Course: Physical Handicaps-II

SEMESTER: AUTUMN, 2018

(3608)

ASSIGNMENT# 1

Q.1 Write a detailed note on the diagnosis, genetic aspects and progress of the duchenne muscular dystrophy.

ANS:

Duchenne muscular dystrophy (DMD, OMIM 310200) is one of the more common and well-known genetic disorders, affecting one in 3,500 live male births. It is the commonest and most significant of the muscular dystrophies. The disease is named after Duchenne de Boulogne who described the disease in a series of papers in the 1860s, though the disease was described before that by Meryon in England and others elsewhere, including perhaps the ancient Egyptians. DMD is an X-linked recessive disease, meaning that it mostly affects boys. The disease, like all muscular dystrophies, results from degeneration and loss of muscle fibres. The natural history of DMD includes the affected boys typically becoming wheelchair bound by age 12, though the advent of steroid therapyand advanced ventilatory support has changed this, significantly improving quality of life and life expectancy of the affected boys.

The DMD gene (*DMD*) was the first major disease gene found using the then 'new genetics'. It turned out to be the biggest human gene, at around 2.5 Mbp. Once the gene was identified, it was established that affected boys were lacking dystrophin, the protein product of the gene.[7]The difference between the severe DMD and the allelic, milder Becker muscular dystrophy (BMD), lies in the effect of different mutations in the gene, with DMD mainly caused by out-of-frame deletions or duplications which lead to complete loss of protein, whereas BMD is mostly caused by in-frame deletions or duplications which lead to altered-size, but still partly functional protein. Dystrophin, the protein product of the gene, is a large structural protein that links the internal actin cytoskeleton of the muscle fibre to a raft of 'dystrophin associated proteins' in the muscle membrane. Absence of dystrophin protein in DMD or abnormal function of dystrophin in BMD leads to muscle membrane abnormalities that in turn lead to damage and ultimately death of the muscle fibre.

Current Molecular Diagnosis of DMD/BMD

The most common molecular defect in the DMD gene, accounting for approximately 65% of cases of DMD (and 85% of cases of BMD), is deletion of one or more exons. Duplication of one or more exons accounts for another 6–10% of cases of both DMD and BMD, while the majority of the remaining cases are due to point mutations, small insertions/deletions or splice site changes. Complex rearrangements and deep intronic changes account for approximately 2% of DMD cases.

The minimum level of diagnostic testing that should be undertaken is a screen that detects the majority of exonic deletions. The most basic method still in regular use involves multiplex PCR of the exons known to be most commonly deleted. This method was first published by Chamberlain *et al.* in 1988 and subsequently further developed by a number of groups to the point where two multiplex sets covering the two mutation hotspots could detect ~98% of all deletions. The advantage of this method is its relative simplicity; however it does not detect duplications, does not characterise all deletion breakpoints, and cannot be used for carrier testing of females.

Newer methods involving quantitative analysis of all exons of the gene have brought about an improvement in mutation detection rate, as they will detect all exon scale deletions as well as duplications. They also fully delineate the exon boundaries of detected mutations, and are able to detect mutations in carrier females. Of the quantitative methods available, multiplex ligation-dependent probe amplification (MLPA – a commercial kit developed by MRC-Holland) is now the most widely used. An important point to note is that with both methods described so far, any apparent mutation indicated by an abnormal reading from a single probe must be confirmed by an alternative method, to account for the possibility of a single nucleotide polymorphism (SNP) under a probe or primer binding site.

A more recent development in quantitative analysis is the use of oligonucleotide-based array comparative genomic hybridisation (array-CGH). This method analyses copy number variation across the entire gene, including intronic and 3′ and 5′ flanking regions, which has the added advantages of detecting complex rearrangements and large scale intronic alterations and delineating mutation break-points much more closely. The high density of probes (probe intervals are in the order of 144 bp across the entire gene) also means that most mutations will be detected by multiple probes, thereby controlling for the possibility of false positives due to SNPs.

If no deletion or duplication is detected, then, in the case of DMD patients, full sequence analysis should be undertaken. Sequencing can be carried out on either genomic DNA or muscle-derived cDNA. Analysis of genomic DNA has the advantage that it does not require the patient to undergo a muscle biopsy; however because of the large number of separate amplicons required to cover all 79 exons it requires a high level of laboratory automation to be viable, though such methods have been described for some time. Analysis of genomic DNA will not detect mutations in the 2% of cases with complex rearrangements or deep intronic changes. Analysis of muscle RNA therefore has a slightly higher sensitivity, and is more amenable to laboratories with less automation, due to the much more manageable number of fragments however the requirement for a muscle biopsy is a drawback.

It should be noted that sequence analysis in BMD patients is of limited value, at least from genomic DNA. In one study of 23 non deletion/duplication patients, only three had variants, and these were of uncertain significance.

To summarise, the optimum molecular testing strategy for DMD, current best practice, that best balances technical and patient considerations is an initial screen, preferably quantitative, to detect deletions/duplications, followed by full sequence analysis from genomic DNA. If this is still negative, a muscle biopsy should be performed to enable protein studies and cDNA analysis if warranted. For BMD, if the deletion/duplication screen is negative the next step is muscle biopsy.

Experimental Treatments being Investigated for DMD

The size and distribution of expression of the dystrophin gene have posed challenges for the development of therapies for DMD. Cell replacement studies appeared so promising in mouse models, but resulted in disappointing failure when applied to boys with Duchenne. The most recent gene replacement study, using an rAAV delivered dystrophin transgene, resulted in low level, transient dystrophin expression and cell-mediated immune responses.

The lack of success in dystrophin gene replacement in DMD prompted the investigation of ready-to-use and indirect interventions that: a) promote muscle regeneration; b) protect muscle from oxidative damage; c) repair or protect membranes; d) alter protein turn-over; e) suppress inflammatory pathways and f) suppress atrophy pathways. However, apart from corticosteroids, no other validated pharmacological therapies for DMD have been available, and none of these experimental strategies address the primary aetiology of DMD: the absence of functional dystrophin. Despite this limitation, treatments that confer *any* benefit in DMD, given the relentlessly progressive nature of the disease, are better than doing nothing, and may have additional utility in combination with 'molecular' therapeutics that do restore the dystrophin associated complex and a degree of sarcolemmal integrity.

Although dystrophin restoration in DMD muscle has long been the primary aim, the application of small molecules to up-regulate the dystrophin homologue utrophin aroused interest, not least because unlike other molecular therapeutics under development, this approach is not restricted by the nature of the disease-causing dystrophin gene lesion. However, phase 1 studies on BMN-195 mediated up-regulation of utrophin were suspended due to 'pharmaceutical and pharmacokinetic challenges'. In addition, utrophin over-expression failed to protect dystrophic (*mdx)* mouse muscle from exercise-associated injury, and data suggest that full-length utrophin cannot anchor nNOS to the sarcolemma.

The best outcomes for DMD patients are likely to result from the early application of treatments that restore expression of the various tissue-specific dystrophin isoforms, under appropriate endogenous control. To date, both nonsense mutation read-through and induced exon skipping have shown potential to deliver this outcome. Nonsense mutations cause about 10–15% of DMD cases. Therapies that induce ribosomal read-through of premature termination codons allow production of a full-length functional protein, and both aminoglycosides and Ataluren (PTC124) have undergone clinical evaluation. The Ataluren trial failed to meet primary and secondary endpoints but the data is undergoing re-evaluation. Aminoglycoside treatment resulted in dystrophin expression and some functional improvements.

One of the more promising approaches to therapy for DMD is antisense oligonucleotide-induced exon skipping, where the cellular machinery is fooled into by-passing an exon containing a disease-causing point mutation or altering a deletion or duplication, such that a null mutation is no longer generated and DMD is converted to a milder BMD phenotype. Theoretically, 83% of Duchenne patients could be treated with anti-sense oligonucleotides. Unequivocal, localised dystrophin expression in DMD patient muscle was induced by the removal of exon 51, mediated by direct intramuscular injection of antisense oligomers: PRO051 (2′-O-methyl modified bases on a phosphorothioate backbone) and AVI-4658 (phosphorodiamidate morpholino oligomer). The first report of systemic administration of PRO051 has shown wide-spread, low level dystrophin expression, with limited side effects. While results from these trials are certainly

encouraging, we should remain mindful of the many obstacles ahead and, that for many families, timely implementation of these therapies is an imperative. Antisense oligomer induced exon skipping demands tailored therapies for different mutations. This is predicated upon accurate genetic diagnosis of young patients at an early stage in the disease, as the benefit will be greatest before substantial muscle is lost. It is necessary that we consider preclinical development of many different therapeutic compounds for DMD, and deliver exon skipping as a personalised genetic medicine. Clinical development of a compound that will only benefit a small sub-population (in some cases a single individual) will require fundamental shifts in drug manufacture, evaluation, validation, approval and supply.

Population Screening for DMD

As stated above, best practice therapy for DMD will require early identification of affected boys, to allow implementation of treatment before muscle tissue is irrevocably lost. This may also include steroid therapy where there is some evidence that early intervention produces highly beneficial results. One problem in detecting boys with DMD is that due to the mathematics of X-linked genetically lethal diseases many have no previous family history and therefore appear as sporadic cases with no warning (33% of affected boys and 33% of mothers have *de novo* mutations). Many suggestions have been made as to how to develop ways of identifying affected boys early, including screening boys with developmental delay. However, all such attempts have failed to move the time of diagnosis earlier, with the average age of diagnosis, in one of the few studies published, being 4 years and 10 months with a range from 1 year and 4 months to 8 years and 3 months. The experience elsewhere is similar, including current experience in Western Australia (unpublished data). The conclusion from published work is that the only way to successfully identify DMD patients early is through population screening. Population screening is currently only performed in a few places in the world. One of the best published programs is that in Wales, which has been running successfully for 20 years and is performed by newborn screening for Duchenne, using high serum creatine kinase levels as the screening tool. Newborn screening detects the first affected boy born in a family shortly after birth. It could be argued as to whether this is too early and population screening should be offered at a slightly later age, but newborn screening does seem to work, and is being investigated, along with programs aimed at older stages, by more and more jurisdictions; for example, parts of the USA. Implementation of population screening programs for DMD would change the landscape of best practice diagnosis, but still rely on the same diagnostic tools and allow early intervention with therapy.

Another major effect of early population screening for Duchenne is that it can allow early genetic counselling and the opportunity to avoid secondary cases in the one sibship or the extended family and offers the possibility of prevention of a significant percentage of DMD cases, whereas this is not possible when early screening is not in place, with the result being multiple affected boys in families with no previous family history.

It has also been suggested over many years, that diagnosis of DMD should focus on diagnosing women who are carriers of DMD, before they are identified through having affected boys e.g. This would be a radical departure from current practice of population screening for DMD, but be more in line with current practice of screening for carriers of other common recessive diseases such as cystic fibrosis.

Molecular diagnosis for DMD is complicated by the large size of the gene and the multiple different mutation types. But an optimum molecular testing strategy and best practice guidelines have been established. The current major interest in DMD is that finally, after more than 20 years of trying since the DMD gene was identified, experimental treatments are looking more promising, with multiple experimental treatments recently or currently in clinical trials. One of the most promising appears to be anti-sense oligonucleotide induced exon-skipping. If any of the treatments in clinical trials prove effective, current thinking is that optimum benefit for the patient will be obtained by starting treatments early, before significant muscle pathology develops. Early intervention will require early diagnosis and the most effective early diagnosis appears to be some form of population screening, either newborn screening, or screening at a slightly later age. For those who have worked with DMD over an extended period, this is yet another exciting time to be involved with the disease.

Q.2 How does the process of amputation affect the psychological and social development of the child?

ANS: Amputation

An amputation is the surgical removal of part of the body, such as an arm or leg.

This topic may be helpful if you or a member of your family has recently had an amputation or is about to have one.

Why amputation may be needed

An amputation may be needed if:

- you have a severe infection in your limb
- your limb has been affected by gangrene (often as a result ofperipheral arterial disease)
- there's serious trauma to your limb, such as a crush or blast wound
- your limb is deformed and has limited movement and function

Assessment before surgery

Unless you need to have an emergency amputation, you'll be fully assessed before surgery to identify the most suitable type of amputation and any factors that may affect your rehabilitation. The assessment is likely to include:

- a thorough medical examination – assessing your physical condition, nutritional status, bowel and bladder function, your cardiovascular system (heart, blood and blood vessels) and your respiratory system (lungs and airways)
- an assessment of the condition and function of your healthy limb – removing one limb can place extra strain on the remaining limb, so it's important to look after the healthy limb
- a psychological assessment – to determine how well you'll cope with the psychological and emotional impact of amputation, and whether you'll need additional support
- an assessment of your home, work and social environments – to determine whether any additional provisions will need to be made to help you cope

You'll also be introduced to a physiotherapist, who will be involved in your post-operative care. A prosthetist (a specialist in prosthetic limbs) will advise you about the type and function of prosthetic limbs or other devices available.

If you're having a planned amputation, you might find it reassuring to talk to someone who's had a similar type of amputation. A member of your care team may be able to put you in touch with someone.

How amputations are carried out

Amputations can be carried out under general anaesthetic (where you're unconscious) or using an epidural anaesthetic (which numbs the lower half of the body).

Once the limb has been removed, a number of additional techniques can be used to help improve the function of the remaining limb and reduce the risk of complications.

These include shortening and smoothing the bone in your remaining limb so it's covered by an adequate amount of soft tissue and muscle, and stitching the remaining muscle to the bones to help strengthen your remaining limb (a technique known as myodesis).

After the amputation, your wound will be sealed with stitches or surgical staples. It will be covered with a bandage and a tube may be placed under your skin to drain away any excess fluid. The bandage will usually need to be kept in place for a few days to reduce the risk of infection.

Recovering after an amputation

After surgery, you'll usually be given oxygen through a mask and fluids through a drip for the first few days while you recover on the ward.

A small flexible tube (a urinary catheter) may be placed in your bladder during surgery to drain away urine. This means you won't need to worry about going to the toilet for the first few days after surgery.

The site of the operation may be painful, so you'll be given painkillers if you need them. Tell a member of your care team if the painkillers aren't working, as you may need a larger dose or a stronger painkiller. A small tube may be used to deliver local anaesthetic to the nerves in your stump to help reduce pain.

Your physiotherapist will teach you some exercises to help prevent blood clots and improve your blood supply while you're recovering in hospital.

Compression garments

You'll notice swelling (oedema) of your stump after surgery. This is normal and it may continue after you've been discharged.

Using a compression garment will help with swelling and the shape of the stump. It may also reduce phantom pain and help support the limb.

You'll be fitted with a compression garment once your wound has healed. It should be worn every day, but taken off at bedtime. You should be given at least two garments, which should be washed regularly.

Rehabilitation

Physical rehabilitation is an important part of the recovery process. It can be a long, difficult and frustrating process, but it's important to persevere. After rehabilitation, you should be able to return to work and other activities.

Your rehabilitation programme will be tailored to your individual needs and requirements, and will aim to allow you to carry out as many of your normal activities as possible.

You'll work closely with physiotherapists and occupational therapists who will discuss with you what you'd like to achieve from rehabilitation so that some realistic goals can be set.

Your rehabilitation programme will usually start within a few days of surgery, beginning with some simple exercises you can do while lying down or sitting. If you've had a leg amputation, you'll be encouraged to move around as soon as possible using a wheelchair.

You'll also be taught "transfer techniques" to help you move around more easily, such as how to get into a wheelchair from your bed.

Once your wound has started to heal, you may start working on an exercise programme with a physiotherapist in the hospital gym to help you maintain your mobility and muscle strength.

If you have a prosthetic limb fitted (see below), your physiotherapist will teach you how to use it – for example, how to walk on a prosthetic leg or grip with a prosthetic hand.

Going home and follow-up

The length of time it will take before you're ready to go home will depend on the type of amputation you've had and your general state of health.

Before you're discharged from hospital, an occupational therapist may arrange to visit you at home to see whether your home environment needs to be adapted to make it more accessible. For example, you may need a wheelchair ramp or a stairlift. If these types of modifications are required, the issue can be referred to your local social services department. Read about mobility, wheelchairs and scooters and assessing your care and support needs.

It can take several months before you're fitted with a prosthetic limb (if you're a suitable for one), so you may be given a wheelchair to help you get around if you've had a lower limb amputation.

You'll probably need to attend a follow-up appointment a few weeks after being discharged to discuss how well you're coping at home and whether you require additional help, support or equipment.

At your appointment, you may also be given details of your nearest amputee support group, made up of both healthcare professionals and people living with an amputation.

Prosthetics

After an amputation, you may be able to have a prosthetic limb fitted.

Prosthetic limbs aren't suitable for everyone who's had an amputation because an extensive course of physiotherapy and rehabilitation is required (see below).

Adjusting to life with a prosthetic limb takes a considerable amount of energy because you have to compensate for the loss of muscle and bone in the amputated limb.

This is why frail people or those with a serious health condition, such as heart disease, may not be suitable for a prosthetic limb.

If you're able to have a prosthetic limb, the type of limb that's recommended for you will depend on:

- the type of amputation you had
- the amount of muscle strength in the remaining section of the limb
- your general state of health
- tasks the prosthetic limb will be expected to perform
- whether you want the limb to look as real as possible or whether you're more concerned with function

If it's thought that you would find it difficult to withstand the strain of using a prosthetic limb, a purely cosmetic limb may be recommended. This is a limb that looks like a real limb, but can't be used.

It's possible to have a prosthetic limb that's both physically realistic and functional, but there may have to be an element of compromise between the two.

Preparing to have a prosthetic limb fitted

If a prosthetic limb is suitable for you, you'll begin a programme of activities while still in hospital to prepare for the prosthetic.

Before a prosthetic limb is fitted, the skin covering your stump may be made less sensitive (known as desensitisation). This will make the prosthetic more comfortable to wear.

Skin desensitisation involves the following steps:

- gently tapping the skin with a face cloth
- using compression bandages to help reduce swelling and prevent a build-up of fluid inside and around your stump
- rubbing and pulling the skin around your bone to prevent excessive scarring

Your physiotherapist will teach you a range of exercises to strengthen the muscles in your remaining limb and improve your general energy levels, so you're able to cope better with the demands of an artificial limb.

Depending on what's available in your local area, it can be several months before you get your first appointment with a prosthetist (specialist in prosthetic limbs).

Stump care

It's very important to keep the skin on the surface of your stump clean to reduce the risk of it becoming irritated or infected.

Gently wash your stump at least once a day (more frequently in hot weather) with mild unscented soap and warm water, and dry it carefully.

If you have a prosthetic limb, you should also regularly clean the socket using soap and warm water.

When taking a bath, avoid leaving your stump submerged in water for long periods because the water will soften the skin on your stump, making it more vulnerable to injury.

If your skin becomes dry, use a moisturising cream before bedtime or when you're not wearing your prosthesis.

Some people find wearing one or more socks around their stump helps absorb sweat and reduces skin irritation. The size of your stump may change as the swelling goes down, so the number of socks you need to use may vary. You should change the socks every day.

Check your stump carefully every day for signs of infection, such as:

- warm, red and tender skin
- discharge of fluid or pus
- increasing swelling

Contact your care team for advice if you think you may be developing a skin infection.

Caring for your remaining limb

After having a leg or foot amputated, it's very important to avoid injuring your remaining "good" leg and foot, particularly if your amputation was needed because of diabetes. Your remaining leg and foot may also be at risk.

Avoid wearing poorly fitting footwear and ensure that an appropriately trained healthcare professional, such as a podiatrist, is involved in the care of your remaining foot. You should also be offered a regular review of your foot by the foot care team.

Read more about diabetes and foot care.

Complications

Like any type of surgery, an amputation carries a risk of complications. It also carries a risk of additional problems directly related to the loss of a limb.

There are a number of factors that influence the risk of complications from amputation, such as your age, the type of amputation you've had, and your general health.

The risk of serious complications is lower in planned amputations than in emergency amputations.

Complications associated with having an amputation include:

- heart complications – such as heart attack
- deep vein thrombosis (DVT)
- slow wound healing and wound infection
- pneumonia
- stump and "phantom limb" pain

In some cases, further surgery may be needed to correct problems that develop or to help relieve pain. For example, if neuromas (thickened nerve tissue) are thought to be causing pain, the affected cluster of nerves may need to be removed.

Stump and "phantom limb" pain

Many people who have an amputation experience some degree of stump pain or "phantom limb" pain.

Phantom limb sensations are sensations that seem to be coming from the amputated limb. Occasionally, these can be painful (phantom limb pain).

The term "phantom" doesn't mean the painful symptoms are imaginary. Phantom limb pain is a real phenomenon, which has been confirmed using brain imaging scans to study how nerve signals are transmitted to the brain.

The symptoms of phantom limb pain can range from mild to severe. Some people have described brief "flashes" of mild pain, similar to an electric shock, that last for a few seconds. Others have described constant severe pain.

Stump pain can have many different causes, including rubbing or sores where the stump touches a prosthetic limb, nerve damage during surgery and the development of neuromas.

Treating stump and phantom limb pain

Stump and phantom limb pain will usually improve over time, but treatments are available to help relieve the symptoms.

Medications

Medications that may be used to help relieve pain include:

- non-steroidal anti-inflammatory drugs (NSAIDs) – such as ibuprofen
- anticonvulsants – such as carbamazepine or gabapentin
- antidepressants – such as amitriptyline or nortriptyline (these medications work directly on the nerves in your leg)
- opioids – such as codeine or morphine
- corticosteroid or local anaesthetic injections

Self-help measures and complementary therapy

There are several non-invasive techniques that may help relieve pain in some people. They include:

- checking the fit of your prosthesis and making adjustments to make it feel more comfortable
- applying heat or cold to your limb, such as using heat or ice packs, rubs and creams
- massage – to increase circulation and stimulate muscles
- acupuncture – thought to stimulate the nervous system and relieve pain
- transcutaneous electrical nerve stimulation (TENS) – where a small, battery-operated device is used to deliver electrical impulses to the affected area of your body, to block or reduce pain signals
- mental imagery (see below)

Research has shown that people who spend 40 minutes a day imagining using their phantom limb, such as stretching out their "fingers" or bunching up their "toes", experience a reduction in pain symptoms.

This may be related to the central theory of phantom limb pain (that the brain is looking to receive feedback from the amputated limb), and these mental exercises may provide an effective substitution for this missing feedback.

Another technique, known as mirror visual feedback, involves using a mirror to create a reflection of the other limb. Some people find that exercising and moving their other limb can help relieve the pain from a phantom limb.

Psychological impact of amputation

The loss of a limb can have a considerable psychological impact. Many people who've had an amputation report feeling emotions such as grief and bereavement, similar to experiencing the death of a loved one.

Coming to terms with the psychological impact of an amputation is therefore often as important as coping with the physical demands.

Having an amputation can have a considerable psychological impact for three main reasons:

- you have to cope with the loss of sensation from your amputated limb
- you have to cope with the loss of function from your amputated limb
- your sense of body image, and other people's perception of your body image, has changed

Negative thoughts and emotions are common after an amputation. This is particularly true in people who've had an emergency amputation because they don't have time to mentally prepare for the effects of surgery.

Common negative emotions and thoughts experienced by people after an amputation include:

- depression
- anxiety
- denial (refusing to accept that they need to make changes, such as having physiotherapy, to adapt to life with an amputation)
- grief
- feeling suicidal

People who've had an amputation as a result of trauma (particularly members of the armed forces) also have an increased risk of developing post-traumatic stress disorder (PTSD).

Talk to your care team about your thoughts and feelings, particularly if you're feeling depressed or suicidal. You may need additional treatment, such as antidepressants or counselling, to improve your ability to cope after having an amputation.

Q.3How does juvenile rheumatoid arthritis disturb the normal physiological activities of the child?

ANS: Child growth is multifactorial, and requires the tightly controlled mobilization and utilization of energy, coordinated by several biochemical and physiological regulatory mechanisms. Impaired linear growth is commonly encountered in children suffering from chronic inflammatory diseases such as juvenile idiopathic arthritis (JIA), both at disease presentation and following treatment with glucocorticoids. In these children, maintenance of growth is a complex process that is influenced by a number of different mechanisms, including not only the steroid therapy, but also other factors such as the disease process, nutritional status, endocrine status and the response of the body to inflammatory mediators. The growth abnormalities observed in children with inflammatory diseases are often associated with delayed onset of sexual maturation and altered bone development. Evidence of an imbalance of proinflammatory cytokines in patients with inflammatory diseases includes the positive correlation of serum and synovial cytokine concentrations with JIA disease activity an increase in antagonists or soluble receptors with a flare of arthritis and the effectiveness of JIA therapies that involve cytokine modulation .The proinflammatory cytokines that have been reported to play a major role in JIA include interleukin 1β (IL-1β), tumour necrosis factor α (TNF-α) and interleukin 6 (IL-6) These proinflammatory cytokines may influence child growth through systemic effects and/or a local effect at the level of the growth plate of long bones.

The growth plate and how bones grow

The articular chondrocyte is well known to the rheumatologist. Its function is to synthesize and maintain an extracellular matrix that is able to withstand physical deformation and facilitate joint articulation. Articular cartilages persist and survive. This is in contrast to the growth cartilage produced at the epiphyseal growth plate, which is progressively synthesized and replaced by bone with accompanying longitudinal (endochondral) bone growth .

The growth plate is a thin layer of cartilage found near the ends of long bones and vertebrae .It comprises both chondrocytes and their extracellular matrix. A characteristic of endochondral bone growth is the precise temporal and spatial organization of chondrocytes within the growth plate, where they differentiate through a series of maturational stages whilst remaining in a spatially fixed location throughout its existence .Undifferentiated stem cell progenitors differentiate into chondrocytes and progress through a proliferative phase. Immediately following cessation of cell division, the cells undergo terminal differentiation into hypertrophic chondrocytes the chondrocytes become more voluminous with increases in rough endoplasmic reticulum and Golgi apparatus, reflecting their increased matrix production .The rate of longitudinal bone growth is determined by a complex interplay of proliferative kinetics, size of the proliferative pool, matrix synthesis and hypertrophic chondrocyte enlargement .The precise control of these processes is still a matter of debate and any perturbation of these synchronized variables may underlie the growth modulatory effects of external agents, such as inflammatory cytokines .

Growth plate gene expression and the chondrocyte maturational phases that may be modulated by the proinflammatory cytokines TNF-α and IL-1β.
Histologically, the chondrocytes are arranged in columns that parallel the longitudinal axis of the bone. Each column and each chondrocyte within a column are respectively separated by longitudinal and transverse septae made up of a collagenous and proteoglycan-rich extracellular matrix. The extracellular matrix of the epiphysis determines the mechanical properties of the tissue and contributes to the structural arrangement of the growth plate by providing a scaffold for chondrocyte attachment and migration During terminal differentiation, the collagenous matrix mineralizes and it functionally changes to an environment allowing vascular invasion from the marrow of the metaphysis, thereby providing a conduit for the recruitment of osteoclasts and differentiating osteoblasts that remodel the newly formed cartilage into bone tissue .During the growth period the rate of cartilage addition and replacement are coupled, so that the width of the growth plate remains constant. From animal studies it has been calculated that eight hypertrophic chondrocytes (including its associated matrix) are eliminated by apoptosis from each column of cells every day .However, towards the end of the growth period the growth plate narrows and finally disappears. It has been widely accepted that growth cessation is a result of systemic control and the fusion of the epiphysis with the metaphysis. However, it is now believed that regulation is intrinsic to the growth plate and that growth plate fusion does not precede, but follows, the cessation of growth
In children, maintenance of growth is a complex process that is influenced by a number of systemic and local autocrine/paracrine mechanisms. This list includes vitamin D metabolites, androgens, fibroblast growth factor and bone morphogenic proteins together with other members of the transforming growth superfamily. Two of the most important and widely studied regulators of postnatal bone growth are growth hormone (GH) and insulin-like growth factor 1 (IGF-1). The dual effector theory of GH/IGF-1 action at the growth plate proposes that GH acts directly on germinal zone precursors of the growth plate to stimulate the differentiation of chondrocytes and then amplify local IGF-1 synthesis, which in turn induces the clonal expansion of chondrocyte columns in an autocrine/paracrine manner .IGF-1 is, however, expressed by chondrocytes situated in all maturational zones of the growth plate, with IGF-1 mRNA expression mainly restricted to the hypertrophic zone. Infusion of hypophysectomized rats with IGF-1 stimulated growth plate chondrocytes at all stages of differentiation, including those in the hypertrophic zone .Although liver-derived IGF-1 is the main determinant of serum IGF-1 levels, it is not as important for postnatal growth as locally derived IGF-1 .
Recent investigations have indicated that the local control of cellular function by parathyroid hormone-related peptide (PTHrP) extends to cells of the skeleton and in particular to the growth plate chondrocytes. Mice lacking the PTH/PTHrP receptor gene have a growth plate morphology similar to that of mice that are homozygous for the ablation of the PTHrP gene .There is widespread accelerated differentiation of chondrocytes and premature mineralization, resulting in a narrow growth plate. In contrast, the phenotype of mice in which the PTHrP gene is overexpressed is characterized by a dramatic slowing down of the differentiation of chondrocytes and a wider growth plate .These and other experiments have led to the acceptance that PTHrP, together with the morphogen Indian hedgehog (Ihh), is one of the major influences on the endochondral growth process .

Sex steroids are of crucial importance in the control of longitudinal growth, and exert direct effects on the growth plate. A number of studies have demonstrated the presence of the androgen receptor and both oestrogen receptors, ERα and ERβ, in growth plate tissue at the mRNA and protein level in several species, including the rat, rabbit and human .indicating that androgens and oestrogens directly regulate processes in the growth plate. Furthermore, the growth plate possesses the ability for steroidogenesis as well as aromatization .However, it has been difficult to prove whether androgens have direct effects on growth plate cartilage. Non-aromatizable androgens, such as dihydrotestosterone, have been shown to regulate both proliferation and differentiation of cultured human epiphyseal chondrocytes, probably by promoting local IGF-1 synthesis and increasing IGF-1 receptor expression .

Oestrogen is the critical hormone in controlling growth plate acceleration and fusion in both females and males .*In vitro* studies have shown that oestrogen alters alkaline phosphatase activity, cell proliferation and proteoglycan synthesis .Indeed, oestrogen has a biphasic effect on proliferation, which is stimulated by low levels and inhibited by high levels of oestrogen .

Linear growth in children with JIA

Maintenance of growth in children with JIA is a complex process that is influenced by a number of different mechanisms, including not only drugs but also other factors, such as the disease process [38]. Estimates of significant short stature (final height standard deviation score (SDS) of less than –2) in children with JIA range from 11% of all patients to 41% of patients with systemic forms of JIA .Clinical studies by our own group and others have shown that growth and skeletal development are reversibly impaired during periods of intensive therapy, especially during treatment with prednisolone and dexamethasone .However, 87% of patients in the retrospective study of 24 children with systemic JIA reported by Simon *et al*. had a final height below their target height .In this study, the authors also noted that, after remission of the disease and discontinuation of glucocorticoid therapy, 30% of the patients did not show any catch-up growth. The patients who showed no catch-up were more likely to be shorter at diagnosis and had a lower target height.

As a group, children with JIA have a unique pattern of growth disturbance; systemic JIA is often associated with general growth retardation whereas oligoarticular JIA is associated with local excess growth. This discrepancy manifests itself as increased growth in the affected limb in young children and premature fusion of the epiphyses in the older child with resultant limb shortening .In the young child, early use of intra-articular steroids has been reported to prevent the leg length discrepancy, but some recent evidence suggests that intra-articular steroids may depress the growth of the contralateral leg .Although hyperaemia to the juxtaposed growth plates is thought to be the mechanism for overgrowth in young children, there is no clear scientific explanation for this phenomenon, especially as the reverse seems to happen in the adolescent child.

Children with JIA and severe growth retardation may have normal pulsatile GH secretion and are reported to have reduced IGF-1 levels, suggestive of GH resistance .After monitoring height velocity for 1 yr, Davies *et al*. treated 20 children for the following year with either 12 IU/m^2 per week or 24 IU/m^2 per week of recombinant human GH (rhGH). There was a significant increase in height velocity in almost all children during the treatment period. Children with mild to moderate disease activity grew at a better rate than those with very active disease and those with

polyarticular disease responded better than those with systemic JIA. In addition, those children receiving high-dose rhGH grew significantly more than those on the low-dose regimen. Touati *et al*. and Bechtold *et al*. have also shown that treatment with a relatively high dose of rhGH (0.35–0.46 mg/kg per week) in children with systemic or polyarticular JIA for a year led to an improvement in height velocity. Overall, these studies suggest that the adverse effects of glucocorticoids and chronic inflammatory disease on growth and skeletal development in children with JIA may be halted, but not reversed, by treatment with recombinant GH.

A number of clinical studies suggest a direct link between factors produced during chronic inflammation and growth failure In systemic JIA, impairment of linear growth is seen during periods of disease activity, with subsequent normalization of growth rate during remission In patients with systemic JIA and growth defect treated with GH, growth velocity during treatment appears inversely correlated with the intensity of inflammation .

It is likely that cytokines may influence the development of these abnormal growth patterns in children with inflammatory diseases, through both systemic effects and local effects at the level of the growth plate.

Systemic effects of cytokines on the GH/IGF-1 axis

Studies using transgenic murine models have examined in detail the mechanisms by which IL-6 induces systemic effects on growth retardation. The murine model NSE/hIL-6 overexpresses IL-6, leading to high levels of circulating IL-6 and reduced growth rate The growth defect is completely abolished by neutralization of IL-6 .The mice show reduced circulating IGF-1 levels, while GH production remains unaltered .This mirrors the observations in patients with systemic JIA and demonstrates that the effect on IGF-1 levels is not mediated indirectly via an effect on GH production.

A relevant portion of circulating IGF-1 is carried in a ternary complex with IGF binding protein (IGFBP)-3 and an acid-labile subunit. This complex prolongs the half-life of circulating IGF-1. Decreased levels of IGFBP3 are observed in NSE/hIL-6 mice and wild-type mice treated with IL-6 Patients with systemic JIA also show markedly reduced levels of IGFBP-3.

The decrease in IGFBP-3 levels in NSE/hIL-6 mice is associated with impaired formation of the ternary complex. This is likely to be, at least in part, due to IGFBP-3 proteolysis, which was also observed in NSE/hIL-6 mice .Proteolytic degradation of IGFBP-3 has also been demonstrated in patients with systemic JIA .It has therefore been proposed that IL-6 decreases IGF-1 levels by increased clearance, as association of IGF-1 in the circulating ternary complex prolongs the half-life of IGF-1 from less than 10 min to 16 h .

Excessive production of TNF-α also causes growth failure in TNF-transgenic mice .However, no studies have specifically examined alterations in the IGF-1/GH axis in these models.

Il-1β has also been shown to reduce plasma concentrations of both IGF-1 and the acid-labile subunit .Increased levels of IGFBP1 inhibit IGF-1 bioactivity, as phosphorylated IGFBP1 has a higher affinity for IGF-1 than the IGF-1 receptor ,and therefore complexes with IGF-1 and prevents IGF-1 receptor binding. Hepatic IGFBP-1 expression is elevated in septic rats; this can be completely prevented by treatment with an IL-1 receptor antagonist .IL-1β also directly stimulates IGFBP-1 protein and mRNA synthesis in the HepG2 hepatoma cell line .

Local effects of cytokines on the growth plate

The cytokines that have been studied most extensively for their ability to regulate bone and cartilage function in cell cultures of chondrocytes are IL-1β, IL-6 and TNF-α. However, whilst many studies have examined the effects of cytokines on articular chondrocytes, relatively few have investigated growth plate chondrocytes.

Local destruction of the growth plate has been observed following inflammatory synovitis, denoted by elevated synovial TNF-α, IL-1β and IL-6 .This suggests that the proinflammatory cytokines present in the fluid can reach the growth plate from the adjacent synovial space. IL-1β and TNF-α inhibit the expression of a number of genes encoding chondrocyte-specific matrix molecules, including collagen types IX and XI and aggrecan .In cultures of rabbit growth plate chondrocytes, IL-1β decreased alkaline phosphatase activity during hypertrophy and suppressed increases in cell size and type X collagen expression, suggesting inhibition of chondrocyte differentiation .IL-1β has been shown to induce a dose-dependent rise in rat growth plate chondrocyte DNA synthesis, which may explain the increased longitudinal bone growth seen in affected limbs of children with arthritis .TNF-α has also been reported to stimulate DNA synthesis in cultured rat and rabbit costal chondrocytes. TNF-α induces apoptosis in chick chondrocyte cultures and suppresses cartilaginous nodule formation and the accumulation of cartilage-specific proteoglycan reduction in the ATDC5 cell line .TNF-α has also been shown to reduce proteoglycan synthesis in fetal mouse metatarsals .Furthermore, this study demonstrated that IL-17 synergizes with TNF-α to further reduce proteoglycan production. IL-1β has also been shown to synergize with TNF-α to inhibit longitudinal growth in fetal rat metatarsal bones .

IL-6 belongs to a cytokine subfamily whose members share a common signal-transducing molecule, gp130, in their respective complexes .In articular chondrocytes, contradictory results have been reported on the effects of IL-6 on proteoglycan synthesis. It must be noted that, in most of the related studies, the IL-6 effect was investigated in connection with that of other cytokines, such as IGF-1 and IL-1. For example, very high doses of IL-6 were found to decrease the enhancing effect of IGF-1 on proteoglycan synthesis .It was also shown that IL-6 is required for the inhibition of proteoglycan synthesis by IL-1 in human articular chondrocytes but these latter results have not been reproduced by others .The contradictory results may be because the IL-6 effects were investigated in the absence of soluble IL-6 receptor. Indeed, it has been shown that the levels of membrane-anchored IL-6 receptor on chondrocytes are lower than those on other cell types, such as hepatocytes, and that *in vitro* addition of soluble IL-6 receptor to IL-6 is required to observe the full inhibitory effect of IL-6 on proteoglycan synthesis .IL-6 in the presence of additional soluble IL-6 receptor also markedly down-regulates the expression of cartilage-specific matrix genes, including type II collagen, aggrecan and link proteins in bovine articular chondrocytes .IL-6 has been reported to have no effect on growth plate chondrocyte dynamics ,however, these studies were undertaken in the absence of soluble IL-6 receptor.

Oncostatin M (OSM) is a cytokine that also belongs to the IL-6 family and has been detected in JIA synovial fluid .Additionally, the injection of an adenovirus vector that expresses murine OSM induces damage to the growth plate cartilage, including proteoglycan depletion and loss of matrix integrity .This damage was shown to be dependent on endogenous IL-1. The authors proposed that OSM could either enhance or modify the autocrine effects of IL-1 on growth plate

chondrocytes, thereby leading to growth plate proteoglycan loss, disorganization and finally growth abnormalities.

Underlying mechanisms

The cellular machinery by which cytokines may act on the growth plate is unclear at present. Transmission of external signals from the cell surface to the internal cellular environment occurs via tightly controlled complex transduction pathways. Alterations in these highly regulated signalling cascades in chondrocytes may play a fundamental role in the functional abnormalities of growth plate cartilage that underlie cytokine-induced growth retardation.

Sox9 gene expression

Sox9 is a master regulatory factor for chondrocyte differentiation and cartilage formation .In mouse chimeric embryos, Sox9-null cells are unable to express the genes for chondrocyte-specific markers, such as collagen types II, IX and XI and aggrecan .Both IL-1β and TNF-α markedly down-regulate the expression of Sox9 in both costal chondrocytes and a chondrocytic cell line .These effects appear to be mediated by the NF-κB pathway, although the precise mechanism remains to be elucidated .

TNF-α and apoptosis

TNF-α has two cell surface receptors, TNFR1 and TNFR2. Binding of TNF-α to TNFR1 initiates an apoptotic response, which is simultaneously activated by TNF-α through the Fas-associated death domain (FADD), a protein that triggers the pro-apoptotic caspases and cell death. TNF-α has been reported to induce apoptosis in chondrogenic cells and fetal rat metatarsal cultures TNF-α-induced apoptosis may be a major contributor to the growth abnormalities observed in children suffering from inflammatory diseases.

IGF-1 signalling

The IGF-1 signalling pathway is unequivocally a major autocrine/paracrine regulator of bone growth .Proinflammatory cytokines may modulate the IGF-1 signalling cascade at one or more junctures: IGF-1 receptor binding; insulin receptor substrate phosphorylation; the p44/42 mitogen-activated protein kinase (MAPK) signalling pathway; the phosphatidylinositol 3-kinase (PI-3K) signalling pathway; and Akt phosphorylation .The effects of proinflammatory cytokines on the major IGF-1 signalling pathways in growth plate chondrocytes have yet to be described in the literature. However, the effects of cytokines on IGF-1 signalling have been investigated in a number of other cell types, which are reviewed in the following text.

Potential junctures at which proinflammatory cytokines may interrupt IGF-1 signalling: (1) increased SOCS 3 expression; (2) insulin receptor substrate phosphorylation (IRS); (3) MAPK-kinase phosphorylation within the p44/42 mitogen-activated protein kinase (MAPK) signalling pathway; (4) the phosphatidylinositol 3-kinase (PI-3K) signalling pathway; and (5) Akt phosphorylation.

The cellular actions of IGF-1 are mediated by a receptor tyrosine kinase (IGF-1R), which is expressed in growth plate chondrocytes. However IL-1β and TNF-α do not down-regulate IGF-1 receptor expression or affect IGF-1 receptor affinity in articular cartilage. Furthermore, IL-1β and TNF-α do not impair the intrinsic tyrosine kinase activity of the IGF-1 receptor in either breast cancer cells or myoblasts .Therefore, it is unlikely that proinflammatory cytokines alter the IGF-1 signalling cascade at the level of the IGF-1 receptor in growth plate chondrocytes.

Binding of IGF-1 to its receptor utilizes a family of soluble receptors, known as insulin receptor substrates (IRSs), to initiate a series of autophosphorylation events. The mammalian IRS family contains at least four members, but only IRS-1 is expressed in epiphyseal cartilage .TNF-α and IL-1β have been shown to induce IGF-1 resistance by inhibiting IRS-1 phosphorylation in both myoblasts and breast cancer epithelial cells .Proinflammatory cytokines may therefore also induce IGF-1 resistance by inhibiting IRS-1 phosphorylation in growth plate chondrocytes. TNF-α and IL-1β receptor activation has been shown to elevate ceramide, a sphingosine-based lipid second messenger, through *de novo* pathways in breast carcinoma, fibrosarcoma and hepatic cells and sphingomyelinase pathways in leukaemic T-cell and pre-B cell lines and breast carcinoma, fibrosarcoma and thymoma cells Ceramide also inhibits IGF-1-induced tyrosine phosphorylation of IRS-1 in myoblast and hepatic cells and may also be a key intermediate by which proinflammatory cytokines impair IGF-1 action in growth plate chondrocytes.
Many proinflammatory cytokines, including TNF-α and IL-1β, stimulate the tissue-specific expression of suppressor of cytokine signalling proteins (SOCS) .SOCS are a group of signalling proteins characterized by their ability to down-regulate cytokine signalling and are critical in modulating GH signalling .Cytokine binding to its receptor activates the JAK-STAT signalling pathway, leading to induction of SOCS mRNA and protein .Studies in adipocytes have shown that TNF-α and IL-1B increase SOCS 3 expression, and this directly inhibits IRS-1 phosphorylation by IRS-1 protein degradation .
Autophosphorylation of IRS-1 results in the activation of two distinct signalling pathways, PI-3K and p42/p44 MAPK, leading to proliferative and anti-apoptotic effects. Therefore cytokine-induced inhibition of IRS-1 phosphorylation in growth plate chondrocytes would be likely to reduce the downstream activity of both pathways. However, proinflammatory cytokines may also act directly on the PI-3K and/or p44/p42 MAPK pathways of growth plate chondrocytes. The MAPK pathway is strongly dependent on tyrosine phosphorylation steps and involves $p21^{ras}$, c-Raf-1 and MAPK-kinase (MKK), which is a direct upstream activator of p44/p42 MAPK. Phosphorylated MAPK translocates to the nucleus, where it participates in the phosphorylation of retinoblastoma pocket protein, resulting in the release of transcription factors and the activation of genes necessary for cell cycle progression and DNA replication .TNF-α has been shown to inhibit MKK phosphorylation in neuronal cells Proinflammatory cytokines may therefore also act directly on the p44/p42 MAPK pathway of growth plate chondrocytes.
TNF-α has also been shown to prevent the intranuclear translocation of PI3K in an osteoblast cell line .Activation of PI-3K activity results in a series of intracellular downstream events, generating phosphorylated phosphatidylinositol (PI) intermediates (such as PI 3,4,5-triphosphate, PIP_3) in the cytosolic leaflet of the plasma membrane. PIP_3 intermediates recruit other downstream signalling molecules, such as Akt, to the plasma membrane, and the subsequent phosphorylation of its several downstream effectors (e.g. NFκB, caspase-9) mediates the effects of Akt on cell growth, proliferation and protection from pro-apoptotic stimuli .Proinflammatory cytokines may inhibit Akt phosphorylation in growth pate chondrocytes through either PI-3K-dependent and/or PI-3K-independent mechanisms. TNF-α has been shown to inhibit the phosphorylation and activation of Akt in neuronal cells .Additionally, studies in erythroleukaemic, adrenal phaeochromocytoma and glioblastoma cell lines have suggested that ceramide induces growth arrest via dephosphorylation of Akt In neuronal cells, ceramide has

been shown to inhibit Akt indirectly ,leading to the proposal of multiple indirect mechanisms for ceramide regulation of Akt. Conflicting results have suggested PI-3K-dependent regulation of Akt by ceramide in fibroblasts as well as PI-3K-independent regulation of Akt by ceramide in kidney cells, fibroblasts and adipocytes .Two molecular PI-3K-independent mechanisms by which ceramide inhibits Akt activation by insulin have been elucidated in pre-adipocytes Ceramide specifically blocks the translocation of Akt to the plasma membrane, while simultaneously promoting the dephosphorylation of Akt by protein phosphatase 2A.

Growth hormone (GH) signalling

Increased levels of inflammatory cytokines may inhibit the effects of GH on the growth plate. It has been suggested that cytokines may act on GH receptor signalling ,although very little research has been undertaken in this area. Members of the SOCS family of proteins make important contributions to the negative regulation of the growth-promoting actions of GH. Mice lacking SOCS2 expression display gigantism accompanied by evidence of deregulated GH signalling .Additionally, IL-6 has been proposed to inhibit liver GH signalling by inducing SOCS 3 ,a phenomenon that may explain GH resistance in inflammatory disease.

The development of abnormal growth patterns in children with inflammatory diseases such as JIA may be modulated by proinflammatory cytokines through both systemic effects and effects acting locally at the level of the growth plate. An improved understanding of the crucial cellular events that may be affected in growth plate development will allow us to be in a stronger position to ameliorate disturbed growth in affected children.

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Q.4Elaborate the complications of the scoliosis. How does scoliosis affect the child in early life of the sufferer?

ANS: Around two to three percent of the U.S. population is afflicted with the chronic medical condition known as scoliosis,[1] a type of abnormal curvature of the spine that usually develops in its sufferers during childhood. The effects of scoliosis vary widely in severity; in the most serious cases, the condition can impose major lifestyle challenges on those who suffer from it. Despite its prevalence among the general population, scoliosis remains a mystery to the majority of people, as few have more than a shadowy idea about what this disorder is. If you've been diagnosed with scoliosis, or you know someone who has, you owe it to yourself to learn about this often uncomfortable condition. Let's take a closer look at scoliosis and the ways that it can negatively impact an individual's day-to-day life.

What Is Scoliosis?

First, you need to be clear on what a "normal" spine is supposed to look like. Contrary to what many believe, a healthy spine has several natural curves, each corresponding to a distinct region. When viewed from the side, the human spine assumes a rough "S" shape:

- It curves slightly outward at the neck—the area known as the **cervical spine**.
- It curves slightly inward at the middle—the area known as the **thoracic spine**.
- It curves slightly outward toward the bottom—the area known as the **lumbar spine**.

Below these regions are the **sacrum** (hip) and the **coccyx** (tail bone).
These curves in the spine provide us with a degree of flexibility and the capacity to absorb bodily stresses.
When examined from the rear, the spine appears straight—if it is healthy. In persons suffering from scoliosis, though, the spine bends noticeably to the left or the right. These abnormal curves generally appear in the thoracic or—less commonly—the lumbar region.
Generally, the curvature of the spine must reach at least 10 degrees to qualify for a diagnosis of scoliosis. As a rule of thumb, the greater the curvature, the more severe the complications that result from it. Mild scoliosis is often no more than an intermittent inconvenience that requires little or no medical intervention. People with substantially more pronounced curvature, however, can develop multiple health issues.

Complications of Scoliosis

Scoliosis can result in a number of physical abnormalities, including uneven shoulders and/or waistline. In advanced cases, the curvature of the spine may cause it to twist, leading to an uneven appearance around the ribs as one side projects further outward than the others.
Scoliosis is often detectable from alternations in the patient's normal gait, as the misalignment of the hips creates an uneven walking pattern. Sometimes clothing will fit poorly.
It must be understood that scoliosis can cause issues that go far beyond affecting one's outward appearance. Scoliosis sufferers sometimes report recurring issues with back pain, although, in many cases, this is mild in nature. In older patients, back pain can be more serious. Even simple everyday tasks can lead to significant discomfort—tying shoes, lifting groceries, sitting in chairs, and so on.
Due to the deformation of the spine, scoliosis patients can even develop breathing and heart disorders as the rib cage presses into the lungs. Potentially life-threatening complications like these are extremely uncommon, but they can happen.
Because scoliosis tends to develop at an early age, it can lead to serious self-esteem issues in growing children, who may become the target of teasing from their peers. They may become insecure about their appearance and develop a poor self-image. That's one reason why it is important to ensure that afflicted children get medical attention as soon as possible. Another reason is that early treatment may prevent serious complications that require more drastic measures.

Types of Scoliosis

Scoliosis can occur at any age, but it usually develops between the ages of ten to fifteen—often immediately prior to puberty. It arises with equal frequency in boys and girls, but it tends to be more serious in girls and more likely to require medical intervention. Scoliosis can be particularly stressful in adolescents, who must cope with the stresses of growing up in addition to their medical disorder.
In approximately 80% of cases, scoliosis has no knowable cause. Where this holds true, it is said to be **idiopathic** ("of unknown cause") in origin.
Scoliosis can be caused by neuromuscular disorders such as Marfan syndrome and muscular dystrophy. This is known, appropriately, as **neuromuscular scoliosis**. When this disorder is traceable to a defect present at birth, such as an improperly formed spine, it is referred to as **congenital scoliosis**.

So-called **degenerative scoliosis** is the type associated with older adults. Degeneration of the spine as the result of aging—osteoporosis is often a contributing factor, here—can interfere with the spine's capacity to retain its normal shape. This type of scoliosis tends to appear in individuals over the age of 40.

Causes of Scoliosis

As we have indicated, scoliosis usually develops without any apparent cause. However, there are a few risk factors that may significantly increase the likelihood of developing this disorder.

Scoliosis seems to run in families—someone with a parent who has this affliction has a greater than average chance of suffering from it as well. According to the Scoliosis Research Society, "About 1 in 3 children whose parents have scoliosis will develop scoliosis."[2] The disorder is believed to have a genetic component but, at the present time, the specific genes involved have yet to be conclusively identified. Parents who have scoliosis need to be especially attentive to physical changes in their children that might indicate the presence of this disorder.

By the same token, it is important to understand what does *not* cause scoliosis. Given that it so often arises in childhood, many parents worry about the potential effect of a child's physical activity, like playing sports, in the development of scoliosis, but there is no reason to fear; scoliosis does not stem from playground injuries or anything of that nature. Likewise, bad posture does not lead to scoliosis—although it may be a symptom of an existing condition.

Diagnosing Scoliosis

If you suspect that your child is stricken with scoliosis, do not hesitate to seek medical attention. Scoliosis can worsen with age, and it is essential to seek treatment as soon as possible to prevent major complications down the road.

The most commonly used diagnostic test for scoliosis—though it is not sufficient in itself to reach a diagnosis—is the **Adams Forward Bend Test**. Many people first become aware of their disorder when a medical practitioner at school leads them through this test.

The test is simple: The patient bends forward at the waist, with arms dangling down until their upper body is at a 90-degree angle. This position enables the medical practitioner to spot asymmetrical features that may indicate scoliosis, such as uneven shoulder blades. Sometimes the practitioner uses a simple screening device called a scoliometer to help detect these irregularities.

If scoliosis is suspected, it will be necessary to undergo x-rays for a closer look. The practitioner will analyze the x-rays and calculate the degree of curvature with the **Cobb angle** measurement. The Cobb angle score will largely determine the recommended treatment for the scoliosis patient. When it is low—indicating relatively mild curvature—the patient will likely require routine monitoring to ensure that the condition does not worsen, but no further treatment will likely be necessary. This is the case for most individuals diagnosed with scoliosis. In children and adolescents, it is particularly vital to continue monitoring the spine because the patient's skeleton is still growing, and a mild case could develop into a more serious one.

Treatment Options

If the curvature of the spine is more advanced, there are several treatment options available:

- **Back Brace** – This is a common option for adolescents with moderate scoliosis. The brace keeps the condition of the spine from worsening, to forestall the need for surgery. Typically, the patient will have to wear the brace for most of the day until they reach physical maturity.

- **Surgery** – In more serious cases, surgery may be necessary. There are several types of surgeries to correct or stabilize scoliosis. The most common one involves fusing two or more vertebrae together, which can markedly improve the patient's condition with only a small degree of lost mobility. Alternatively, fusionless surgery involving growing rods, vertebral stapling, and similar techniques may achieve positive results as well.
  Scoliosis can cause serious difficulties to children and adolescents who are afflicted with this disorder, but help is available. Don't wait to seek out treatment—call a qualified medical professional today.

Q.5 What is the role of a class teacher in the management of episodic asthmatic in children of elementary level?

ANS:Asthma, a chronic inflammatory disorder of the airways, affects 6.8 million children in the United States .Children of lower socioeconomic status and ethnic minority backgrounds bear a disproportionate share of the burden of asthma ,and despite an overall decrease in asthma morbidity, these disparities continue to increase .

Asthma has been shown to have an impact on the physical, psychological, and social functioning of youth .It also may have a negative impact on children's education. Children with asthma miss more days of school than asymptomatic children and uncontrolled asthma is associated with diminished school performance .When children stay home from school, parents often miss work to care for them, and the combined costs of lost school days, lost parent productivity, and medical expenses for school-aged children with asthma in the U.S. have been estimated to be almost two billion dollars per year .

Schools are an important environment for asthma care. During the academic year, children spend about a third of their waking hours in school each weekday. Furthermore, schools are significant sources of exposure to asthma-triggering allergens ,and the rates of asthma diagnosis among students have been found to be associated with the presence of allergens in the school environment .Thus, children and school personnel, including teachers, school administrators, nurses and custodial/environmental staff face all the issues of asthma management that the family faces at home. To provide a seamless blanket of care for children with asthma, school personnel need to be educated about asthma, to take steps to prevent asthma exacerbations, and to communicate with parents, medical providers and each other to coordinate care for students with asthma during the school day .

Despite this, studies consistently show that teachers from U.S. rural areas and other countries have limited knowledge of asthma, with scores on both investigator-written and standardized measures ranging from a low of 46% to a high of 69% correct. They often inadvertently interfere with appropriate management of symptoms and guidelines for physical activity Even more troubling, delayed response or hesitancy of school staff to provide medical assistance may have contributed to some deaths from asthma in schools .

Furthermore, communication between school personnel and parents is poor, which hampers efforts to manage asthma in schools. School nurses consider lack of communication with parents a major obstacle to managing students' asthma .Sometimes no one at school, including the

school nurse, is aware that a given student is diagnosed with asthma .Students often do not have asthma management plans on file at school

Although several studies have examined staff knowledge and management behaviors, few have focused on staff who serve low-income, urban, ethnic minority students ,the population that is most vulnerable to asthma and most in need of comprehensive asthma management in schools. The goal of this preliminary study is two-fold: (1) to add to the existing literature on elementary school teachers' (a) knowledge about asthma, (b) strategies to prevent the occurrence of symptoms, and (c) strategies to manage symptoms when they occur at school in this understudied population; and (2) to explore whether there are differences in asthma knowledge, prevention behaviors, and communication with the school nurse and with parents among teachers who report having students who experience asthma symptoms in school (i.e., have active asthma) compared to teachers whose students do not have active asthma. We hypothesized that relative to colleagues whose students did not exhibit asthma symptoms during the school day, elementary school teachers whose students did exhibit symptoms (a) would have greater asthma knowledge, (b) would be more likely to take steps to prevent asthma symptoms in their students and (c) would be more likely to communicate with parents and school nurses.

Measures

Students' with Asthma

Teachers specified the number of students who had asthma in their classroom and indicated whether students exhibited symptoms during the school day (i.e., had active symptoms; yes/no). The number of students with active symptoms was not reported by teachers.

Asthma Prevention Steps

Teachers indicated (yes/no) if they took steps to prevent their students from developing asthma symptoms, and if yes, what they did. The steps taken were coded into one of the following seven categories: (1) trigger avoidance (e.g., reduce chalk dust; reduce pets from the classroom); (2) activity limitation (e.g., encourage moderate play; limit amount of time in the cold); (3) relaxation exercises (e.g., allow students to rest; child was permitted to get a drink of water); (4) education for students (e.g., advised on maintaining a clean home; informed them about breathing exercises); (5) monitor children (e.g., watched children carefully for signs of an attack; checked the children to see how they felt); (6) coordinate medical care (e.g., have inhalers on hand for trips); and (7) unscorable (e.g., yard/hot weather; access to air). Limited detail in some teachers' responses precluded scoring the potential effectiveness of the preventive steps.

Asthma Management

Teachers who indicated that they had students in their classroom who exhibited symptoms during the school day (i.e., had active symptoms; yes/no) also reported what they did when this occurred. Responses were categorized into one of 8 possible management steps: (1) contacting the nurse for medication (e.g., sent to nurse for pump); (2) contacting the nurse, reason not specified; (3) helped or reminded student to take medication (e.g., I gave them their inhaler); (4) permitted use of medication in class (e.g., child knew how to use his inhaler; he would go to the bathroom to use his inhaler); (5) assist student to relax (e.g., help calm down; reassured him); (6) relaxation, not specified if assisted student (e.g., they could also stay in the room and relax); (7) notify parents; (8) unscorable (e.g., I was not in school at the time). As with prevention steps,

determining the potential effectiveness of management steps was not possible due to limited detail provided by some teachers.

Asthma Communication

Four questions evaluated communication about students' asthma between teachers, the school nurse, and parents. Teachers indicated (yes/no) whether they initiated communication with the school nurse, whether the nurse initiated communication with them, whether they spoke to the parents/guardians of their students, and whether they received information about asthma from the school nurse or other sources.

For the three questions regarding communication with the nurse and parents, if teachers indicated there was communication with the nurse or parents, they also provided information on the nature of the conversation. Responses regarding teacher initiated communication with the nurse were coded into one of 10 categories. Five categories involved the teacher requesting information about (1) medication (e.g., we needed to discuss medication and its application in school); (2) asthma management (e.g., what to do if they have an attack – what she has to help them); (3) student activity limitations at school (e.g., discussed what activities the children could partake in); (4) asthma symptoms (e.g., signs of asthma); and (5) about other topics (e.g., what to tell the parent). The remaining categories were (6) informing the nurse about asthma cases, (7) informing the nurse about the occurrence of symptoms and other asthma-related morbidities, (8) passing medical information or paperwork to the nurse from the parent, (9) school absences due to asthma, and (10) the asthma education program *Open Airways*.

Communication initiated by the school nurse was coded into one of 10 categories. Six categories involved the nurse providing information about (1) medication (e.g., she explained the use of an asthma pump), (2) symptoms (e.g., she made me aware of…signs of asthma), (3) case identification, (4) activity limitation (e.g., during cold days and weather changing periods some asthmatic children should stay inside), (5) asthma management (e.g., I was told what to do in an emergency situation), and (6) other (e.g., the nurse told me of the student's past history); four additional categories were: (7) medical paperwork, (8) asthma education program offered by nurse (i.e. *Open Airways*), (9) requests to communicate with parents (e.g., she asked me to give information to the parent of the child in my class); and (10) school absences due to asthma.

Responses regarding communication with parents were coded into one of 10 categories: (1) medication (e.g., I asked about the use of the asthma pump the child brought to school); (2) asthma management (e.g., how to handle an episode should it occur) ; (3) symptoms (e.g., I asked her to describe the symptoms and severity of the asthma); (4) triggers (e.g., I asked if they knew what triggered their child's attacks); (5) student absences due to asthma; (6) activity limitations (e.g., The mom told me… if he needed to sit out in dance, let him); (7) case identification; (8) medical paperwork, (9) other (e.g., anything needed to know, how the child was doing, etc); and (10) unscorable (e.g., parent told me about her concerns).

Coding of Open-Ended Questions

Research assistants, with input from the first author, developed the response categories for each of the five open-ended questions regarding prevention steps taken, management steps taken, teacher initiated communication with the nurse, nurse initiated communication with the teacher and teacher-parent communication. A pediatric pulmonologist reviewed and confirmed the appropriateness of each response category as well as sample items for each category. Responses

to each question were coded by two independent raters. Kappa values indicated good initial agreement among raters (range = .74 to .98). All discrepancies were reviewed and resolved by the raters and two other researchers with input from the pediatric pulmonologist.

DISCUSSION

This preliminary study sought to assess knowledge and management behaviors among teachers in a large, urban school district, using sites that predominantly serve low-income, ethnic minorities. Teacher knowledge, while equal to or higher than knowledge levels reported in previous studies ,was still somewhat limited in some areas. The vast majority knew that dust, airborne irritants, changes in weather, animals with fur, colds and the flu, and mold were asthma triggers, and recognized that wheeze and shortness of breath were symptoms of asthma. However, only half of the teachers correctly identified three other important signs and symptoms of asthma that may occur independently of wheeze: tight chest, persistent cough without wheeze and hunched shoulders. It is recommended that teachers be taught about these signs and symptoms as way of realizing early on a student may be in need of medical assistance.

Furthermore, consistent with prior research ,teachers did not understand the relationship between exercise and medication. Among those who knew exercise triggered asthma, few knew that medication taken prior to exercise prevents symptoms and under these circumstances students with asthma need not avoid exercise. To facilitate student participation in physical activities in a safe manner while at school, it is recommended that teachers be educated about the relationship between exercise and asthma.

This research also examined steps teachers take to prevent asthma symptoms in their students. Among the steps teachers reported taking to prevent asthma, trigger avoidance was the most common followed by activity limitation. Helping teachers identify and eliminate allergens that may trigger asthma (e.g., removing rugs and furry pets from classrooms and limiting exposure to chalk dust) may assist in minimizing students' exposure to allergens throughout the school environment .

Less than half the teachers with a student with asthma obtained information about asthma from the nurse or communicated in other ways with the school nurse or with parents. Communication was worse between teachers and the school nurse than between teachers and parents. Interestingly, when nurses and teachers did communicate, regardless of who initiated the communication, the topics of their conversations were similar.

Another goal of the study was to examine differences in knowledge and asthma prevention behaviors among teachers who had a student with active asthma and those who did not. Teachers who had a student with active asthma were more likely to become involved in the asthma management of their students than colleagues who did not have a student exhibit asthma symptoms. Specifically, they were more likely to take prevention steps, communicate with parents, and initiate communication with the school nurse. They also had higher knowledge scores.

These results suggest that teachers may cope with asthma reactively, waiting until students exhibit symptoms before learning how to assist them. School and district policies may be partially responsible for this reactive behavior. Snow et al assessed the asthma management policies of NYC schools, the school district used in this study, and found that 51% of their participants (administrators, teachers, counselors, and school nurses) learned that a student had

asthma through informal conversations with the student or parent .Only 10% learned of a student's having asthma through district protocols. They concluded that limited knowledge of the asthma status of students may create a barrier to effectively managing asthma in schools. Additionally, for a variety of reasons, including limited knowledge of district policies or school-based health resources, range of symptom severity, or the episodic nature of asthma, families in the current study may not have reported students' asthma to the nurse and/or teacher or may not have sought school-based support. Also, while some teachers may have learned about a student having asthma because the student participated in OAS, this would have been limited to only 3rd to 5th graders. Thus, in the current study, despite potential opportunities to learn about a student's asthma status, it is plausible that teachers became aware of students' asthma status once students experienced symptoms in class. This may then lead to a reactive rather than a preventive style of asthma management aimed at all students with asthma.

School policy and administrators need to support teachers in proactively learning the asthma status of their students and working to prevent asthma; a communication network is essential to helping teachers accomplish this. Specifically, teachers need to be encouraged to observe students in order to determine if they are experiencing asthma symptoms while at school, to become astute at identifying students' early warning signs, to communicate with the nurse to learn how to assist students with asthma, and to learn about effective asthma prevention and management steps, including the importance of medication plans. Home-school partnerships, including communication between the two, enhance school success and promote shared values between settings, creating a seamless environment for children .Such communication may also help teachers learn who has asthma and how to best help these students, ensuring children with asthma receive optimal care while at school. Additionally, such communication may benefit asthma management at home by allowing the parents to learn if the child experienced symptoms or needed medication while at school. As such, a continuous system of asthma care is created which enhances the likelihood that the same prevention and management strategies are implemented at home and school.While teachers have many responsibilities and thus have limited time for non-academic tasks, interventions lasting only a few hours have greatly improved teacher knowledge .Educating teachers about asthma may assist them to take prevention steps and may give them the confidence to react appropriately when symptoms occur. Elementary school teachers may feel protective of and responsible for their young students, which in turn may motivate them to want information about asthma and ways they can assist their students with active asthma. If they are educated about simple things they can incorporate into their classroom routines to assist their students, such as not spraying air fresheners or avoiding furry animals, they may comply.This study was limited by the fact that teachers' qualitative responses were too vague for more in-depth analyses. When considering the correctness of prevention and management steps, it was difficult to assess whether or not they were appropriate because teachers often did not write in full sentences. For example, they may have written "limit physical activity," which is generally not an acceptable means of preventing asthma, but might be appropriate if the student was symptomatic. Future studies would benefit by assessing the efficacy of teachers' prevention and management efforts.Another limitation was the definition of active asthma. Having a student with active asthma was defined by teacher report of having a student exhibit symptoms during the school day. This requires teachers to be

knowledgeable about asthma symptoms and to attend to the child. Teachers may have erroneously indicated they had a student with active asthma because they thought something was an asthma symptom when it was not (e.g., a runny nose or congestion). Conversely, others may have indicated they did not have students with active asthma because they were not attending to the children in a way that would allow them to see the symptoms. Also, while teachers reported the number of students with asthma in their classroom, they were not asked to specify how many of those students had active asthma. Therefore, the association of teachers' prevention efforts and communication behaviors to the number of students with active asthma could not be determined. Moreover, teachers were not asked if they had students with active asthma in prior school years. It is plausible that teachers currently without a student with active asthma had students with active asthma in prior school years, and they learned appropriate prevention steps then. Future studies should use more objective measures of active asthma and should consider if teachers ever had students with active asthma in their classrooms as well as the number of students with active asthma.Despite its limitations, this preliminary study was an important first step to begin understanding the knowledge and asthma management behaviors of classroom teachers serving low income, ethnic minority students, and to determine if there are differences among classroom teachers with and without students with active asthma. It is recommended that future research examine the knowledge and communication patterns of cluster teachers who, unlike classroom teachers, do not teach the same group of students throughout the day every day. As such, their response to asthma may be different than classroom teachers, and would be interesting in its own right as a topic for further study. Additionally, teacher's willingness to implement asthma management steps should also be considered, with careful attention to potential differences in schools with a school nurse or school-based clinic versus schools without such healthcare resources.
ma in schools and to ensure students receive optimal asthma care while at school.