeding.

The effect of intraoperative products related to bleeding could not be included in our risk factor analysis in study II, as products such as tranexamic acid were involved as a part of our clinical protocol. Also, some laboratory levels had to be excluded

from the risk factor analysis due to the small number, as there was a lack of preoperative results from these factors in the clinical reports.

In addition, when evaluating the results of the studies, it must be considered that neuromuscular patients are generally smaller in size, the extent of surgery is more extensive and there are more comorbidities in comparison to their AIS controls. This might impact the bleeding characteristics, which we have tried to control by adjusting the bleeding with weight and the level of fusion in Study II. However, the lack of strong association between size and bleeding in study II also indicates to low significance of this issue.

Since the marker total blood loss links the different subtypes of perioperative bleeding together, the strongly significant correlations observed in individual bleeding subtype analysis might have a strong or more prominent effect on total bleeding than the interaction of all bleeding types, the results for total bleeding are clinically less interesting than other individual subtype analysis results.

One limitation of the study is that more specific coagulation factor tests such as antithrombin III, fibrinogen, fibrin d-dimer, thrombin time, Factor VIII or other coagulation factors were not analyzed as a part of preoperative laboratory testing. Differences in these markers could explain the differences in bleeding between NMS and AIS patients.

6.1.2 Study III

In study III a study sample of 60 NMS patients and age and sex matched controls of 120 AIS patients were included, which is acceptable.
Differences between patient groups must also be considered when assessing HRQoL. Generally, NMS patients have lower baseline situation and requirements, as well as more extensive surgery. However, this should lead to a larger change than AIS peers and the differences should be more pronounced.

What is more, some of the neuromuscular patients were not able to answer the questionnaire themselves, and in those cases the HRQoL was assessed by the caregiver. Longo et al. found out in their study, that parents or caregivers reported significantly worse quality of life outcomes in comparison to the answers from the cerebral palsy patient itself. (Longo, et al., 2017) This phenomenon was also seen in paper from Suk et al concerning NMS patients, where in scores answered by patients, improvement was seen, and in scores assessed by a caregiver, little to no improvement was observed. (Suk, et al., 2015) As the quality of life of NMS patients in our study was not inferior in comparison to AIS and at some markers superior, this should not create a bias that reinforces the results of the study but on the contrary. Those NMS patients whose caregivers had answered the questions, might have in

reality had even better final results and this would have led to an even more pronounced improvement in quality of life.

In study III, we used the SRS-24 questionnaire to assess the health-related quality of life pre- and postoperatively. We recognize that the questionnaire has received some criticism concerning validity, and an updated questionnaire SRS-22 has been developed to replace the SRS-24 questionnaire. (Asher, et al., 2003, Rothenfluh, et al., 2012) Also, it must be noted that it has been designed for AIS patients and is not therefore ideal for NMS. However, our retrospective data collection in our spine register dates back to 2009, and as the majority of patients in our register are AIS, and the data collection was originally initialized using SRS-24 questionnaire, it was used in this study to allow direct comparison. The case-control matching is not age-wise ideal, as the matches were eventually up to ±3.5 years, due to the fact that the age span of neuromuscular scoliosis patients was broad in comparison to AIS, while the age distribution of AIS patients was denser.

6.1.3 Study IV

In study IV, is the first paper to report bone health and BMD in neuromuscular patients after GFSI pre-treatment. It is a prospective study with two control groups of SMA and healthy adolescents. The BMD measurements with quantitative computed tomography provide more accuracy in comparison to traditional DXA BMD measurements.

Study IV aims to assess the bone health in GFSI treated SMA children and has multiple limitations. The number of patients is relatively small due to the rarity and severity of the disease, and as effective pharmaceutical therapies have not been available for a very long time, the number of patients suitable for surgery has been limited. The interobserver error of BMD measures was rather high, yet that was eventually controlled by performing additional re-measurements. Additionally, only a cross-sectional evaluation was possible due to the nature of radiation exposure of CT scans, as additional pre-GFSI-treatment, without any clinical demand, or post-fusion CT-imaging, with trabecular alteration and pedicle screw related signal distortion, would have been clinically unjustified.

Patients' calcium, parathyroid hormone and vitamin D status or plasma concentrations were not considered in the study, which could explain some of the differences between patients especially in comparison to the healthy controls. However, nearly all SMA patients (83%) received a regular vitamin D supplement.

6.2 Perioperative bleeding

Our studies I and II aimed to assess the characteristics and risk factors for perioperative bleeding of NMS patients compared to AIS patients. We found a clear difference in amounts of all types of bleeding between these two patient groups, with NMS patients bleeding significantly more than AIS patients. This difference was visible even when the size of the patients and the different extent of surgery were considered. Risk factor profiles differed between patient groups; however, the length of surgery had a clear effect on bleeding rates in both patient groups.

In terms of blood transfusions, our study indicates that the need for allogenic red blood cells and fresh frozen plasma transfusions was increased in patients with NMS compared to AIS patients. Meert et al. described similar phenomenon also previously, as allogenic red blood cell transfusions were more often required for smaller patients with underlying neurological disease. (Meert, et al., 2002) Similar tendency was observed concerning autogenic red blood cell transfusions, however, it must be noted that the autogenic transfusions are also directly linked to the amount of intraoperative bleeding, as Cell-saver device was utilized as a part of our protocol.

6.2.1 Intraoperative blood loss

In our Study II, Ferritin and operative time had positive correlations to greater intraoperative bleeding in NMS patients. As a comparison, Male sex, larger fusion level, and longer operative time were linked with more voluminous bleeding in AIS patients.

Studies concerning risk factors for massive intraoperative blood loss in NMS and AIS datasets have been conducted also previously, yet a division of the patients to massive (> 30% of estimated blood volume) and non-massive (<30% of the estimated blood volume) has been used in multiple studies. Song et al. conducted a large study of 1859 AIS patients, and Maio et al. and Jia et al. conducted similar studies with NMS patients. (Jia, et al., 2017, Maio, et al., 2020, Song, et al., 2021)

As a curiosity and to enable more accurate comparison to these previous studies, we also did a similar categorization to our data: 36 (44%) of our NMS patients and 11 (5.5%) of our AIS patients exceeded the threshold limit of 30% of EBV. In NMS group we could not find any significant influencing factors, which is contrary to Maio et al. findings, as they found out that lower BMI was a risk factor for massive blood loss in NMS. Jia et al. also converted the risk factors into categorical variables, and stated that greater number of fusion levels, BMI lower than 16.8. an age greater than 15 years and an operation duration longer than 4.4 hours were risk factors for massive blood loss in NMS children undergoing spinal fusion. On the other hand, our original analysis is in line with this finding of operation duration as a risk factor for massive blood loss. Concerning AIS patients, our additional analysis states that

a greater number of levels fused (p=0.0036), younger age (p=0.0067) and higher INR (p=0.0157) were independent risk factors for massive intraoperative bleeding. Song et al. found out that longer operation duration, larger number of fusion levels, lower BMI, larger perioperative Cobb angle, lower preoperative platelet count and higher INR were risk factors for more massive bleeding. In a comparison to Song's findings, our original analysis supports the influence of longer operation time and greater fusion level in AIS group.

Tamim et al. investigated the effect of preoperative INR value on perioperative massive bleeding in their study which covered a study population of more than 600 000 patients. They found that a higher INR value can be independently and significantly associated with major bleeding in surgical patients. This study was done in adult patients, and covered several types of surgery, but our results on INR as a risk factor for massive bleeding support this notion. However, analyses using categorical variables nor outcomes are not as statistically impactful as analyses performed using continuous data. Therefore, the results of the original analysis should be considered more significant.

6.2.2 Drainage bleeding

Characteristics related to drain output in NMS patients undergoing spinal fusion have been researched very limitedly. Kasimian et al. described the beneficial effect of antifibrinolytic agent Aprotinin© on perioperative bleeding, and simultaneously also reported the amount of drainage at 48h follow-up, mean of 524ml (25% of the total EBL) in the drug-native NMS group. (Kasimian, et al., 2008)

In current study, drainage bleeding in AIS and NMS groups showed only small differences (566 ± 208 mL and 489 ± 188 mL, p=0.0294), which is surprising concerning the large difference in intraoperative bleeding. The fusion of NMS patients is typically greater in extent, which might contribute to this finding. However, in NMS group mean drainage bleeding per level was actually smaller than in AIS, 32 ± 9 ml/level, and 43 ± 17 ml/level, respectively. On the other hand, it is possible that a single subfascial drain is not effective enough to remove all postoperative secretion from the surgical site, which may further contribute to an increase in the amount of hidden bleeding and explain the differences between groups.

Study II indicates that more levels fused correlates with more drainage bleeding in NMS patients. This adds to the literature, as no previous studies concerning the risk factors in NMS patients have been conducted previously.

Concerning AIS patients, male sex and number of osteotomies were independent risk factors for more voluminous drainage bleeding in our analysis. In AIS patients, the risk factors for drainage bleeding have previously also been studied limitedly. Li

et al. conducted a study with categorical risk factor variables with threshold limits, and found out that lower BMI, larger preoperative curvature angle, lower platelet count, greater number of fusion levels and the use of osteotomies increased the risk for more voluminous drainage bleeding in dataset of AIS patients. They also included the volumes of transfusions, colloids and crystalloids, and the number of screws in their analysis, and found them to increase the drainage bleeding. (Li, et al., 2017) Choi et al. found an association between drainage bleeding and number of osteotomies performed in AIS patients. (Choi, et al., 2019) Our analysis is in line with these previous findings concerning the effect of osteotomies yet was not consistent with previous studies on other factors and showed that male sex had an effect on drain output in AIS.

Dong et al. report the effect of combined intravenous and topical tranexamic acid as reducing the drainage bleeding after spinal fusion in AIS patients. The topical tranexamic acid was injected retrogradely through a subfascial drain. The combined tranexamic acid administration reduced the volume of drainage bleeding and the length of hospital stay significantly, in comparison to iv-TXA alone.

6.2.3 Hidden blood loss

As our studies I and II are the first to investigate the subject of hidden blood loss in patients with neuromuscular scoliosis, no literature concerning the issue could be found for comparison. However, a handful of studies have been conducted concerning the hidden blood loss in other types of scoliosis.

Quarto et al. studied the amounts of bleeding and influencing factors for hidden blood loss in fusion for AIS and other adult spinal deformities. Their estimated of hidden blood loss amounts (556.6 ± 381.8 ml (60.6 ± 42.8 ml per level) exceeded ours (398 ± 411, 40 ± 29 ml/fusion level) and they stated that hidden blood loss can constitute up to 50% of total blood loss in spinal fusion. This makes it crucial to investigate the risk factors and later try to control them in order to reduce the total blood loss in spinal fusion. Their study suggests that older age and higher BMI were associated with more significant hidden blood loss. (Quarto, et al., 2023) In our analysis, higher BMI was also a possible risk factor for hidden blood loss in bivariate analysis, yet only MCV levels and duration of operation were linked in multivariate analysis with more voluminous hidden blood loss. It should be noted that the study of Quarto et al. also included adult patients. Wang et al. reported similar amount of hidden blood loss, as in their cohort, HBL accounted for 50% of the total blood loss. (Wang, et al., 2021)

Kolz et al. presented a study of 67 AIS patients and found out that HBL can account for more than 80% of the total bleeding. Their analysis found an association between older age (>14), higher BMI (>25), longer operation time (>3.5) and

allogenic transfusions to increased HBL. (Kolz, 2022) Our results support the effect of longer operation time to more voluminous HBL, yet the results differ concerning the other factors. Their study consists of smaller number of patients in comparison to ours and uses categorical variables instead of continuous data in comparison to current study, both of which might explain the differences. In our cohort, the estimated hidden blood loss accounted for only approximately 30% of the total bleeding, which is a major difference from the report of Kolz et al. However, their study did not report drainage bleeding separately, which might contribute to the higher proportion of hidden blood loss in total bleeding.

An association between HBL and number of fused levels was found by Li et al. in their study of AIS patients. Similar correlation could not be observed on our dataset. (Li, et al., 2022)

In their large retrospective review of 765 AIS patients, Bai et al. aimed to assess the risk factors for HBL in spinal fusion. They found out that HCT levels and allogenic blood transfusions were associated with increased HBL, while tranexamic acid resulted decreasingly to the amount of estimated HBL. (Bai, et al., 2019) Wang et al. also presented a correlation between HCT and HBL in spinal fusion for AIS patients (Wang, et al., 2021), which could not be observed in the current study. Concerning transfusions, our primary analysis did not include blood transfusions, and a further analysis could not observe correlation to hidden blood loss. Tranexamic acid was already included in the study protocol.

Amount of hidden blood loss have also been estimated for patients with congenital scoliosis undergoing posterior hemivertebra resection, with hidden blood loss accounting for approximately 40% of the total bleeding. (Liu, et al., 2022) However, these results provide only a rough indication, as they are not directly comparable to NMS patients undergoing spinal fusion, due to the fact that the type of surgery differs significantly from spinal fusion.

In the current study, the bleeding amounts of AIS and NMS patients differed significantly, and there was a statistically significant difference in HBL between AIS and NMS groups ($p=0.0332$), NMS patients bled more. This difference was also visible in multivariable regression analysis. However, the proportion of HBL of total bleeding was approximately 30% in both NMS and AIS (31% for NMS and 27% for AIS, $p=0.3055$). This indicates, that as NMS patients' overall bleeding is more prominent, the proportion of HBL in spinal fusion on a controlled study setting remains similar despite the etiology of scoliosis. Our study I aimed to assess the differences between NMS and AIS groups concerning different types of bleeding related to spinal fusion, and the weight and fusion level adjusted HBL reached only a borderline significance, $p=0.053$. When adjusting the bleeding only with weight, the results were significant, (16.4 ± 1.3 ml/kg vs 7.1 ± 0.77b ml/kg, $p<0.001$. This

indicates that hidden blood loss in NMS patients, might not be influenced by the number of vertebrae in fusion.

6.2.4 Total bleeding

Our study indicates that total blood loss in NMS patients is linked positively with preoperative MCV levels and longer operative time. On the contrary, it did not show correlation between total bleeding and fusion level in NMS patients, which has been described in literature in several previous studies. (Cristante, et al., 2014, Jia, et al., 2017, Meert, et al., 2002). Meert et al. and Cristante et al. did not demonstrate a comparison between NMS and AIS patients, and Jia et al. used categorical data as described previously. In Jia et al. dataset, the mean numbers of fused levels were notable smaller, means of 11.2 ± 1.84 and 12.24 ± 1.19, in comparison to our dataset, with mean of 15.5. ± 1.4. Altogether 80% (65/81) of NMS patients in our cohort received a fusion of 15 or more vertebrae. The correlation of fusion level might be blurred in our cohort as the fusions were very similar in extent for most of the patients.

6.3 HRQoL

In study III significant improvement of HRQoL was observed in NMS patients. The Total-SRS Score, and all its domains improved in our 2-year follow-up, and the improvement was mainly similar to AIS, yet superior considering SRS total score, and inferior concerning pain score. Post-operative self-image score at final follow-up of 2 years was significantly better in NMS than in AIS.

Concerning clinical relevance, predetermined MCID levels of SRS-22r were utilized. The changes of pain and general activity exceeded the threshold limits of MCID in NMS group, and 65% of patients were above the threshold for pain, and 59% concerning general activity. In AIS group, pain was the only domain to exceed the MCID thresholds for changes. Yet, out of AIS patients, 85% were above the threshold.

Research concerning HRQoL after spinal fusion in NMS population has been done previously with slightly different focus. A similar study setting was conducted by Ersberg et al. as they analyzed the HRQoL differences in their group of 13 NMS and 123 AIS patients in their retrospective study using SRS-22r questionnaire. In terms of domain changes, neuromuscular patients experienced improved function, and AIS patients decreased pain. In the current study III, a similar difference in pain domain was observed, however, differences in function domains were not observed. Postoperative self-image improvement was observed in both Ersberg et al. and in the current study, concerning both patient groups. The correction rates were not

reported, so comparison or conclusions or concerning clinical results cannot be made. (Ersberg and Gerdhem, 2013)

Bohtz et al. assessed the postoperative HRQoL in their study of 50 CP patients. They stated that the HRQoL improved significantly after the operation, and the degree of correction did not significantly affect the HRQoL results. A postoperative satisfaction rate of as high as 92% was observed. What is more, they did not find a correlation between pelvic fusion and HRQoL. This contrasts with the results of current study, which might be due to the fact that a different "Caregivers Priorities and Child Health Index of Life with Disabilities" -questionnaire was used in the study of Bohtz et al. (Bohtz, et al., 2011)

In their study of NMS patients, Obeid et al. reported increased postoperative HRQoL evaluated with PEDI (pediatric disability inventory) and GMFS (gross motor function score). The clinical outcomes were not reported, and no control group was used. (Obid, et al., 2013)

Suk et al. assessed the postoperative quality of life and compared two separate questionnaires, muscular dystrophy spine Questionnaire (MDSQ) and short-form questionnaire 36 (SF-36). MDSQ results implied that there was an improvement in sitting balance, whereas the SF-36 only showed improvements in pain and social function scales. It must be noted that the postoperative residual curvature means were notable larger than in our study, with means of 39° ± 20° and 19° ± 11° respectively, which might have an effect on the differences.

Pelvic instrumentation has been shown to improve radiological outcome and future facilitate patient handling in non-ambulatory patients. (Tondevold, et al., 2020). Current research showed that quality of life was impaired as a result of pelvic instrumentation, making clinical decision-making concerning the extent of fusion challenging. We also compared the postoperative HRQoL differences between S2AI-technique and iliac screw technique. In our study, function domain score was superior in iliac screw subgroup. Previous literature describes the benefits of S2AI-instrumentation, as it requires less subcutaneous muscle dissection, deeper implant positioning and no need of connectors. All of these decrease the risk of implant prominence. This discrepancy may be explained by coincidence, or the longer lever arm provided by the iliac screw -technique might be useful for correcting pelvic obliquity.

6.4 Bone Health

Study IV demonstrated an association between reduced bone mineral density and pre-treatment of neuromuscular scoliosis with GFSI prior spinal fusion in SMA children, when compared to scoliotic SMA children without previous surgical

treatment. The impact was most prominent at lower thoracic and upper lumbar vertebrae.

In our study, both GFSI treated and without GFSI treated SMA children had notable lower BMD levels in comparison to healthy age and sex matched controls. This is in line with the current understanding, as the SMA patients tend to have poor bone health. (Hensel, et al., 2020, Khatri, et al., 2008) Wasserman et al. observed the influence of SMA severity measured in subtype to bone health and found out that risk for low BMD had high prevalence in all subtypes, yet the BMD severe type of SMA I was the poorest. (Wasserman, et al., 2017) Peng et al. reported results in line with this as in their study, BMD of SMA II patients were inferior to patients with SMA III.(Peng, et al., 2021) Our cohort could not verify this phenomenon, as differences in BMD regarding subtypes were only inspected visually and not statistically. This might be since the majority of our patients were subtype 2, which evidently blurs the statistical power. Bone health has also been associated with physical activity; higher physical function leads to higher BMD values. (Ballestrazzi, et al., 1989, Vai, et al., 2015) In this study this is irrelevant to the results, as 95% (N=40) of the SMA patients were non-ambulatory, so physical activity should not be a confounding factor in BMD differences, and what is more, GFSI should not have had a reducing impact on physical activity either.

An estimate of incidence for fragility fractures in SMA children has been reported at 5 to 46% in previous literature.(Peng, et al., 2021, Vai, et al., 2015, Vestergaard, et al., 2001) The present study corresponds to this, with fracture incidence of 24%. When analyzing the BMD of patients with history of fractures, a clear difference was observed in comparison to patients without history of fractures.

Our study is unique in its field and previous research concerning the direct effect of GFSI on BMD is non-existent. However, there are several studies to assess the bone health from different perspectives. Rigid implants have been reported to impact negatively to bone health both in canine models (Dalenberg, et al., 1993, McAfee, et al., 1989), and also in long term follow ups (Akazawa, et al., 2017, Ohashi, et al., 2018, Watanabe, et al., 2019). In these decades' long follow-ups multiple factors such as amount of physical activity and nutritional status might blur the effect of implants, hence this perspective is not comparable to GFSI implants in adolescents with SMA for a shorter period but suggests the influence of rigid spinal instrumentation to bone health.

The biomechanics of the vertebrae after MCGR implantation have been studied preclinically in a spinal model where the MCGR-implanted pig spine was compressed in the upright position. The implants were found to cause reduction of mechanical load, consequently stress-shielding and eventually lead to osteoporosis. (Wong, et al., 2021) It must be noted that the study did not have a follow-up period

so the assessment of the consequences of off-loading is mainly speculation about possible effects on bone health.

In adult spine surgery, the phenomenon of stress shielding caused by spinal instrumentation was widely studied decades ago (Farey, et al., 1989, Gurr, et al., 1989, Johnston, et al., 1990, Smith, et al., 1991), but since then the literature has grown more slowly (Teles, et al., 2018). Stress-shielding refers to the phenomenon in which implants take some of the load off the bone elements themselves, leading to bone mass resorption, lower BMD and slower remodeling. (Kleiner, et al., 1995)

Vertebral morphology changes and growth modulation after GFSI-treatment have also been an interest of couple of recent studies on pediatric spine research. Hasler et al. assumed, that VEPTR-implants lead to reduction of mechanical load, which impairs anteroposterior growth of spinal vertebrae. (Hasler, et al., 2015) Cognetti et al., Hell et al. and Lippross et al. also report pedicle size and vertebral body changes after GFSI treatment. (Cognetti, et al., 2019, Hell, et al., 2022, Lippross, Girmond, et al., 2021, Lippross, Grages, et al., 2021) These previous studies support the stress-shielding phenomenon also to be relevant in case of GFSI implants. The current study on bone health in SMA children is in line with this theory and adds the aspect of reduction of BMD to the understanding of the impact of GFSI implant on spinal bone health.

6.5 Reflection of clinical impact of the studies

The common denominator in these studies concerning different surgical aspects of the treatment of neuromuscular scoliosis is the fact to be clinically justified, major and challenging operations must produce clinically indisputable benefits for the patient. To ensure this, attention should be paid both to the optimization of perioperative factors and the management of possible risk factors, and also to a critical examination of the outcomes to be achieved.

Bleeding related to surgery could be described as a sort of obligatory complication of all operations, the minimization of which is beneficial in many ways. Firstly, wound healing problems, pain and swelling are reduced by minimizing bleeding. (Ferraris, et al., 2012)Secondly, for larger bleeding volume minimizing bleeding leads to a reduction in the use of infusions and transfusions, and thus avoidance of transfusion-related complications such as adverse reactions. (Yoshihara and Yoneoka, 2014) Poor clinical outcome has been linked to massive transfusions in scoliotic spine surgery. (Kim, et al., 2018)

Naturally, minimizing surgical bleeding starts with the knowledge of what kind, when and why there is surgical bleeding in the first place. In our studies I and II, we provide valuable new information, especially regarding bleeding in NMS patients. Although we did not find independent risk factors for hidden blood loss in our risk

factor analysis at this time, it is undeniably clear from our study and previous literature that hidden bleeding also accounts for a significant proportion of bleeding in NMS patients undergoing lumbar spinal fusion surgery, and its consideration in perioperative management is essential to optimize treatment outcome.

Theoretically estimating the amount of hidden blood loss in clinical work would not be challenging either, as standard postoperative follow-up practice includes postoperative blood count monitoring during the length of stay, and the hematocrit required for the calculation is an integral part of this. In addition, only an estimate of the measured bleeding is required. However, estimation of absolute bleeding rates is less essential than general awareness; bleeding does not stop with wound closure or even drainage, but an estimate of 30% is yet unnoticed.

Patients receive blood transfusions in situations where it has been assessed that the body's own blood volume or blood cell count is insufficient for the current need. In case of surgery, this is in practice most often due to excessive surgical bleeding. However, blood transfusions always possess risks, and an allergic reaction, hemolysis, or other reaction in these situations complicates the patient's overall recovery. (Vossoughi, et al., 2018) In pediatric patients, transfusion reactions are more common than in adults. (Lavoie, 2011, Morley, et al., 2016) Autologous transfusion is better option concerning complications, yet the best overall option would be to be able to avoid transfusions altogether. (Thompson and Luban, 1995) This reinforces the importance of examining the bleeding characteristics related to operations, in this case spinal fusion. When evaluating the importance of assessing the risk factors related to intraoperative bleeding, it cannot be overemphasized that spinal fusion for (neuromuscular) scoliosis is a massive operation that possesses high surgical risks.

The same reasoning of identifying the underlying risk factors and characteristics applies to bone mineral density in orthopedic operations. Spinal abnormality, such as vertebral body shapes, pedicle size or poor bone quality should be investigated and recognized prior spinal surgery, as these might lead to difficulties in fusion surgery, for example considering implant insertion and size. (Rajasekaran, et al., 2018)

The general health status, morbidity and comorbidities of neuromuscular patients are often worse than those of otherwise healthy patients, such as AIS patients, in almost all markers, and therefore the risks associated with surgery are also much higher. The scale of the fusion poses an additional challenge, as it increases the risks. Therefore, risk assessment in NMS patients in particular is crucial. When considering the justification for fusion surgery, curvature progression is usually of main concern. In neuromuscular patients, fusion is often chosen on clinical reasoning of prevention of the curvature development and improvement of the patient's quality of life. Based on the MCID values of HRQoL for both groups (NMS and AIS) of

pain and NMS patients concerning the general activity, our HRQoL improvement results should be considered clinically significant. Pain is rarely the main clinical issue in NMS patients' everyday life, but improvement in general activity is an important component of overall quality of life. On the contrary in AIS, pain might be notable in daily life.

The benefit of pre-treatment for scoliosis curvature with GFSI implants have been described in previous studies. (Calderaro, et al., 2020, Catteruccia, et al., 2015, Lorenz, et al., 2020, Mesfin, et al., 2012) Curvature correction is also the main outcome factor when measuring successful surgical outcome in spinal fusion. In our Study IV, we could not observe a significant difference in patient demographics, other than preoperative Cobb angle benefit in GFSI group, which might implicate that the effect of reduced BMD is not directly linked to the correction achieved in the final spinal fusion. However, reduced BMD might make the operation more prone to complications such as implant failure or screw insertion error, which were not included in the current analysis in study IV. Longer operation time has also been linked to increased risk of infection. (Maisat and Yuki, 2023, Toll, et al., 2018) Our cross-sectional study lacks a follow up period, so the latter result of correction remains unknown. This would be an important detail to analyze this effect, as loss of correction related to spinal fusion for scoliosis in longer follow-ups has been described previously. (Sink, et al., 2003)

On the other hand, as with any treatment, the justification for GFSI implantation should be considered not only in terms of clinical markers such as curvature development, but also in terms of the patient's quality of life. It would be important to assess whether the quality of life during implant use or after final fusion surgery differs from patients who have not been pre-treated with GFSI implants. Previously, Hell et al. found no correlation between GFSI implant type, correction percentage or number of surgeries. (Hell, et al., 2019) Additionally, Haapala et al. found no differences concerning HRQoL due to the implant type. (Haapala, et al., 2020) Yet the latter quality of life remains unclear.

6.6 Future perspectives

In this study, we found out that hidden blood loss is a major contributor to bleeding in neuromuscular patients undergoing spinal fusion surgery as it consists of up to one third of the total blood loss. Our study was unable to identify clear risk factors for major hidden blood loss, so future research is still needed to investigate this issue. To investigate the risk factors and characteristics associated with hidden blood loss, studies with similar controlled protocols should be constructed in order to answer this open question. Perioperative methods to control the hidden blood loss should also be studied.

Topical administration of tranexamic acid has been assessed to further reduce bleeding related to fusion surgery in AIS patients: George et al. found a reduction of intraoperative bleeding and requirement of blood product transfusions with use of TXA soaked sponges intraoperatively (George, et al., 2021). In addition, Dong et al. observed a reduction of postoperative drainage bleeding in patients receiving a dose of topical TXA retrogradely through a drain as a supplement to iv-TXA at the end of surgery in comparison to iv-only TXA administration group. (Dong, et al., 2021) This has not yet been studied in children with NMS, yet theoretically this technique could reduce both drainage and hidden blood loss also in NMS patients.

As a recent progressive step on the field, Julien-Marsollier et al. recently investigated the effect of hydroxyapatite charged collagen sponge in reduction of blood loss in age, sex, and fusion level matched control group in cohort of AIS patients and found a significant reduction of 27% of drainage bleeding on 3rd day of drain output. (Julien-Marsollier, et al., 2023) Although this is the first paper to report this method in scoliotic spinal fusion, it might help to reduce the postoperative bleeding after spinal fusion in the future. As the difference was observed not early but rather late postoperatively, this could theoretically also reduce the amount of later hidden blood loss if subfascial drain is removed already at 24 hours postoperatively as in our study. The results are not directly comparable to NMS, and more research needs to be done regarding this finding, yet this is a thought-provoking advance also concerning hidden blood loss.

Concerning bone health, the study IV demonstrated that there is an association between pre-treatment with GFSI and impaired bone mineral density in SMA patients presented with neuromuscular scoliosis prior spinal fusion. Due to the limitations of our study such as the small cohort, it remains for future studies to show whether this is a direct causality, or whether GFSI treatment is just another factor associated with low BMD in SMA patients. Also, the clinical relevance of lower BMD for fusion results, growth, and function and HRQoL should be addressed separately. Nevertheless, the bone quality of SMA patients is poor, and both SMA children in general and especially SMA children requiring spinal fusion might benefit from and pharmaceutical therapy such as bisphosphonates for bone health (Nasomyont, et al., 2020), yet more research is required to determine the optimal treatment.

Perhaps on a rather speculative thought to reduce the contribution of stress shielding and reduced bone health caused by GFSI implant would be to consider the effect of implant material and characteristics on the reduction of mechanical load in the future. In the field of pediatric orthopedics, a similar phenomenon has received attention in the past with regard to fractures, since it was partly for the problems caused by stress shielding that led originally to the development of titanium elastic nails (TEN): long bone fracture bridging with internal locking fixation led to delayed

healing or re-fractures after the removal of the implants. TE nails provide stability for the fracture, however, allow the cyclic mechanical bone stimulation to promote fracture healing. (Barry and Paterson, 2004, Ligier, et al., 1983) Naturally, the physiological factors underlying fracture healing and curvature progression in neuromuscular scoliosis are markedly different, but the same phenomenon of stress shielding caused by the instrumentation applies on both. In adult lumbar and cervical spine surgery, the effect of composite material on reduction of mechanical load in bone aspect has been investigated, and studies concerning have provided promising results in terms of stiffness, durability, and flexibility. (Luoma, et al., 2022, Mavrogenis, et al., 2014, Seaman, et al., 2017, Tahal, et al., 2017) Perhaps such possibilities could also exist in future scoliosis research. On the other hand, in the case of final fusion the implants and the reduction of mechanical load are supposedly permanent, so in this case stress shielding as an aspect is clinically less relevant, but maybe in case of GFSI the idea is worth discussing.

Also, Lemans et al. and Miladi et al. have been investigating new potential GFSI systems: Spring Distraction System (SDS) with a compressed spring to create distraction, and the One-Way Self-Expanding Rod (OWSER) which is a one-way sliding rod with split locking ring system. (Lemans, et al., 2023) Both of these methods require still more research but are designed to address the challenges of GFSI implants; reduce the need of surgery, allow normal spinal growth, and maintain curvature correction. How these methods affect bone mineral density remains to be studied in the future.

7 Conclusions

The following conclusions have been drawn based on the results of our studies:

6. NMS patients have more excessive perioperative bleeding related to spinal fusion. Blood product transfusions are more often needed in spinal fusion of NMS patients as compared with AIS patients.
7. Hidden blood loss constitutes one-third of blood loss in patients with neuromuscular scoliosis in spinal fusion. The patients with NMS have significantly larger hidden blood loss in spinal fusion in comparison to AIS patients.
8. No significant risk factors for hidden blood loss for spinal fusion in NMS patients could be found based on these studies.
9. Spinal fusion with posterior segmental pedicle screw instrumentation significantly improves the health-related quality of life of patients with neuromuscular scoliosis. The pre- to postoperative improvement in health-related quality of life of adolescents undergoing spinal fusion is significantly better in neuromuscular scoliosis compared to adolescent idiopathic scoliosis.
10. Bone mineral density in SMA children is lower after pre-treatment with growth friendly spinal implants in comparison to no pre-treatmen

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Somewhere in the Finnish archipelago, 25.8.2023
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