Pain Mechanisms in Adolescent Females with Chronic Low Back Pain Compared with Healthy Controls

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Synopsis:

Introduction: Chronic low back pain (CLBP) is a multifactorial entity encompassing a biopsychosocial model. Changes in pain mechanisms have been reported in adult populations as an increase in peripheral and central sensitization. Muscle hypertonicity is present in other chronic pain conditions, however it is unknown to what extent it plays a role in CLBP. Pain catastrophizing (PC) is a comorbidity to CLBP. Most of the literature regarding pain mechanisms in CLBP patients is directed towards adults. There is a lack of knowledge regarding pain mechanisms, muscle tone and PC in adolescents with CLBP.

Method: 33 females between 15-19 years (CLBP n = 22) participated. Handheld pressure algometry and computerized pressure algometry (CPA) was used to investigate the presence of local and widespread hyperalgesia. CPA was used to investigate temporal summation (TS) and conditioned pain modulation (CPA). A myotonometer was used to investigate muscle tone. The Pain Catastrophizing Scale (PCS) was used to control for the impact of psychosocial factors on pain.

Results: The CLBP group has lower pressure pain thresholds (PPT) compared with the control group. There was significantly higher muscle tone in the left m. gluteus medius in the CLBP group compared with the control group. TS and CPM was present in both the CLBP group and the control group, but there was no significant difference between the two groups. PC scores were significantly higher in the CLBP group than in the control group. There was no significant correlation between PC and TS and CPM.

Conclusion: Adolescent females with CLBP share some of the pain mechanisms seen in adults in terms of peripheral sensitisation and widespread hyperalgesia; however, there is a need for further research regarding the impact that PC may have on the development of TS and CPM. It appears that muscle hypertonicity in the left gluteus medius muscle could be a risk factor for developing CLBP and further studies should investigate this relationship.
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Preface

This Master’s Thesis was written by Katherine Anne McGirr, Fridel Laursen and Stine Ibsen Harring during the final semester of the Masters in Clinical Science and Technology at Aalborg University, Spring 2015. The purpose of this thesis was to investigate pain mechanisms in 15-19 year old females with chronic low back pain compared to a healthy control group, and the presence of muscle hypertonicity and pain catastrophizing.

All three authors have had several years of interest in the area of back pain, chronic pain disorders and adolescents suffering from pain. It has been a privilege to be able to investigate chronic low back pain in adolescents and the authors hope that their contribution to this area will be of interest to others interested in chronic low back pain in female adolescents, and the relationship to pain mechanisms, muscle tone and pain catastrophizing.

Prior to this study, the Ethics Protocol was prepared by the project group with assistance from the supervisor. Additionally applications for funding were made by the project group. The study was kindly supported by Danske Fysioterapeuder (DKK 30,000) and Siemensfonden (DKK 30,000).

The authors would like to thank Line Lindhardt Egsgaard, Ph.D., M.Sc. Assistant Professor for supervision throughout the entire project. Lastly, a special thanks to the principals and staff at the high schools in Northern Jutland, who assisted us with recruitment and to the girls who participated in this study, which would not have been possible without them.
Reading Guide

The Vancouver reference system is used in this Master’s thesis. References are given a number corresponding to their placement in the report and the list is arranged alphabetically.

The thesis is prepared following the IMRaD principle, containing Introduction, Method, Results and Discussion, and a conclusion has been added. Each chapter starts with a short presentation of the content.

All figures and tables are mentioned in the body of the assignment, and presented with a descriptive text underneath. Each figure or table is numbered according to its placement in the report. A list of abbreviations is provided on the following page. The full phrase is written the first time it is mentioned in the text, as well as in headings, and then subsequently abbreviated. A list of figures and tables is provided, and finally appendices are listed at the end of the thesis.
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List of Abbreviations

CLBP: Chronic Low Back Pain
CNS: Central Nervous System
CPA: Computerized Cuff Algometry
CPM: Conditioned Pain Modulation
CRF: Case Report Form
CS: Central Sensitization
DNIC: Diffuse noxious inhibitory control system
LBP: Low Back Pain
NRS: Numeric Rank Scale
PAG: Periaqueductal gray matter
PC: Pain Catastrophizing
PCS: Pain Catastrophizing Scale
PPT: Pressure Pain Threshold
PTT: Pain Tolerance Threshold
QST: Quantitative Sensory Testing
RVM: Rostral ventromedial medulla
Std: Standard deviation
TS: Temporal Summation
VAS: Visual Analogue Scale
1 INTRODUCTION

Chronic low back pain (CLBP) is one of the most common chronic musculoskeletal pain disorders. Back pain costs the public health system DKK 13 billion per year\(^1\) posing a sizeable socioeconomic burden, and affecting quality of life.\(^2,3\) There is a reported lifetime prevalence of low back pain (LBP) of 60-80%. The prevalence of LBP in adolescents is reported to be 18–51%\(^4\) where up to 18.2% of these will develop CLBP\(^5\) typically persisting into adulthood\(^6\).

The cause of CLBP may stem from both peripheral and central mechanisms. Changes occurring in the Central Nervous System (CNS) resulting in pain hypersensitivity are common in many chronic pain conditions.\(^7-10\) This suggests that the location of the pain in CLBP is perhaps not as relevant as the underlying mechanisms. Quantitative Sensory Testing (QST) has provided a growing body of evidence regarding the presence of abnormal central pain processing in adult chronic pain patients.\(^11\) QST allows for standardized stimulation of deep tissue affected in chronic musculoskeletal pain and the subsequent quantification and documentation of the resulting pain sensation provoked.\(^11\) Assessment of Pressure Pain Thresholds (PPT), Temporal Summation (TS) and Conditioned Pain Modulation (CPM) are three common uses of QST to investigate central sensitization.\(^12-14\) These methods have shown the presence of central sensitization expressed as widespread hyperalgesia and imbalances between descending inhibition and facilitation of pain in a variety of chronic pain conditions in adults.

In addition to central pain mechanisms, studies have shown that muscle tone is associated with hyperalgesia in tension type headache\(^15\), however it is unknown to what extent muscle tonus is associated with CLBP either in adult or adolescent populations. Theoretically, an injury can occur in a muscle, provoking nociceptive signals that continue to fire after nociception has stopped.\(^16\) The activation of nociceptors has been reported to provoke muscle hypertonicity, designed to guard or protect the joint\(^17\), which could be a factor in chronic pain conditions.\(^18\)

CLBP cannot only be regarded as a physical sensation\(^19\) as the experience of pain may be modulated by mental and emotional processes. Psychosocial factors, for example pain catastrophizing (PC), have been proven to contribute to pain perception in chronic pain conditions.\(^20,21\)

CLBP is a multifactorial entity where central pain mechanisms, pain catastrophizing and muscle hypertonicity are not thoroughly investigated in the literature in adolescent populations, despite the
high prevalence of CLBP in this group. An understanding of the involvement of these factors could facilitate prevention and treatment options.
2 BACKGROUND

This section will briefly explain the prevalence of chronic low back pain in adults and adolescents and the underlying pain mechanisms. The physiology of pain as well pain modulation and some of the methods to quantify the experience of pain will be clarified. The physiology of muscle tone, the impact of hypertonicity on pain and current methods available for measuring muscle tone are explained. Finally pain catastrophizing and the influence of pain catastrophizing on pain mechanisms is described.

2.1 CHRONIC LOW BACK PAIN

One of the most prevalent chronic pain syndromes is CLBP. CLBP is an umbrella term for a variety of different pain syndromes occurring in the spine. In 85% of CLBP cases, a diagnosis will not be made.\textsuperscript{22}

According to Flor et. al, there is no one cause of CLBP, yet a number for factors contribute to the syndrome. Factors such as degeneration of the spine including intervertebral discs, paravertebral muscle spasms, and other non-physiological factors are involved.\textsuperscript{23}

Several studies have investigated the presence of hyperalgesia and central sensitization (CS) in adults with CLBP. This is seen as lower pressure pain thresholds (PPT) both locally (at the site of pain) and globally (all areas combined), compared with healthy controls.\textsuperscript{24,7,25} These findings, corroborated through MRI scans, showed subjects with CLBP experienced neuronal activation in five pain related cortical areas of the brain; contralateral primary somatosensory cortex (S1) and secondary somatosensory cortex (S2), inferior parietal lobule, cerebellum, and ipsilateral S2, where the healthy controls only experienced activation in the contralateral S2.\textsuperscript{7} One study investigated groups of patients with non-mechanical CLBP and mechanical CLBP. No differences were found in PPT values between the two groups. This suggests that it is not the type of action provoking the pain that is important, but more the impact of the barrage of nociception on the pain system in terms of peripheral and central sensitization.\textsuperscript{26}
2.1.1 Chronic Low Back Pain in Adolescents

The prevalence of chronic pain in children and adolescents has increased during the last 20 years\textsuperscript{27}, and is reported to be up to 44\%, with more females than males affected.\textsuperscript{6,28,29} LBP is common amongst adolescents; where up to 18.2\% of those who experience LBP will go on to develop CLBP, which typically persists into adulthood. An early onset of LBP is a predictor for CLBP in the future\textsuperscript{30}, and the occurrence of LBP in adolescents increases with age, this is particularly true during early adolescence.\textsuperscript{28}

CLBP in adolescents, like that in adults, should be seen in terms of the biopsychosocial model.\textsuperscript{31} Psychosocial factors commonly associated with CLBP are depression, anxiety, and pain catastrophizing. Studies show that standing postural factors and scoliosis do not play an important role in the development of LBP.\textsuperscript{32-34} However, there is an association between self-reported seated slumping and particular lying postures and LBP.\textsuperscript{35}

CLBP in adolescents is a significant problem in society, not only because of the increased risk of chronic pain in adulthood leading to loss of working years, but also because of the deleterious effects on the individual adolescent. Adolescents with CLBP are at an increased risk of absence from school, withdrawing from social activities, and developing internalizing symptoms because of their pain.\textsuperscript{27} Despite the large body of evidence reporting the high prevalence of CLBP amongst adolescents, and the knowledge that LBP early in life is a predictor for CLBP in the future, little is known about adolescent pain mechanisms and if they mirror that which is reported in the literature regarding adult CLBP.

2.2 Pain

The sensation of pain provides information about the occurrence of injury or potential tissue damage and is thereby a vital function of the nervous system.\textsuperscript{36} Pain is defined as:

“An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” \textsuperscript{37}
Pain is therefore both a subjective and emotional experience and not the direct response from a noxious stimulus, but a result of the brain processing noxious stimuli.\(^{38}\)

Pain has three components; sensory, affective and cognitive. The sensory component includes the sense of intensity, location, quality and duration of pain. The affective component is the feeling of discomfort and the urge to avoid the pain. The cognitive component covers earlier experiences, cultural values and distraction.\(^{36}\) The experience of pain has a biological, psychological and social element\(^{36}\), and is therefore highly individual.\(^{38}\) In the past, research has mainly focused on a purely biomedical approach, which has been found lacking especially in chronic pain conditions. Focus has recently been placed on a biopsychosocial model when investigating chronic pain conditions. This model recognizes the interaction between biological and psychosocial influences on chronic pain.\(^{39,40}\)

Pain can be acute or chronic. Acute pain has the purpose of preventing injury.\(^{41,42}\) When the nociceptive system is subjected to repetitive or particularly intense noxious stimuli, it will become sensitized (peripheral sensitization). This phenomenon is a protective mechanism where the lowered threshold, is intended to avoid situations where further tissue damage could occur. In most instances, the nociceptive system will return to normal once there is an absence of further tissue damage.\(^{41,42}\) Chronic pain however has no protective role as the injury typically has healed but the pain is still present.\(^{38,42}\)

The definition of chronic pain has been widely discussed in the literature, with no final consensus. The International Association for the Study of Pain\(^{37}\) states that:

\[\text{“chronic pain is recognized as pain that persists past the normal time of healing”}\]

In some instances chronic pain it is defined as pain lasting longer than three months, in other instances longer than six months.\(^{37}\) As opposed to defining chronic pain through time limits, research has aimed to discover the physiological mechanisms involved in chronic pain.

Several factors influence the development of chronic pain, of which central sensitization is deemed to play an important role.
2.2.1 Pain Physiology

The receptors that respond to noxious stimuli are nociceptors. There are three main types of nociceptors; thermal, mechanical and polymodal nociceptors. Thermal receptors are activated by extremes in temperatures (below 5ºC or greater than 45ºC), mechanical through pressure and polymodal through high intensity mechanical, chemical or thermal stimuli. In addition there is a fourth type, called silent nociceptors. Silent nociceptors exist in skin, joints, muscles and viscera and are mostly activated by inflammation and chemical agents that reduce their threshold. It is thought that they contribute to central sensitization and secondary hyperalgesia.

The axon terminations are the same for all nociceptors and are usually described as free nerve endings. The afferents of the nociceptors can be subdivided into groups according to their axon conduction velocity (Aδ and C fibres). Aδ fibres are thin myelinated axons with a velocity of 5 to 30 m/s, and C fibers are thin unmyelinated with a velocity less than 1 m/s. Aδ fibres are responsible for the first, informative pain whereas C fibres are responsible for the second pain, which serves to change the behaviour of the person to avoid further tissue damage.

When a noxious stimulus triggers the nociceptors, action potentials are generated and transported to the dorsal horn of the spinal cord, where they are mainly distributed to laminae of the dorsal horn. Neurons in lamina I and lamina II respond to noxious stimuli carried by the Aδ and C fibres. Some Aδ fibres go directly to lamina V. In lamina VI neurons receive innocuous input from joints and muscles. The neurons in lamina VII are thought to play a role in the diffuse pain sensation in many pain conditions. The nociceptive information is thereby projected directly to the thalamus from lamina I. All laminae including lamina I project to the brain stem and thalamus directly or indirectly via interneurons from other laminae, see figure 1.
The transmission from the various laminae in the spinal cord to the thalamus is provided by five major ascending pathways. The spinothalamic tract is the most prominent and includes neurons from lamina I and V containing nociception-specific, thermos-sensitive and wide-dynamic-range neurons. The axons cross the midline in the spinal cord run through the white matter before entering the thalamic nuclei. The spinothalamic tract plays an important role in the transmission of nociceptive information. A lesion will lead to a reduction in pain sensation to the contralateral side of the body. The spinomesencephalic tract also transports the projection neurons from laminae I and V. Transmission in this tract is thought to be a part of the affective component of pain. The axons in this tract enter the mesencephalic reticular formation, periaqueductal gray matter and on to the parabrachial nucleus, which projects to the amygdala – the part of the limbic system that regulates emotional state. The projection neurons from laminae VII and VIII run in axons in the spinoreticular tract. It terminates in both the thalamus and reticular formation and do not cross the midline. The cervicothalamic tract receives input from neurons in laminae III and IV. The tract runs in the lateral white matter in the two top cervical segments of the spinal cord. Most of them cross the midline and terminate in the midbrain nuclei and two nuclei in the thalamus. The spinohypothalamic tract contains axons from projection neurons in laminae I, V and VIII. They project to hypothalamic nuclei responsible for the regulation of neuroendocrine and vascular responses that are present in pain conditions.
The thalamus is an important part of the central processing of nociceptive information. Neurons in the thalamus have a topographic representation of the human body and there is a close relationship between the activity of spinothalamic neurons and the degree of pain experienced. These receiving areas of the thalamus expand in chronic pain conditions and Aβ which normally do not respond to painful stimuli become activated so that normal touch can be experienced as painful. This is seen in situations where allodynia and hypersensitivity occurs. The two most important regions of the thalamus are the lateral nuclei group and the medial nuclei group. The lateral nuclei group is associated with the ability to establish the precise location of pain. The medial nuclei group responds optimally to noxious stimuli. The information is projected to the basal ganglia and cortical areas such as SI, SII, parietal and frontal cortices.

Neurons in S1 and S2 have small receptive fields and therefore do not contribute to the diffuse sensation of pain. The cingulate gyrus, a part of the limbic system (frontal cortex), is active in the emotional processing of pain. The insular cortex (parietal cortex) receives information from the thalamus directly and contributes to the autonomic processing of pain responses. Pain processing occurs in the limbic system, anterior cingulate gyrus and insular cortex affected by factors such as fear, attention and expectancy regarding pain.

2.2.2 Pain Modulation

2.2.2.1 Descending pain modulation

Neurons from supraspinal areas, like the periaqueductal gray matter (PAG), the nucleus raphe magnus and adjacent structures of the rostral ventromedial medulla (RVM), also called the PAG-RVM system, project signals through a network of descending pathways to the dorsal horn of the spinal cord, and play a complex role in pain modulation. These pathways can either inhibit (descending inhibition) or facilitate (descending facilitation) the activity of nociceptive signals to the brain. This modulation of the nociceptive information to the brain occurs in the dorsal horn and is caused by a number of neurotransmitters. These neurotransmitters are located in the descending pathways themselves, inhibitory and excitatory interneurones and primary afferent fibre terminals. Neurotransmitters like GABA, glutamate, neurotensin, nitric oxide and cholecystokinin can both act inhibitory and facilitory. Histamine, enkephalin, substance P, neuropeptide, and beta-endorphin are inhibitory neurotransmitters.
while noradrenalin and opioid are examples of facilitory neurotransmitters.\textsuperscript{46} RVM contains on-cells and off-cells. The literature suggests that off-cells promote descending inhibition and decrease the nociceptive transmission to the brain. On-cells appear to facilitate nociceptive transmission from the dorsal horn to the brain.\textsuperscript{36,46}

The descending system is a major network that controls the nociceptive transmission. In addition to the PAG-RVM system, other pain-modulating systems are working in parallel. For example the direct inhibition of projection neurons and the activation of inhibitory interneurons\textsuperscript{36} as described in the gate control theory. The descending modulation system can be influenced by psychological mechanisms, which can thereby increase or decrease the sensation of pain.\textsuperscript{36}

\subsection*{2.2.2.2 Ascending Pain Modulation}

There are areas of the brainstem that regulate pain in other areas of the brain. This regulation is both direct and indirect. Direct pain regulation uses opioids to reduce or block nociceptive information through the brainstem. Indirect pain regulation is an activation of nerve pathways that go up to the cerebrum and influence the processing of nociceptive information in other areas of the brain, for example the thalamus, frontal and parietal cortices. Indirect pain regulation, is however, not well understood and it is difficult to distinguish the direct effect on each area of the brain.\textsuperscript{43,47}

\subsection*{2.2.3 Pain Mechanisms}

\subsubsection*{2.2.3.1 Peripheral sensitization}

As briefly mentioned above, peripheral tissue damage leads to sensitization of the nociceptor terminals, with a reduction in threshold and an amplification of the nociceptive response. This is caused by the local release of inflammatory mediators\textsuperscript{43,48,49} and is limited to the site of injury, also known as primary hyperalgesia,\textsuperscript{42,49} see figure 2. Maintenance of peripheral sensitization generally requires ongoing peripheral pathology and with an absence of tissue injury the sensitivity will, in most cases, disappear over time and return to baseline.\textsuperscript{42}
2.2.3.2 Central sensitization

Persistent nociceptive input can lead to changes in the central nociceptive system causing CS. CS has been defined as:

‘An amplification of neural signalling within the CNS that elicits pain hypersensitivity’\(^{48,50}\)

With the presence of CS, the CNS responds to sensory stimuli in an altered way and the pain is not only coupled to the presence of peripheral stimuli. A variety of changes can be seen in the CNS, which leads to an increased action potential output.\(^{42}\)

CS manifests as pain hypersensitivity seen as facilitated temporal summation (TS), decreased conditioned pain modulation (CPM) and widespread hyperalgesia.\(^{48,49}\) CS is thought to be an important factor in many chronic pain conditions\(^{51}\) including CLBP.\(^{50}\)

2.2.3.2.1 Temporal Summation

TS is an increase in pain perception in response to repetitive stimulations of the same intensity, which can be evoked in different tissues including skin and musculoskeletal structures.\(^{52}\)

For centrally mediated TS the increased pain perception is evoked by noxious stimuli with an inter-stimulus interval below 3 seconds,\(^{53}\) for example 10 stimuli at 1s inter-stimulus intervals.\(^{11}\) The input from the C fibres in human beings has been shown to stay the same, which indicates TS to be a central mechanism.\(^{54}\) Animal experiments have shown that repeated C fibre stimulation can result in a
progressive increase in electronic discharge from the second order neuron in the spinal cord caused by release of sensory neuropeptides, primarily substance P.\textsuperscript{54}

When CS is present, central pain mechanisms are upregulated, which results in a facilitated TS of pain.\textsuperscript{11} This has been shown through the investigation of TS in several musculoskeletal chronic pain syndromes like osteoarthritis,\textsuperscript{55} and fibromyalgia\textsuperscript{56} where CS has been suggested to be involved.\textsuperscript{57}

Furthermore patients with CLBP have increased pain sensitivity, when compared to healthy controls\textsuperscript{7,58} which suggests the presence of facilitated TS in CLBP patients.

2.2.3.2.2 Conditioned pain modulation

An imbalance between descending inhibition and facilitation of pain is a possible cause of CS, and may be a factor in the development and continuation of chronic pain.\textsuperscript{11,59} For the assessment of pain inhibitory pathways in humans, CPM is commonly used. This is done by the evaluation of a painful stimulus with and without another painful stimulus.\textsuperscript{10} Normally the experience of a painful stimulus will be reduced with the presence of another painful stimulus. It is presumed that this is because the extent to which pain is inhibited during the conditioning stimulus reflects how good the diffuse noxious inhibitory control system (DNIC) is functioning. The DNIC system is defined as:

\textit{“a physiological process by which the perception of pain at a local area of the body is inhibited by a second painful stimulus administered at a distal body site.”}\textsuperscript{60}

When DNIC is activated, neuronal activity of the dorsal horn in the spinal cord decreases pain and hyperalgesia.\textsuperscript{8} The precise anatomical basis for the DNIC system is uncertain, also it is thought to include areas of the PAG-RWM network, which differs to that shown in animal studies.\textsuperscript{10} Studies have shown the presence of altered CPM in patients with chronic musculoskeletal pain conditions such as osteoarthritis, fibromyalgia\textsuperscript{10} and recently, in patients with CLBP.\textsuperscript{8,59} One particular study showed that the DNIC system functioned in both healthy subjects and CLBP subjects, however the modulating effect lasted for a much shorter duration in CLBP subjects.\textsuperscript{59} Another study showed lowered PPT in CLBP subjects compared with healthy controls during CPM.\textsuperscript{8}

Despite the growing body of evidence regarding CPM in chronic pain, there are inconsistencies in the literature \textsuperscript{8,10} and further research is required within this complex area.
2.2.3.2.3 Widespread Hyperalgesia

Widespread hyperalgesia is pain at a site distant to the original source of the pain and is attributed to processes within the CNS. Widespread hyperalgesia has been reported in a number of different chronic pain conditions, including CLBP. 7

2.3 Quantitative Sensory Testing

QST of musculoskeletal pain involves the standardized stimulation of deep-tissue nociceptors and the subsequent quantification of the sensation of pain experienced by the subject. 11

There are two types of techniques: response dependent and stimulus dependent. With the response dependent technique, different stimulation intensities are performed and the subject is requested to score the experience of pain on a Visual Analogue Scale (VAS), Numeric Rank Scale (NRS) or through the use of other verbal descriptors. 11 The VAS is a numerical scale, typically from zero to ten on a horizontal line where the subject is required to mark where their pain corresponds. A score of zero corresponds to no pain, and a score of 10 corresponds to worst imaginable pain.

The stimulus dependent technique establishes a pre-defined perception, for example a detection threshold, pain threshold or a tolerance threshold. 11 QST allows for the evaluation of pain sensitivity and somatosensory sensitivity in both local areas of the body, and in instances of widespread pain. 11 These techniques are seldom used alone, due to the multifactorial nature of pain. QST is often combined with questionnaires in order to assess other dimensions of pain, such as general function and disability. 11

There are several options available to assess musculoskeletal pain sensitivity. The choice of modality depends on what kind of pain one wishes to provoke. Handheld pressure algometry is a valid and widely used method to activate nociceptors in deep tissue. 61, 62 The area stimulated by pressure algometry is small - typically 1 cm² and the stimulation is of short duration. 11

Another widely used method, CPA, enables the assessment of larger volumes of tissue. Cuff algometry is the process of inflating a cuff around the subject’s extremity and measuring the subject’s pain response to the mechanical pressure. CPA can be used to provoke mechano-nociceptors deep within muscle tissue, 11 and has previously been used to evaluate deep tissue sensitivity 14, TS 9, 13 and CPM 9.
2.4 MUSCLE TONE

2.4.1 The Physiology of Muscle Tone

Muscle tone can be defined as;

“... its resting tension, clinically determined as resistance to passive movement.”

In other words, muscle tone is the force with which a muscle resists the action of being stretched and depends on the stiffness of the muscle. The two main components of muscle tone are the contractile component and the viscoelastic component. The contractile component of muscle tone comes from low-frequency activation of motor units within the muscle. It is important for maintaining an erect posture of the body. A “motor unit” represents every muscle cell in which a single a-motor neuron innervates. Contractions in the motor units are assumed to be maintained by muscle spindle afferent activity. The viscoelastic component is the passive properties of muscle tissue, for example the tension of the elastic muscle fibres, and elastic properties of the tendinous insertions, and connective tissues in the muscle without the involvement of nerve activity.

Injury and psychosocial factors are two contributors to changes in muscle tone. Injury can occur in a muscle or joint, provoking nociceptive signals that continue to fire after nociception has stopped. The activation of nociceptors provokes muscle hypertonicity, designed to guard or protect the joint. In back pain hypertonicity is most often seen in the extensor muscles of the spine such as m. erector spinae. Little evidence is available regarding the role of hypertonicity in chronic pain.

2.4.2 Measuring Muscle Tone

Manual palpation is commonly used in clinical settings to examine for muscle hardness and clinicians often find that muscles reported as tender during palpation are harder than others. Manual palpation however is subjective, largely due to difficulties in standardizing and quantifying the various techniques.

Muscle tone can be measured, as previously mentioned, through palpation, however other methods have been designed to provide quantitative measurements. A relatively new method for measuring
muscle tone is through the use of myotonometry. Previous studies have found the myotonometer to be a reliable and valid method in measuring viscoelastic stiffness in the muscles of the biceps brachii, quadriceps, and trapezius. Myotonometers are used to measure the oscillation frequency characterizing muscle tension, and how the muscle resists changes in shape, characterizing muscle stiffness.

2.5 **Pain Catastrophizing**

PC is a co-morbidity to CLBP and is strongly associated with pain intensity in adolescents with chronic pain. PC is defined as:

"..an exaggerated negative mental set brought to bear during actual or anticipated painful experience." 

PC is associated with facilitated TS, and is suggested to play a facilitory role in the way pain related information is processed. It is unknown what the exact pathways underlying this facilitation are. No previous studies have examined the association of PC and pain mechanisms in adolescents. In addition to pain mechanisms, there also appears to be an association between PC and muscle hypertonicity. PC may be associated with increased severity of LBP, due to extreme muscle activity in the area close to the site of the injury. Another study found that PC is associated with increased clinical pain severity in LBP - especially for patients with a higher resting tension in the lower paraspinal muscles. A combination of high resting tension of the lower paraspinal muscles and high PC may be a risk factor of high pain severity in LBP. This increase in paraspinal activity may be due to voluntary guarding and a change in CNS activity, where muscle activity is provoked in order to prevent unwanted or unanticipated movement.

2.6 **Summary**

CLBP is a multifactorial entity encompassing a biopsychosocial model. Changes in pain mechanisms have been reported in adult populations where an increase in peripheral and central sensitization is present. PC is a comorbidity to CLBP and has a strong correlation with pain intensity as well as muscle
hypertonicity. Muscle hypertonicity is present in other chronic pain conditions, however it is unknown to what extent it plays a role in CLBP. Most of the literature regarding pain mechanisms in CLBP patients is directed towards adults. There is a lack of knowledge regarding pain mechanisms in adolescents with CLBP, as well as the role of muscle hypertonicity and PC.
3 Research Questions and Hypotheses

This section describes the study’s aims and hypotheses.

The aims of this study are to investigate:

- Pain mechanisms in adolescent females with CLBP compared with healthy controls.
- The association between pain catastrophizing and pain mechanisms
- Muscle tone in adolescent females with CLBP compared with healthy controls, and the relationship to primary hyperalgesia and pain catastrophizing

It is hypothesized that:

- Widespread hyperalgesia is present in the CLBP group
- Temporal summation is increased in the CLBP group when compared with healthy controls
- Conditioned pain modulation is reduced in the CLBP group when compared with healthy controls
- There is an association between;
  - Conditioned pain modulation and pain catastrophizing
  - Temporal summation and pain catastrophizing
  - Muscle tone and primary hyperalgesia
  - Muscle tone and pain catastrophizing
4 METHODS

*In the following chapter, methods used to perform this study will be described.*

4.1 DESIGN

This study is a case control study with 33 female adolescent participants divided into a CLBP group (n=22) and a healthy control group (n=11).

4.2 LITERATURE SEARCH

Literature for this study was obtained by systematic literature searches in scientific databases, including PubMed, Web of Science, Scopus and Google scholar. Free text and chain searches were also performed. The literature search was limited to Danish, English, Norwegian and Swedish articles. The literature search included only human studies and no limitations were made in relation to the year of publication.

The literature search was conducted from June 2014 until June 2015.

Each article was evaluated by its title and abstract. In cases where the abstract contained relevant information in relation to the study aims, the article was read and cited in the report.

The searches were conducted by the use of MeSH terms and relevant keywords.

MeSH terms used in this study were: Low Back Pain, Pain, Adolescents, Chronic Pain, Muscle Hypertonia, Catastrophization, Hyperalgesia. Relevant keywords were: quantitative sensory testing, temporal summation, conditioned pain modulation, central sensitisation, peripheral sensitisation, muscle tone, handheld, algometry, pressure, threshold, pain perception, pain catastrophizing.

4.3 PARTICIPANTS

4.3.1 Recruitment

Sixteen schools in Northern Jutland were contacted regarding participation, of which six schools agreed to take part. The Headmaster from each school was contacted by telephone to discuss the possibility of recruiting participants from the student population. With the agreement of the Headmaster the study was presented at the school, where female students meeting the inclusion criteria had the opportunity to
contact the project group if they were interested in participating. Students who were interested in participating in the study received written information (Appendix 1) to take home. Students that were not of legal age were requested to give the written information to their parents or guardians to read. Thereafter, a meeting in person or by telephone with the parents or guardians was arranged in order to give oral information. The students and their parents had at least 24 hours of deliberation time, before giving written informed consent.

In addition to recruitment via high schools, social media, such as Facebook and forsoegsperson.dk were used. The recruitment notice, approved by the Ethics Committee was posted online. (Appendix 2). The recruitment process is shown in the CONSORT diagram below, see figure 3.

![Consort Diagram](image-url)
### 4.3.2 Inclusion and Exclusion Criteria

All participants were screened using the inclusion and exclusion criteria as shown in figure 4 below.

<table>
<thead>
<tr>
<th>Healthy Controls</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td><strong>Exclusion criteria</strong></td>
</tr>
<tr>
<td>Aged 15-19</td>
<td>Recurring pain syndromes within the last 3 months</td>
</tr>
<tr>
<td>Female</td>
<td>Pain in the lower back, pelvis or legs within the last week</td>
</tr>
<tr>
<td>Healthy</td>
<td>Neurological disorders</td>
</tr>
<tr>
<td>Fluent Danish reading, speaking and comprehension</td>
<td>Musculoskeletal disorders</td>
</tr>
<tr>
<td></td>
<td>Rheumatologic diseases</td>
</tr>
<tr>
<td></td>
<td>Psychiatric disorders</td>
</tr>
<tr>
<td></td>
<td>Consumption of primary and secondary analgesics within 24 hours</td>
</tr>
<tr>
<td></td>
<td>Consumption of alcohol within 24 hours</td>
</tr>
<tr>
<td></td>
<td>Increase or decrease in intensity of training activities within the last 72 hours</td>
</tr>
<tr>
<td></td>
<td>Present or previous substance abuse</td>
</tr>
<tr>
<td></td>
<td>Pregnant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CLBP group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td><strong>Exclusion criteria</strong></td>
</tr>
<tr>
<td>Aged 15-19</td>
<td>Neurological disorders</td>
</tr>
<tr>
<td>Female</td>
<td>Psychiatric disorders</td>
</tr>
<tr>
<td>Recurring pain in the lower back within the last 3 months</td>
<td>Rheumatologic diseases</td>
</tr>
<tr>
<td>Fluent Danish reading, speaking and comprehension</td>
<td>Consumption of primary and secondary analgesics within 24 hours</td>
</tr>
<tr>
<td></td>
<td>Increase or decrease in intensity of training activities within the last 72 hours</td>
</tr>
<tr>
<td></td>
<td>Consumption of alcohol within 24 hours</td>
</tr>
<tr>
<td></td>
<td>Present or previous substance abuse</td>
</tr>
<tr>
<td></td>
<td>Pregnant</td>
</tr>
</tbody>
</table>

*Figure 4 Inclusion and Exclusion Criteria for CLBP Group and Control Group*
4.3.3 Demographics

A list of demographics for the CLBP and control group are listed below, see table 1.

<table>
<thead>
<tr>
<th></th>
<th>CLBP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>16.9 (±1.3)</td>
<td>17.4 (±1,1)</td>
</tr>
<tr>
<td>BMI</td>
<td>21.9 (±2.9)</td>
<td>21.5 (±2.5)</td>
</tr>
<tr>
<td>Weekly physical activity</td>
<td>8.9 (±5.6)</td>
<td>5.1 (±3.7)</td>
</tr>
<tr>
<td>VAS</td>
<td>5 (±1.3)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 1: Demographics for the CLBP group and Control group, mean (± Std.)

4.4 Protocol

4.4.1 Equipment

The following equipment was used in this study:

- Force Ten, handheld algometer with a 1cm² probe.
- Two single chambered pneumatic tourniquet cuff. The cuff is produced by VBM Medizintechnik GmbH, Sulz, Germany.
- A computerized air compressor produced by Condor MDR2, JUN-AIR International A/S, Nørresundby, DK, connected to an electric pneumatic converter (ITV2030, SMC Corp., Tokyo, Japan) which is controlled by a computer.
- CuffControl, by Knud Larsen, for cuff pressure algometer (CorTex Technology) Version 1.4.0.0.
- A 10cm long electronic visual analogue scale, Aalborg University
- MyotonPRO hardware produced by Myoton, Estonia
- MyotonPRO software: MyotonPRO.com

4.4.2 Quantitative Sensory Testing

4.4.2.1 Pressure Pain Thresholds

PPT will be measured using a handheld pressure algometer with the participant lying prone on a massage plinth. The applied pressure will be slowly increased. The participant is told to say “now” as soon as the applied pressure becomes painful (PPT), where the pressure is immediately stopped and the
PPT is noted. PPT is measured bilaterally in three locations on the lower back and at one reference point on the arm. M. deltoideus is used as reference point as it is normally not a site for trigger points. These locations are as follows: (see figure 5):

1. The muscle belly of m. deltoideus
2. 3 cm lateral to the spinous process of Th12/L1
3. 3 cm lateral to the spinous process of L4/L5
4. Muscle belly of m. gluteus medius.

PPT will be measured three times for each location. The PPTs will be measured in randomized order. The seven points will be measured once in succession, thereby insuring at least 30 second break between measurements of each point. The handheld pressure algometer is shown in figure 6.
4.4.2.2 Central Pain Mechanisms

The primary central pain mechanisms to be investigated are TS and CPM. Each of the following three tests will be performed once. See figures 7 and 8 for illustrations of the equipment.

1. **PPT and PTT**: Will be measured and used as stimulation intensity in TS which will be described below. The cuff will be placed on the participant’s non-dominant lower leg. The cuff will be slowly inflated (1 kPa/second) until the PTT is reached. The participant will be asked to evaluate the pain during the inflation on an electronic VAS scale and are instructed to push the stop button when the pain becomes intolerable. PPT will be noted during the assessment. PTT is reached when the participant presses the stop button or if the upper limit (maximum) for pressure is reached. The upper limit will be set to 100 kPa.

2. **TS**: The cuff remains on the participant’s non-dominant leg and will then be inflated and deflated 10 times using the intensity found during the PTT measurement. Inflation and deflation each have a duration of 1 second (Inter Stimulus Interval: 1 second) and the total duration of the test is 20 seconds. The participant will evaluate the pain during the 10 inflations, and if the pain becomes intolerable, the participant may discontinue the test by pressing the stop button.

3. **CPM**: A second cuff will be placed around the participant’s dominant arm in addition to the cuff placed around the participant’s non-dominant leg. The cuff around the arm will immediately be inflated to 60 kPa which is the pre-set limit and apply to all participants unless the participant cannot tolerate this pressure, then the pressure will be reduced to 30 kPa. The first test is then repeated (see item 1 above) while the pressure stimulation on the arm is maintained. The participant will be asked to concentrate on the pressure applied to the leg and to try to ignore the pain in the arm. The participant will then evaluate the leg pain as per the first test. When the pain becomes intolerable, or when the upper limit of 100 kPa is reached, the test will be discontinued.
A myotonometer, MyotonPro, will be used to measure muscle tone and stiffness, see figure 9. The measurements will be performed with the participant lying on a massage plinth in a fully relaxed position. The MyotonPro is a handheld device and the measurement of muscle tone is performed by holding the MyotonPro perpendicular to the skin surface above the muscle being measured and applying a light constant pre-pressure (0.18N), as indicated by light diodes, thereby compressing the subcutaneous superficial tissue. Three quick released mechanical impulses are exerted (0.58N) at a constant mechanical force.
Myoton measurements will be made bilaterally over three locations on the lower back, one location on the abdomen, and a reference point on the arm, see figure 10.

The locations on the back are:

1. The muscle belly of m.deltoidus
2. 3 cm lateral to the spinous process of Th12/L1
3. 3cm lateral to the spinous process of L4/L5
4. Muscle belly of m. gluteus medius.

The location on the front is:

5. The upper part of m. rectus abdominus
4.4.3 Pain Catastrophizing Scale

The Danish version of the PCS includes questions regarding the participants’ thoughts and feelings associated with their experience of pain. The degree of which they experience 13 different thoughts and feelings associated with when they feel pain, is recorded on a 4-point Likert Scale ranging from “0 = not at all” to “3 = all the time”. The total score is calculated by the sum of the scores from the answers to all 13 items, ranging from 0-49. PCS is a valid and reliable measure of PC.⁷⁵

4.5 Pilot test

Pilot testing was performed on five subjects to familiarize the investigators with the equipment and to evaluate the time required to complete the test protocol, which took 45-60 minutes. After the pilot test, it was decided to include a familiarization measurement, before data collection, in order to put the participants at ease with the procedures. Due to excessive movement during the muscle tone and stiffness testing, it was decided that the participants will be requested to hold their breath for approximately ten seconds whilst the measurements are performed.

4.6 Practical execution

All data is registered on a Case Report Form (CRF) (Appendix 3). Additionally, data that is recorded for muscle tone, TS and CPM are saved as files in the respective software systems. The experimental session will take place at the institution where the participant attends school, in order to lessen the travel burden (time/cost) and facilitate participation. In the event that this is not possible, the experimental session will take place at Aalborg University. Furthermore, the session will take place in a private room to avoid interruptions. The session will last approximately 45 - 60 minutes.

4.6.1 Investigators

Three investigators are involved in collecting data in this study. All investigators are physical therapists. The investigator with the most clinical experience in manual therapy (4 years) localized and marked all the test points on the subjects’ back.
Data collection is allocated according to experience. The investigator with the most experience will perform the handheld pressure measurements, as investigator experience can have an impact on the quality of the data obtained. The investigator performing the handheld pressure measurements has experience collecting data from over 50 research subjects. Previous studies have reported low inter-rater bias with MyotonPRO and Computerized Cuff Algometry.

4.6.2 Participant Information and Informed Consent
The participants are welcomed and informed about the program for the test procedures. They are asked whether they have any questions about the study and their participation. When questions have been answered participants of legal age are asked to sign the consent form. Consent forms for participants that are not of legal age have been collected from the parents or guardians prior to the test day.

4.6.3 Pain Catastrophizing Scale
The participants are instructed to complete the PCS without thinking too long about the questions. The participant may ask the investigator questions regarding the PCS if there are words they do not understand, or they are in doubt as to what the question means. The participant is given a quiet spot to complete the PCS so they will not be disturbed.

4.6.4 Measurement of Muscle Tone and Stiffness
The participant is informed about the test procedures and the use of MyotonPro is demonstrated on the participant’s arm. The participant is asked to remove clothing obscuring their back, stomach and hips. The investigator marks the test sites on the participant’s body with a coloured pen. The participant is asked to lie down on the massage plinth in supine or prone position depending on the first point to be measured (as per the randomization process). The investigator ensures that the participant’s position allows her to be fully relaxed during the testing procedure. The participant is instructed to hold her breath for ten seconds during the measurements, in order to reduce involuntary movement of the MyotonPro apparatus. The investigator places the MyotonPro at the test site with the probe perpendicular to the skin. The measurements are performed in randomized order. The investigator evaluates the quality of each measurement based on the coefficient of variance, which should be less
than 3%. The coefficient of variance indicates the total variability of the measurements due to factors such as the subject, operator, device accuracy and environment. If a measurement is higher than 3% it should be repeated. Data is automatically saved in the MyotonPro software. The investigator also enters the data in the CRF after each measurement.

4.6.5 Handheld PPT
The investigator informs the participant about the test procedures and first demonstrates the use of the handheld algometer on their own arm before applying pressure to the participant’s arm and requesting that they say “stop” when the pressure becomes painful. This is done in order to familiarize the participant with the sensation of a PPT. The participant is informed that pressure will be applied to six places on the back and one place on the arm and three times in each location. The participant is instructed to say “now” as soon as the applied pressure becomes painful. The participant is asked to lie prone on the massage plinth in a position that allows them to be fully relaxed. The investigator performs the measurements in randomized order. Each measurement is recorded in the CRF by the investigator.

4.6.6 Computerized Pressure Algometry
The participant is asked to lie supine on the massage plinth. The investigator informs the participant about the test procedures and instructs the participant to evaluate her pain on the electronic VAS during the test and to disrupt the test when the pain becomes intolerable. The tests are then performed as described above under TS and CPM. Data generated by the software is saved as .txt files and each participant’s ID number. Data is also entered into the CRF after each test is performed.

4.7 SAFETY AND ETHICAL CONSIDERATIONS
The project group who performed the study prepared the protocol approved by the ethics committee and a copy of the entire protocol can be found in appendix 4. The study was approved by the local ethics committee (N-20140082). CPA and handheld pressure algometry have been used in several other studies\textsuperscript{14,24,59} with no prolonged negative effects. The procedures will induce a short lasting pain, which will disappear within a short time period after the experiment has been completed. Further, the procedures can leave bruises in the
locations where they were applied which will disappear within a few days. CPA has several inbuilt safety mechanisms to ensure that the pressure applied does not exceed levels that could cause long lasting harm. The maximal amount of pressure is set to 100 kPa. The pressure is increased by 1 kPa per second and therefore the participant will not receive pressure for longer than a maximum of 100 seconds. The participant will be given a stop button, which will immediately release the pressure when pushed. The computer is also equipped with a safety button, which enables the investigator to release the pressure in case of malfunction.

The pain experienced by the participant is short-lived. Thus, the risks involved in this study are minimal compared to the potential benefits.

The study population includes minors. CLBP is a common problem amongst adolescents and most prevalent in the female population as previously described in the Background section. Further, LBP increases in severity until the age of 18. Using female minors is therefore a necessity. Minors are unable to provide full consent themselves and therefore the responsibility of consent for participation of minors (15-17 years old) in this study is vested in parents or guardians. For minors informed consent will be obtained (Appendix 5) from both parents or guardians, prior to study participation, where both parents or guardians have legal custody. Alternatively, one parent or guardian may authorise the other parent or guardian to give informed consent on their behalf. Single parents or guardians with full legal custody may give informed consent without the involvement of a parent without legal custody. In the event that a minor becomes of legal age during their participation in the study, a new informed consent (Appendix 6) will be obtained. Further, the parents or guardians are encouraged to accompany the participant during study participation.

The study will be conducted in accordance with national regulations and the Helsinki Declaration. After oral information is given, the participants and the parents or guardians of those participants not of legal age will have a deliberation time of at least 24 hours prior to giving informed consent. A written consent form will be obtained from all participants prior to participation. Data will not be collected before informed consent has been obtained. The investigator will ensure that participants will be anonymised by way of ID number coding and data will be stored in a locked room.
4.8 DATA PROCESSING

Data from the Cuff Control software is saved as .txt files. For the registration of VAS scores the threshold was set to 1.00 VAS, due to interference from the electronic VAS instrument.

The Cuff Control software extracts values for VAS during TS by localising the start and end point for each of the ten repetitions of applied pressure and the mean VAS score for this interval is calculated. Mathworks MATLAB R2014a was used for extraction of the time from PPT to PTT during CPM. Thereby two different parameters are used for the analysis of differences in CPM between the CLBP group and the control group:

- CPM – PPT
- CPM – time from PPT to PTT

Measurement of muscle tone and stiffness is done by recording of the damped natural oscillation of soft tissue, by use of an acceleration signal by which subsequent computation is associated with state of tension, and viscoelastic properties.

The muscle tone indicates the oscillation frequency (Hz),

The muscle stiffness is calculated by the “max acceleration” multiplied by the “mass of measurement” divided by the “max displacement of tissue.

The average of the three measurements for each of the two parameters, muscle tone and stiffness, will be used for statistical analysis. The MyotonPro software calculates the muscle parameters automatically.

Data from the CRFs, PCS scores, handheld PPT and the extracted parameters from MATLAB were entered into an Excel spreadsheet (Microsoft Excel version 14.4.1).

The average of the three handheld PPT values for each point were calculated.

The degree of TS was calculated by subtracting the VAS score from the first stimulation from the tenth VAS score.

A global measurement for muscle tone and stiffness was calculated for each participant by calculating the mean of all test points, in order to investigate the association between PC and muscle tone.
4.9 **Statistical Analysis**

Data from the Excel spreadsheet was imported into SPSS (IBM SPSS statistic version 22).

All data were initially analysed in relation to normal distribution and homoscedasticity. The Shapiro-Wilk test was used, which is appropriate for small sample sizes \(^{77}\) and Levene’s test for homogeneity of variance.

4.9.1 **Differences Between the CLBP group and the Control Group**

The majority of data did not meet the assumptions for the use of parametric tests. Mann Whitney U was therefore applied to determine differences between the CLBP group and the control group in relation to handheld PPT, muscle tone, muscle stiffness and TS.

Data from CPM and PCS were normally distributed and had equal variances. Independent sample t tests were applied in order to determine difference between the two groups.

4.9.2 **Correlations**

Several correlation analyses were made in order to test for significant correlations between different parameters for each of the two groups. Spearman’s correlation coefficient (\(\rho\)) was used as none of the data met the assumptions for the use of parametric tests.

Correlation analyses were made for the following parameters:

- Muscle tone and handheld PPT
- Muscle stiffness and handheld PPT
- CPM and PC
- TS and PC
- NRS and PC
- Global muscle tone and PC
- Global muscle stiffness and PC

The level of significance for all statistical tests is set to 0.1 due to the relative small sample size.
5 RESULTS

This chapter presents the results from the study. All data are presented by mean (± std.)

5.1 HANDHELD PPT

Significant differences were found between the CLBP group (n=22) and the control group (n=11) for all seven test points, see table 2.

<table>
<thead>
<tr>
<th>Point</th>
<th>CLBP</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th12/ L1 LS</td>
<td>2.33 (±1.98)</td>
<td>4.11 (±1.95)</td>
</tr>
<tr>
<td>L4/L5 LS</td>
<td>1.86 (±1.15)</td>
<td>4.57 (±2.48)</td>
</tr>
<tr>
<td>m. gluteus medius LS</td>
<td>1.57 (±0.87)</td>
<td>3.16 (±1.68)</td>
</tr>
<tr>
<td>Th12/ L1 RS</td>
<td>2.42 (±1.73)</td>
<td>4.19 (±2.22)</td>
</tr>
<tr>
<td>L4/L5 RS</td>
<td>1.97 (±1.30)</td>
<td>4.47 (±2.58)</td>
</tr>
<tr>
<td>m. gluteus medius RS</td>
<td>1.62 (±0.92)</td>
<td>3.22 (±1.71)</td>
</tr>
<tr>
<td>m. deltoideus</td>
<td>1.75 (±1.03)</td>
<td>2.91 (±1.63)</td>
</tr>
</tbody>
</table>

Table 2 Handheld PPT for CLBP and control group, mean (± std.)

Figure 11 Handheld PPT for CLBP and Control Group. 1=Th12/L1 LS (p=0.02), 2=L4/L5 LS (p<0.001), 3 = m. gluteus medius LS (p=0.001), 4=Th12/L1 RS (p=0.001), 5=L4/L5 RS (p=0.001), 6= m. gluteus medius RS (p=0.001) 7= m. deltoideus (p=0.17). Significant differences between all points.
5.2 **Muscle Tone**

A significant difference was found for one test point (m. gluteus medius LS) between the CLBP group (n=22) and the control group (n=11) (p=0.027), see table 3.

<table>
<thead>
<tr>
<th>Point</th>
<th>CLBP</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th12/ L1 LS</td>
<td>14.10 (±0.95)</td>
<td>14.44 (±0.95)</td>
<td>0.245</td>
</tr>
<tr>
<td>L4/L5 LS</td>
<td>13.08 (±1.23)</td>
<td>12.87 (±1.17)</td>
<td>0.322</td>
</tr>
<tr>
<td>m. gluteus medius LS</td>
<td>11.31 (±0.52)</td>
<td>10.83 (±0.82)</td>
<td>0.027*</td>
</tr>
<tr>
<td>Th12/ L1 RS</td>
<td>13.95 (±0.79)</td>
<td>14.13 (±1.22)</td>
<td>0.400</td>
</tr>
<tr>
<td>L4/L5 RS</td>
<td>13.05 (±1.05)</td>
<td>12.71 (±1.28)</td>
<td>0.283</td>
</tr>
<tr>
<td>m. gluteus medius RS</td>
<td>11.05 (±0.74)</td>
<td>11.03 (±0.94)</td>
<td>0.315</td>
</tr>
<tr>
<td>m. deltoideus</td>
<td>13.89 (±1.37)</td>
<td>13.69 (±1.45)</td>
<td>0.240</td>
</tr>
<tr>
<td>m. rectus abdominis LS</td>
<td>11.85 (±1.63)</td>
<td>12.60 (±1.85)</td>
<td>0.195</td>
</tr>
<tr>
<td>m. rectus abdominis RS</td>
<td>11.97 (±1.85)</td>
<td>12.67 (±1.85)</td>
<td>0.130</td>
</tr>
</tbody>
</table>

*Table 3 Muscle tone for CLBP and control group, mean (±std.), p values. *Significant difference.*

5.3 **Muscle Stiffness**

No significant difference was found between the two groups in relation to muscle stiffness, see table 4.

<table>
<thead>
<tr>
<th>Point</th>
<th>CLBP</th>
<th>Control</th>
<th>n(CLBP/control)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th12/ L1 LS</td>
<td>226.11(±53.15)</td>
<td>241.20(±54.81)</td>
<td>22/11</td>
<td>0.43</td>
</tr>
<tr>
<td>L4/L5 LS</td>
<td>191.44(±34.09)</td>
<td>183.50(±21.15)</td>
<td>22/11</td>
<td>0.94</td>
</tr>
<tr>
<td>m. gluteus medius LS</td>
<td>140.78(±17.61)</td>
<td>145.40(±17.90)</td>
<td>22/11</td>
<td>0.80</td>
</tr>
<tr>
<td>Th12/ L1 RS</td>
<td>214.89(±47.32)</td>
<td>228.50(±63.82)</td>
<td>22/10</td>
<td>0.46</td>
</tr>
<tr>
<td>L4/L5 RS</td>
<td>185.44(±34.74)</td>
<td>180.10(±23.20)</td>
<td>22/11</td>
<td>0.79</td>
</tr>
<tr>
<td>m. gluteus medius RS</td>
<td>135.33(±17.39)</td>
<td>136.70(±16.51)</td>
<td>21/11</td>
<td>0.94</td>
</tr>
<tr>
<td>m. deltoideus</td>
<td>234.00(±36.48)</td>
<td>238.90(±39.54)</td>
<td>22/11</td>
<td>0.94</td>
</tr>
<tr>
<td>m. rectus abdominis LS</td>
<td>172.44(±47.06)</td>
<td>190.10(±55.18)</td>
<td>22/11</td>
<td>0.36</td>
</tr>
<tr>
<td>m. rectus abdominis RS</td>
<td>177.72(±46.54)</td>
<td>188.80(±49.53)</td>
<td>22/11</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*Table 4 Muscle stiffness in CLBP group and control group, mean (±std.). No significant differences between groups.*
5.4 CORRELATION BETWEEN MUSCLE TONE AND HANDHELD PPT

Significant negative correlations were found between muscle tone and PPT for L4/L5 LS for the CLBP group, see figure XX. No significant correlations for the control group between handheld PPT and muscle tone were found, see table 5.

<table>
<thead>
<tr>
<th>Point</th>
<th>CLBP (n=22)</th>
<th>Control (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th12/ L1 LS</td>
<td>-0.29 / 0.19</td>
<td>-0.18 / 0.60</td>
</tr>
<tr>
<td>L4/L5 LS</td>
<td>-0.38 / 0.08*</td>
<td>-0.20 / 0.56</td>
</tr>
<tr>
<td>m. gluteus medius LS</td>
<td>0.01 / 0.94</td>
<td>-0.38 / 0.25</td>
</tr>
<tr>
<td>Th12/ L1 RS</td>
<td>0.02 / 0.94</td>
<td>-0.01 / 0.97</td>
</tr>
<tr>
<td>L4/L5 RS</td>
<td>-0.27 / 0.23</td>
<td>-0.09 / 0.79</td>
</tr>
<tr>
<td>m. gluteus medius RS</td>
<td>0.28 / 0.90</td>
<td>0.09 / 0.80</td>
</tr>
<tr>
<td>m. deltoideus</td>
<td>-0.17 / 0.46</td>
<td>0.01 / 0.98</td>
</tr>
</tbody>
</table>

Table 5 Spearman’s Correlation between muscle tone and handheld PPT for CLBP and control group: ρ / p value. * Significant difference (p<0.1)

5.5 CORRELATION BETWEEN MUSCLE STIFFNESS AND HANDHELD PPT

One significant correlation was found in the CLBP group for L4/L5 LS, see table 6.
### Table 6
Spearman’s Correlation between muscle stiffness and handheld PPT for CLBP and control group: ρ / p value. * Significant correlation.

<table>
<thead>
<tr>
<th>Point</th>
<th>CLBP</th>
<th>Control</th>
<th>n(CLPB/Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th12/ L1 LS</td>
<td>-0.21/0.35</td>
<td>-0.25/0.45</td>
<td>22/11</td>
</tr>
<tr>
<td>L4/L5 LS</td>
<td>-0.49/0.02*</td>
<td>0.06/0.86</td>
<td>22/11</td>
</tr>
<tr>
<td>m. gluteus medius LS</td>
<td>-0.05/0.82</td>
<td>0.04/0.92</td>
<td>22/11</td>
</tr>
<tr>
<td>Th12/ L1 RS</td>
<td>-0.24/0.29</td>
<td>0.22/0.53</td>
<td>22/10</td>
</tr>
<tr>
<td>L4/L5 RS</td>
<td>-0.31/0.16</td>
<td>0.26/0.45</td>
<td>21/11</td>
</tr>
<tr>
<td>m. gluteus medius RS</td>
<td>-0.11/0.62</td>
<td>-0.05/0.88</td>
<td>22/11</td>
</tr>
<tr>
<td>m. deltoideus</td>
<td>-0.04/0.87</td>
<td>-0.06/0.85</td>
<td>22/11</td>
</tr>
</tbody>
</table>

5.6 **CPA PPT**

No significant difference (0.95) was found between the CLBP group 24.19(±12.84) (n=16) and the control group 22.35(±7.12) (n=7).

5.7 **CONDITIONED PAIN MODULATION**

No significant difference (p=0.43) was found between the CLBP group 15.67 (±12.90) (n=15) and the control group 12.74 (±14.89) (n=8) for CPM - time from PPT to PTT.
5.8 TEMPORAL SUMMATION

No significant difference (p=0.96) was found between the CLBP group 1.59 (±1.42) (n=15) and the control group 1.67 (±1.77) (n=8) in relation to TS.

5.9 COMPARISON OF PAIN CATASTROPHIZING IN THE CLBP AND CONTROL GROUP

A significant difference (p=0.07) was found between the CLBP group 19.24 (±9.85) (n=21) and the control group 11.8(±11.7) (n=10) in relation to PC where CLBP had higher PC than controls.

5.10 CORRELATIONS WITH PAIN CATASTROPHIZING

No significant correlations were found between PC and CPM, TS, NRS or global muscle tone and stiffness, see table 7.

<table>
<thead>
<tr>
<th>Correlations</th>
<th>CLBP</th>
<th>Control</th>
<th>n (CLBP/control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC and CPM</td>
<td>0.15/0.64</td>
<td>-0.5/0.25</td>
<td>15/7</td>
</tr>
<tr>
<td>PC and TS</td>
<td>-0.45/0.14</td>
<td>0.09/0.83</td>
<td>15/8</td>
</tr>
<tr>
<td>PC and NRS</td>
<td>0.23/0.30</td>
<td>.</td>
<td>21/-</td>
</tr>
<tr>
<td>PC and global muscle tone</td>
<td>0.08/0.73</td>
<td>-0.09/0.80</td>
<td>21/10</td>
</tr>
<tr>
<td>PC and global muscle stiffness</td>
<td>0.06/0.80</td>
<td>0.03/0.93</td>
<td>21/10</td>
</tr>
</tbody>
</table>

*Table 7 Spearman’s correlation between PC and CPM, TS, NRS and global muscle tone and stiffness.*
6 DISCUSSION

This chapter will discuss the main results from the study and the materials and methods used.

The main findings of this study are that the CLBP group has lower pressure pain thresholds (PPT) compared with the control group. There was significantly higher muscle tone in the left m. gluteus medius in the CLBP group compared with the control group. Temporal summation (TS) and conditioned pain modulation (CPM) was present in both the CLBP group and the control group, but there was no significant difference between the two groups. Scores from the Pain Catastrophizing Scale (PCS) were significantly higher in the CLBP group than in the control group. There was no significant correlation between PCS and central pain mechanisms (TS and CPM).

6.1 DISCUSSION OF RESULTS

6.1.1 Peripheral Sensitization

This is the first study of its kind to investigate PPT in adolescent females with CLBP compared with a healthy control group. The results showed significantly lower PPT values in the CLBP group compared with the healthy controls for all test points. These results compare favourably with other studies that have reported lower PPT values in adult CLBP patients.8,24

The results from this study showed the PPT levels in the control group to be considerably lower than those reported in healthy adult females; m. deltoideus: 37%, m. erector spinae: 21% and m. gluteus medius: 44% lower in the adolescent group. It is possible that age is a reason for these differences. There are mixed results from other studies regarding the extent to which age has an impact on PPTs. It has been reported that young children (6-8 years) have higher PPTs than adolescents (13-16 years).78 However, it is possible that these differences are due to a response bias component (reaction time), where younger children are slower to respond.78 The fact that both young children and adults have higher PPT values than adolescents could indicate physiological and psychological changes during adolescence impacting pain sensitivity.

The significantly lower PPTs measured in the CLBP group distally to the area of pain suggests the presence of widespread hyperalgesia, reported also in adult populations with CLBP.8,25 Lowered PPTs
in response to mechanical stimuli have also been found in adolescents with chronic fatigue syndrome\cite{79} and patellofemoral pain syndrome\cite{80}, and could reflect a loss of descending inhibition.\cite{81}

### 6.1.2 Central Pain Mechanisms

The results from this study showed the presence of CPM and TS in both the CLBP and control group. These findings are supported in other studies assessing CPM and TS in adults with chronic pain conditions and in healthy controls. There was however no difference between the two groups, which is contrary to findings reported in other musculoskeletal pain conditions.\cite{8,12-14} It should be noted that females have a more effective pain modulation during the ovulatory phase of their menstruation cycle\cite{82}.

The participants’ menstruation cycle was not recorded and therefore it is not possible to say if this has impacted the results from this study. Additionally, there is evidence that the effectiveness of CPM decreases with age\cite{83,84} and TS increases with age\cite{85}, and therefore it is possible that central pain mechanisms in adolescents are still under development and hereby not affected by CS in the same way that adults are. Van Wijk et al. reported that patients with current chronic pain could potentially have a more effective pain inhibition due to their pain acting as an increased conditioning stimulus during assessment of experimental CPM.\cite{84} It is possible that a similar phenomenon occurred in this study, explaining why there was no significant difference in CPM between the two groups.

There were no significant differences in the central pain mechanisms between the CLBP and control groups, measured with CPA. This is contrary to the handheld PPT measurements, which suggest widespread hyperalgesia. Previous studies have found the presence of widespread hyperalgesia measured with CPA in adults with fibromyalgia\cite{14} and chronic knee pain.\cite{9} The reference point for measuring widespread hyperalgesia for the handheld PPT measurement was m. deltoideus, and the point for the CPA PPT measurement was the lower leg. The lower handheld PPT measurements suggest widespread hyperalgesia; however, lower PPT values were not found with CPA. If widespread hyperalgesia is involved, then one would expect to find lowered PPTs in the lower leg, and not just in the arm. It is unknown if this inconsistency is because of the possible pattern of widespread hyperalgesia (that it first presents in the upper extremity) or if it was due to the two different methods of testing.
To the authors’ knowledge, there are no previous studies investigating CS in adolescents with CLBP compared to healthy controls. Research shows that CLBP is complex and heterogeneous where there is no ‘one size fits all’ diagnosis. Sensitization in CLBP patients can be due to changes in the periphery, spinal cord and/or the brain. This complex nature could perhaps explain the inconsistency in some of the pain mechanisms investigated in this study.

6.1.3 Pain Catastrophizing and Central Pain Mechanisms

It is widely known that affective and psychological states are of importance to a person’s response to noxious stimuli. Research suggests that brainstem structures under the influence of cortical structures, such as the prefrontal cortex and anterior cingulate cortex, might explain why CPM is affected by affective and psychological states. Therefore, CPM can be influenced by cognitive and affective components such as distraction, expectation and PC, and is not just an isolated sensory component. Despite the fact that there were significantly higher PC scores in the CLBP group in this study, there was no evidence of reduced CPM. Weismann-Fogel et. al reported a correlation between higher PC scores and lower CPM yet the results of this study did not show a significant correlation. Research shows a relationship between PC and TS, however the strength of this relationship depends on the type of PC. Two different measurements for PC can be made, a situation specific PC immediately after a painful event, or a general PC (as investigated in this study) relative to thoughts of pain in general. The situation specific PC has been shown to have a stronger relationship to TS and therefore could account for the fact that there was no significant correlation found between the two in this study.

6.1.4 Muscle Hypertonicity – Time to get to the Bottom of it

The results from this study showed that the CLBP group had significantly higher muscle tone in the left m. gluteus medius compared with the control group. There were no significant differences between the two groups for any of the other test points. A correlation between both higher muscle tone and stiffness was found with lower PPTs in L4/L5 LS.

The m. gluteus medius plays an important role in transferring forces from the lower extremity up to the spine during walking, and it is thought that this may influence the development of LBP. M. gluteus medius is responsible for stabilizing the pelvis during single limb stance. Weakness of the m. gluteus
medius has been reported in individuals with LBP, where people with weak m. gluteus medius are significantly more likely to develop LBP. Weakness in the m. gluteus medius has been related to increased activity in m. gluteus medius in patients with CLBP, possibly due to increased attempts to recruit the weakened muscle. Strength measurements of m. gluteus medius were not obtained from the participants in this study, so it is therefore not possible to comment on whether the increase in muscle tone in the CLBP group is because of weakness.

Weakness in m. gluteus medius can be compensated for by increased activity of the lateral trunk stabilisers. It is possible that this increased activity could lead to overloading of the spine and hereby LBP.

Why is muscle tone only higher on the left side in the CLBP group? The left leg is usually used for stance and posture and right-handed people tend to use their left foot to support them, while for example kicking a ball, while left handed people will also use their left foot as the stabiliser 60-80% of the time. Weak m. gluteus medius are reported to have increased activation, possibly due to failed attempts to activate a weak muscle that will not cooperate. If the hypertonicity in the CLBP is due to a weak m. gluteus medius, this could explain why there was a difference between the two groups. This is supported by a study that found that increased strength of m. gluteus medius on the left side may prevent LBP.

No previous studies were found that could explain the the correlation between higher muscle tone and stiffness with lower PPTs in L4/L5 LS. Anatomically, segment L4/L5 provides many functions such as supporting the upper body and allowing for motion in multiple directions. This segment is therefore heavily loaded and prone to pain. It is therefore likely that overloading can cause muscle injury leading to hypersensitivity and increased muscle tone.

### 6.2 DISCUSSION OF METHOD

#### 6.2.1 Recruitment

A vital part of the recruitment process was obtaining the cooperation of the high schools to participate in the study. Out of the 16 schools that were contacted only six agreed to participate. Reasons for not cooperating included time constraints, exams, and upcoming school trips. The degree of cooperation from each school had an impact on the sample size. Some schools allowed their pupils to participate
during school hours, without consequence for their attendance record. In these cases recruitment levels were much higher than for those schools where participation negatively affected their pupils’ attendance record, or if the pupils had to participate in their own time. Research shows that it is a challenge to get adolescents to participate in clinical research, especially when it involves the recruitment of minors.\(^6\) In many circumstances, minors will attend typical places of recruitment, such as clinics, with their parents. This allows the practitioner to inform the parents and adolescent about the study face to face, thereby increasing their willingness to participate in the study.\(^6\) The recruitment strategy in this study was different and did not allow for a face to face meeting with the parents. Instead, the parent contact was based purely on written information. Higher success rate in recruitment may have been achieved using a different recruitment strategy. During recruitment, the adolescents were briefly informed about the purpose of the study and the criteria for participating. It was up to each individual to honestly decide if they met the criteria. Ideally, there should have been more time allocated to recruitment so that the participants could be examined by the investigators, to ensure that they met the criteria.

6.2.2 Participant sample

It is important to note that those who participated in this study were students who turned up to school. Research shows that adolescents that come from families with lower socioeconomic status tend to have a higher prevalence of musculoskeletal pain. Adolescents from families with lower socioeconomic status have poorer attendance at school\(^9\) and are less willing to participate in clinical research.\(^9\) This could have had an impact on this study in relation to the representation of this group in the participant sample size.

6.2.3 Outcome measures

6.2.3.1 Handheld Pressure Algometer

Using mechanical pressure as a means of investigating pain is reported to be the best correlate of clinical pain than any other measurement in CLBP patients.\(^7\) However, it has been show that handheld algometry only has moderate to good reliability.\(^2\) Differences in reaction time, compression rate and examiner expectancy can be possible sources of bias when performing PPT measurements.\(^1\) To reduce
these limitations, the investigator with the most experience performed all the handheld PPT measurements.

Skin sensitivity can also have an impact on PPT, where the subject will experience pain from the skin, rather than from the deeper muscle tissue.\textsuperscript{80,81,98} Furthermore, the investigator was not blinded as to whether the participant had pain or not which could be a possible source of bias. Additionally it has been shown that PPT is affected by the thickness of adipose tissue, however subcutaneous fat was not measured in this study and therefore cannot be ruled out as a possible source of bias.\textsuperscript{99}

\textbf{6.2.3.2 Computerized Pressure Algometry}

\textbf{6.2.3.2.1 Placement of the cuff}

PPT, TS and CPM were tested with the CPA cuff placed around the participants’ leg, which is a common method used in other studies investigating pain mechanisms.\textsuperscript{14,57} Although this study excluded adolescents with neurological disorders, \textsuperscript{40} of back pain cases in adults involve discogenic leg pain,\textsuperscript{100} and it cannot be ruled out that some of the participants in this study experienced discogenic pain. This could have had an effect on the participants’ experience of the test stimulus if they had sensory disturbances in the leg. In future studies it may be prudent to place the cuff around the subjects’ arm to remove the risk of possible bias from sensory disturbances.

\textbf{6.2.3.2.2 VAS Threshold}

The threshold for CPA PPT was set to 1.0 VAS as an automatic setting in the CPA software. It can be discussed whether this threshold was too high. The threshold of 1.0 could result in incorrect PPT values for participants who slowly increase their pain, hereby delaying the PPT values. On the other hand, a lower threshold could result in incorrect VAS values due to interference from the VAS system. To ensure measurements that are more valid, the amount of interference could have been investigated which would allow for the possibility of using a lower threshold for PPT.

\textbf{6.2.3.2.3 Temporal Summation and Conditioned Pain Modulation}

In this study TS was calculated by subtracting the VAS score registered from the first stimulus from the VAS score registered from the last stimulus, a method commonly used in the literature. It was observed that two participants did not register a VAS score until the second stimulus. Other participants
registered a VAS score on the first stimulus but then reduced the score considerably after the second stimulus. It can be discussed to which degree a delayed reaction time and fear of pain could have influenced these VAS scores. One possibility may be to exclude the VAS scores from the first stimulus so that TS was calculated by subtracting the second score from the last to account for delayed reaction times and initial fear. However, there are no previous studies that have used this method and therefore the validity of using this method as a means for calculating TS in adolescents is unknown.

There is convincing evidence that a person’s expectations towards pain has an impact on CPM. Subjects expecting the conditioning stimulus to have an analgesic effect report a reduction in pain intensity, likewise if the same stimulus was expected to be pain enhancing then CPM was decreased.

The instructions given to the participants were standardized in this study. It was not mentioned what the participant should expect to feel during the CPM test, only that they should try not to think about the conditioning pain in their arm, and instead focus on the slowly increasing pressure applied to the leg. Therefore, it is unlikely that the participants’ expectations could have had an impact on CPM in this study.

6.2.3.3 MyotonPro

According to the MyotonPro user manual the point of measurement should be located at the point above the biggest cross section of the muscle belly. Studies have found the MyotonPro to be valid and reliable when used according to the manual. To the authors’ knowledge, no previous studies have investigated using the MyotonPro on back and stomach muscles. In this study the points for measurement on the back were standardized in relation to the distance to the body midline (3cm). Therefore, the validity of these measurements is not certain.

The MyotonPro manual states specifically that the MyotonPro is not valid for use on muscles with more than 2 cm subcutaneous fat. Ideally, participants should have been scanned with an ultrasound apparatus, or have been measured with a skin fold calliper, to avoid this possibility for error. The participants in this study were not examined in regards to subcutaneous fat and it is unknown what impact this would have had on the validity of the measurements.
6.2.3.4 Pain Catastrophizing Scale

In this study it was chosen to use the adult version of the PCS, due to the child version not being available in the Danish language. One can question whether the younger adolescents were able to completely understand the questions. Consequently, it cannot be excluded that erroneous answers may have been given and could be a source of bias.

Studies have investigated the impact of social desirability bias in research involving questionnaires. Social desirability bias entails the possible influence of a participant’s cautiousness about revealing sensitive details about themselves or endangering their self-esteem. This phenomenon could lead to participants answering favourably to please the investigator, or to hide something about their personality or thoughts to avoid possible negative consequences. It is recommended when conducting research regarding sensitive matters, that questionnaires be self-administered or even web based. This is particularly relevant for adolescent females who are reportedly more cautious and self-protective when responding to questionnaires.

In this study it was chosen to administer the PCS while the participant was present, both in order to avoid the risk of low response rate and to allow the participants to ask questions if need be as the adult version of the PCS was used. It is possible that because there was an investigator present while the participant was completing the questionnaire, that the participant was not inclined to respond in a completely truthful manner. An example of this could be that participants, knowing that they were in the “healthy” group, tried to provide answers relating to this role. Likewise, participants in the CLBP group may also have felt they needed to live up to a particular role, and selected answers trending towards an “unhealthy” role.
7 Conclusion

It was possible to show the presence of peripheral sensitisation and widespread hyperalgesia in female adolescents with CLBP. This is the first study of its kind and the results compare favourably with those reported in adult populations with CLBP. These findings suggest the importance of focussing on examining not only the pathological reasons behind CLBP but also the presence of altered central pain mechanisms.

This study found the presence of temporal summation (TS) and conditioned pain modulation (CPM) in both the CLBP and the control group, as previously reported in adults; however, there was no significant difference between the two groups in either of these pain mechanisms. This suggests that the degree to which central pain mechanisms are altered in adults is not necessarily the same in adolescents. Treatment of adolescents should therefore not only be based on evidence regarding adult pain mechanisms.

The CLBP group had significantly higher levels of pain catastrophizing (PC) than the healthy control group. There was however no relationship between PC and increased TS or decreased CPM. This could indicate that the impact of PC has not yet manifested itself in adolescents to the same extent as in adults where it has begun to affect central pain mechanisms.

An interesting discovery was an increased muscle tone found in the left gluteus medius muscle in the CLBP group. Increased muscle activity in the gluteus medius muscle has previously been associated with weakness, and could be a risk factor for developing CLBP. It is unknown to what extent increased muscle activity relates to muscle tone, and this area requires further investigation. The findings in this study could contribute to a greater understanding of the mechanisms involved in the development of LBP and future research should be aimed towards examining muscle tone compared with muscle weakness in chronic pain conditions.
8 REFERENCES

1. Vinding B. Lænderygsmarter plager danskerne mest. 2014; Available at:


Appendices

1. Participant Information
2. Participant Recruitment Notice
3. Case Report Form
4. Ethics Protocol
5. Informed Consent 15-17 Year Olds
6. Informed Consent 18-19 Year Olds
Appendix 1 Participant Information

Forsøgets titel: Ændringer i smertemekanismer hos unge piger mellem 15-19 år med kroniske uspecifikke lænderygsmarter

Vi vil spørge, om du vil deltage i et videnskabeligt forsøg, der udføres ved Center for Sanse-Motorisk Interaktion, Aalborg Universitet.

Før du beslutter, om du vil deltage i forsøget, skal du fuldt ud forstå, hvad forsøget går ud på, og hvorfor vi gennemfører forsøget. Vi vil derfor bede dig om at læse denne deltagerinformation grundigt.

Du vil blive inviteret til en samtale om forsøget, hvor denne deltagerinformation vil blive uddybet, og hvor du kan stille de spørgsmål, du har om forsøget. Du er velkommen til at tage et familiemedlem, en ven eller en bekendt med til samtalen.

Hvis du beslutter dig for at deltage i forsøget, vil vi bede dig om at underskrive en samtykkeerklæring. Husk, at du har ret til betænkningstid, før du beslutter, om du vil underskrive samtykkeerklæringen.

Det er frivilligt at deltage i forsøget. Du kan når som helst og uden at give en grund trække dit samtykke tilbage.

Formål med forsøget

Lænderygsmerter er meget almindelige hos unge, men hvorfor, disse smerter opstår, er endnu ikke klarlagt. Studier viser, at 86% af unge oplever lænderygsmerter og at 35-45% af unge udvikler kroniske lænderygsmarter. Lænderygsmerter, der starter tidligt i livet har større sandsynlighed for at udvikle sig til kroniske smerter, når personen bliver voksen. Formålet med dette forsøg er derfor at klargjøre årsager og risikofaktorer til lænderygsmarter hos unge, så det kan forebygges, at smerterne bliver kroniske senere i livet.

Hvem kan deltage i forsøget?

Projektet i sin helhed omfatter 100 testpersoner, og du kan deltage i forsøget, hvis du er pige, i alderen 15-19 år og er enten rask eller har lidt af periodiske lændesmerter inden for de seneste tre måneder. Du skal endvidere have et BMI mellem 18,5 og 29,9 samt kunne tale, læse og forstå dansk.

Hvordan forløber forsøget?

Den samlede tid for din deltagelse i forsøget vil være ca. 1 time.

Vi vil måle, hvordan du reagerer på forskellige smertestimuli samt måle muskelstivhed af dine rygmuskler. Nedenfor finder du et program for din deltagelse i forsøget:

Udfyldelse af spørgeskemaer
Du skal udfylde 4 spørgeskemaer omkring smerter og dit generelle velvære.

Et år efter din deltagelse i forsøget beder vi dig udfylde de samme fire spørgeskemaer (skemaerne bliver sendt til dig).

Måling af kropsholdning


Måling af muskelstivhed i ryggen og på maven

Et håndholdt målerapparat bliver anvendt til at undersøge stivhed i ryggen. Muskelstivheden vil blive målt på 16 forskellige punkter på ryggen og 8 forskellige punkter på maven. Denne procedure gør ikke ondt.

Smertemåling med håndholdt trykmåler

Et håndholdt trykapparat, som trykkes mod din hud på din læn og arm, bliver anvendt til at undersøge din oplevelse af, når tryk bliver til smerte. Smertemålingerne vil blive udført på otte forskellige punkter på ryggen og to steder på dine arme. Du skal ved hjælp af en knap angive, når du føler at trykket forandrer sig fra tryk til smerte. Du vil føle let til moderat smerte under trykøverdige.

Smertemåling med trykmanchet

Denne procedure består af 3 dele:

(1) Du vil få en trykmanchet placeret omkring dit ben, som bliver blæst op med luft. Du skal registrere følelsen af smerter på en skala fra 0 til 10 (hvor 0 er ingen smerte og 10 er den værste tænkelige smerte). Du bestemmer selv, hvornår smertemålingen skal afbrydes.

(2) Trykmanchetten omkring dit ben vil blive blæst op 10 gange af 1 sekunds varighed og med 1 sekunds mellemrum. Du skal også under denne del vurdere smerten på en skala fra 0 til 10.

(3) Samtidig med at du har trykmanchetten omkring dit ben, bliver en anden manchet sat omkring den modsatte arm. Trykmanchetten omkring din arm bliver herefter blæst op. Samtidig med at trykmanchetten omkring din arm er blæst op, vil trykmanchetten omkring dit ben blive blæst langsamt op. Du skal fokusere på smerten i benet og forsøge at ignorere smerten i armen. Du skal under denne procedure også registrere følelsen af smerten i benet på en skala fra 0 til 10. Du bestemmer selv, når smertemålingen skal afbrydes.

Generelt vil du føle let til moderat smerte under manchet-forsøgene, men smerten ophører umiddelbart efter, at manchetten afmonteres.

De data, vi indsamler om dig, opbevares i anonym form efter forsøgets afslutning.

Hvis du er i alderen 15-17 år, anbefaler vi, at dine forældre er til stede under forsøget.

Risici, bivirkninger og ulemper
Der er ingen risici ved de anvendte metoder, som anvendes rutinemæssigt både ved Center for Sanse-Motorisk Interaktion samt andre institutioner i ind- og udland. Der er ingen permanente bivirkninger af stimulering med trykmåler og manchet, men målingerne kan medføre forbigående ubehagelig i form af smerte, mens målingerne står på samt efterfølgende ømhed og blå mærker. Dette forsvinder dog relativt hurtigt igen.

Der kan være risici ved forsøget, som vi endnu ikke kender. Vi beder dig derfor om at fortælle, hvis du oplever problemer med dit helbred, mens forsøget står på. Hvis vi opdager bivirkninger, som vi ikke allerede har fortalt dig om, vil du naturligvis blive orienteret med det samme, og du vil skulle tage stilling til, om du ønsker at fortsætte i forsøget.

Nytte ved deltagelse

Der ikke være nogen personlig gevinst for dig ved deltagelse i projektet, udover at du gennem projektet hjælper til en bedre forståelse og behandling af rygsmerter hos unge.

Udelukkelse fra og afbrydelse af forsøg

Reagerer du efter forsøgslederens vurdering uventet på forsøgets procedurer, eller viser du dig på anden vis ikke egnet til videre deltagelse i forsøget, kan forsøget til ethvert tidspunkt afsluttes. Forsøget som helhed vil blive stoppet, hvis det skulle vise sig, at forsøgspersonerne generelt ikke tolererer procedurerne i forsøget eller finder forsøget for udmattende.

Oplysninger om økonomiske forhold

Projektet er initieret af adjunkt Line Lindhardt Egsgaard, Center for Sanse-Motorisk Interaktion, Aalborg Universitet.

Projektet finansieres af Center for Sanse-Motorisk Interaktion, Aalborg Universitet med 10.000kr. Der er blevet søgt om økonomisk støtte fra Danske Fysioterapeuter og Siemens Fonden og derudover vil der løbende blive ansøgt støtte fra andre eksterne fonde.

Forskerne bag protokollen er uafhængige af interesser fra andre instanser som f.eks. lægemiddel-industrien.

Der udbetales ingen kompensation for din deltagelse i forsøget.

Adgang til forsøgsresultater

Den Videnskabsetiske Komité kan få direkte adgang til resultaterne af denne undersøgelse.

Forsøgsresultaterne søges offentliggjort i internationalt anerkendte videnskabelige tidsskrifter.


Vi håber, at du med denne information har fået tilstrækkeligt indblik i, hvad det vil sige at deltage i forsøget, og at du føler dig rustet til at tage beslutningen om din eventuelle deltagelse. Vi beder dig også om at læse det vedlagte materiale “Forsøgspersonens rettigheder i et sundhedsvidenskabeligt forskningsprojekt”.
Hvis du vil vide mere om forsøget, er du meget velkommen til at kontakte undertegnede.

Med venlig hilsen

Line Lindhardt Egsgaard, Ph.d.

Center for Sanse-Motorisk Interaktion, Aalborg Universitet

Frederik Bajers Vej 7, E1-115, 9220 Aalborg Ø

Tlf.: 9940 9829, E-mail: egsgaard@hst.aau.dk

Forsøgspersonens rettigheder i et sundhedsvidenskabeligt forskningsprojekt

Som deltager i et sundhedsvidenskabeligt forskningsprojekt skal du vide at:

- din deltagelse i forskningsprojektet er helt frivillig og kan kun ske efter, at du har fået både skriftlig og mundtlig information om forskningsprojektet og underskrevet samtykkeerklæringen
- du til enhver tid mundtligt, skriftligt eller ved anden klar tilkendegivelse kan trække dit samtykke til deltagelse tilbage og udtræde af forskningsprojektet. Såfremt du trækker dit samtykke tilbage påvirker dette ikke din ret til nuværende eller fremtidig behandling eller andre rettigheder, som du måtte have
- du har ret til at tage et familiemedlem, en ven eller en bekendt med til informationssamtalen
- du har ret til betænkningstid, før du underskriver samtykkeerklæringen
- oplysninger om dine helbredsvforhold, øvrige rent private forhold og andre fortrolige oplysninger om dig, som fremkommer i forbindelse med forskningsprojektet, er omfattet af tavshedspligt
- opbevaring af oplysninger om dig, herunder oplysninger i dine blodprøver og væv, sker efter reglerne i lov om behandling af personoplysninger og sundhedsloven
- der er mulighed for at få aktindsigt i forsøgsprotokoller efter offentlighedslovens bestemmelser. Det vil sige, at du kan få adgang til at se alle papirer vedrørende din deltagelse i forsøget, bortset fra de dele, som indeholder forretningshemmeligheder eller fortrolige oplysninger om andre
- der er mulighed for at klage og få erstatning efter reglerne i lov om klage- og erstatningsadgang inden for sundhedsvæsenet

(Dette tillæg udgives af det videnskabsetiske komitésystem og kan vedhæftes den skriftlige information om det sundhedsvidenskabelige forskningsprojekt. Spørgsmål til et projekt skal rettes til den regionale komité, som har godkendt projektet)
Appendix 2 Participant Recruitment Notice

Titel: Åndring af smertemekanismer hos unge piger med rygsmmerter

Vi søger kvindelige forsøgspersoner i alderen 15-19 år.

Du kan være med, hvis du er sund og rask eller hvis du har lænderygsmmerter.

På Aalborg Universitet er vi interesserede i unge med lænderygsmmerter, fordi vi gerne vil forstå, hvordan smertene udvikler sig og forsøge at finde de bedste mulige måder til at undersøge og evt. behandle lænderygsmmerter.

Forsøget har derfor til formål at undersøge smertemekanismer i unge kvinder med og uden lænderygsmmerter for at kunne klargøre årsager og risikofaktorer til lænderygsmmerter hos unge kvinder. Målet er, at kunne forebygge at smertene bliver kroniske senere i livet.

Vi vil måle, hvordan du reagerer på forskellige smertestimuli samt måle kurven af din rygsojle og muskelstivhed af dine rygmusklar.

Du modtager ikke kompensation for din deltagelse i forsøget.

Forsøget er godkendt af Den Videnskabsetiske Komité for Region Nordjylland, sagsnummer N- 20140082

Er du interesseret, så ring eller skriv til:

Line Lindhardt Egsgaard
Center for Sanse-Motorisk Interaktion
Aalborg Universitet
Frederik Bajers Vej 7D3
9220 Aalborg Ø

Tlf.: 9940 9829
E-mail: egsgaard@hst.aau.dk
## Appendix 3 – Case Report Form

### Studiespecifik side

<table>
<thead>
<tr>
<th>Tidsintervaller</th>
<th>Filnavn (Subject number)</th>
<th>Værdier</th>
<th>Enheder</th>
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<tr>
<td><strong>Digital body schema</strong></td>
<td>0-5 min</td>
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<td></td>
</tr>
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<td><strong>Optegning af punkter</strong></td>
<td>5-10 min</td>
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**MyotonPRO**

- **M1 (T12/L1 venstre)**
  - 15-30 min
  - 
  - 
  - 
  - 
  - 
  - 

- **M2 (L4/L5 venstre)**
  - 
  - 
  - 
  - 
  - 
  - 

- **M3 (Glut med venstre)**
  - 
  - 
  - 
  - 
  - 
  - 

- **M4 (T12/L1 højre)**
  - 
  - 
  - 
  - 
  - 
  - 

- **M5 (L4/L5 højre)**
  - 
  - 
  - 
  - 
  - 
  - 

---

Appendix 3 – Case Report Form

Subject Number:_______

Alder________

Vægt________

Højde________

Smerter__________

Fysisk aktivitet________
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<table>
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<table>
<thead>
<tr>
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<td></td>
</tr>
<tr>
<td>Tryk-algometer – Kgf</td>
<td>15 min</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>1 (T12/L1 venstre)</td>
<td>______</td>
<td></td>
</tr>
<tr>
<td>2 (L4/L5 venstre)</td>
<td>______</td>
<td></td>
</tr>
<tr>
<td>3 (Glut med venstre)</td>
<td>______</td>
<td></td>
</tr>
<tr>
<td>4 (T12/L1 højre)</td>
<td>______</td>
<td></td>
</tr>
<tr>
<td>5 (L4/L5 højre)</td>
<td>______</td>
<td></td>
</tr>
<tr>
<td>6 (Glut med højre)</td>
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<td>7 (Arm)</td>
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ID nummer:_____

Cuff algometer – enkelt cuff

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<td>PDT</td>
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<tr>
<td>PTT</td>
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<tr>
<td>VAS ved slutmål</td>
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Cuff algometer - repetitive

<table>
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<tr>
<td>#2.: #7.:</td>
</tr>
<tr>
<td>#3.: #8.:</td>
</tr>
<tr>
<td>#4.: #9.:</td>
</tr>
<tr>
<td>#5.: #10.:</td>
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Cuff algometer – CPM

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<td></td>
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<tr>
<td>PTT</td>
<td></td>
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<tr>
<td>VAS ved slutmål</td>
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</table>
Appendix 4 – Ethics Protocol

FORSØGSPROTOKOL

Projekttitel
Ændringer i smertemekanismer hos unge piger mellem 15-19 år med kroniske uspecifikke lænderygsmorerer

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Katherine Anne McGirr, Fysioterapeut, Stud. M.Sc., Klinisk Videnskab og Teknologi
Institut for Medicin og Sundhedsteknologi, Aalborg Universitet

Stine Ibsen Harring, Fysioterapeut, Stud. M.Sc., Klinisk Videnskab og Teknologi
Institut for Medicin og Sundhedsteknologi, Aalborg Universitet

Fridel Laursen, Fysioterapeut, Stud. M.Sc., Klinisk Videnskab og Teknologi
Institut for Medicin og Sundhedsteknologi, Aalborg Universitet
Experimental Protocol

Background

Back pain is common in adolescents. Studies show that up to 86% of adolescents experience back pain and that 35-45% of adolescents develop chronic lower back pain (LBP). Additionally, chronic non-specific pain is more prevalent in girls than in boys (54% versus 34%) (Hoftun, Romundstad et al. 2012). LBP that starts early in life has a tendency towards pain becoming worse up until the age of 18 where the pain begins to develop into pain patterns typically seen in adults. Research shows that there are many factors involved in the development of LBP in adolescents (Aartun, Jan Hartvigsen et al. 2014). Psychosocial factors like stress, anxiety and depression have been shown to have an impact on pain. Girls showing symptoms of anxiety and depression have an increased risk of developing chronic pain (increasing from 48% to 81%) (Hoftun, Romundstad et al. 2012).

Quality of life for adolescents with LBP is also negatively impacted, and many adolescents exercise less because of LBP (Hartvigsen, Natvig et al. 2013) which may increase the risk of the development of life style illnesses like diabetes, arthritis and heart problems later in life. On a global scale, LBP is the most common reason for years lived with disability and is the primary reason for sick days and early retirement in the adult population. It is estimated that approximately 632 million people in the world suffer from LBP (Hartvigsen, Natvig et al. 2013). Therefore, it is important to understand the reasons and risk factors for development of LBP in adolescents, enabling early treatment and prevention.

One of the risk factors for development of LBP may be multisite pain. It has been shown that the risk of chronification is increased six-fold for individuals with multisite pain (Hartvigsen, Natvig et al. 2013). Studies show that individuals with LBP typically experience multisite pain and that individuals with multisite pain have a worse prognosis than individuals with localized pain. A Danish study reported a prevalence of 33% for adolescents with multisite pain (Rathleff, Roos et al. 2013). Additionally, it has been shown that 46% of individuals with multisite pain do not report changes in pain patterns after 14 years (Hartvigsen, Natvig et al. 2013).

Strategy for Literature Search

Background research of the project was found among publically available and Aalborg University’s access to peer-reviewed articles. A systematic and structured literature search of relevant databases within PubMed gives over 28,000 research articles for ‘lower back pain.’ However, when ‘lower back pain’ and ‘adolescent’ are used as MESH terms, this number drops to 3600. Further, ‘lower back pain’ and ‘adolescent’ and ‘non-specific’ give 98 and adding ‘chronic’ gives 34 research articles. Few of these MESH searches provide information regarding quantification of pain and identification of risk factors. This project will fill a gap in our current knowledge and identify possible risk factors to prevent the development of chronic non-specific lower back pain in adolescents.
- **Purpose**

The prevalence of LBP is higher in females (Hoftun, Romundstad et al. 2012) therefore the purpose of this study is to investigate pain mechanisms, risk factors, psychosocial aspects and the impact of multisite pain on LBP in an adolescent female population.

- **Subjects**

Participants will be recruited from schools in North Jutland area. The Headmaster from each school will be contacted by telephone to discuss the possibility of recruiting participants from the student population. With the agreement of the Headmaster the study will be presented at the school, where the students will have the opportunity to contact us if they are interested in participating... Students who are interested in participating in the study will receive written information (Deltagerinformation_v1.1_27102014) to take home. Students that are not of legal age will be requested to give the written information to their parents or guardians to read. Thereafter, a meeting in person or by telephone will be arranged in order to give oral information. The students and their parents will have at least 24 hours of deliberation time, before giving written informed consent. Social media, such as Facebook and forsoegsperson.dk, will also be used for recruitment purposes, where the approved recruitment notice will be posted (see Opslag_v1_27102014).

- **Inclusion and Exclusion Criteria**

All participants will be screened using the inclusion and exclusion criteria as shown in the tables below. Written informed consent will be obtained prior to inclusion in the study.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged 15-19</td>
<td>Recurring pain syndromes within the last 3 months</td>
</tr>
<tr>
<td>Female</td>
<td>Pain in the lower back, pelvis or legs within the last week</td>
</tr>
<tr>
<td>BMI between 18.5-29.9</td>
<td>Neurological disorders</td>
</tr>
<tr>
<td>Healthy</td>
<td>Musculoskeletal disorders</td>
</tr>
<tr>
<td>Fluent Danish reading, speaking and comprehension</td>
<td>Rheumatologic diseases</td>
</tr>
<tr>
<td></td>
<td>Psychiatric disorders</td>
</tr>
<tr>
<td></td>
<td>Consumption of primary and secondary analgesics within 24 hours</td>
</tr>
<tr>
<td></td>
<td>Consumption of alcohol within 24 hours</td>
</tr>
<tr>
<td></td>
<td>Increase or decrease in intensity of training activities within the last 72 hours</td>
</tr>
<tr>
<td></td>
<td>Present or previous substance abuse</td>
</tr>
<tr>
<td></td>
<td>Pregnant</td>
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### LBP group

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aged 15-19</td>
<td>• Neurological disorders</td>
</tr>
<tr>
<td>• Female</td>
<td>• Psychiatric disorders</td>
</tr>
<tr>
<td>• BMI between 18.5-29.9</td>
<td>• Rheumatologic diseases</td>
</tr>
<tr>
<td>• Recurring pain in the lower back within the last 3 months</td>
<td>• Consumption of primary and secondary analgesics within 24 hours</td>
</tr>
<tr>
<td>• Fluent Danish reading, speaking and comprehension</td>
<td>• Increase or decrease in intensity of training activities within the last 72 hours</td>
</tr>
<tr>
<td></td>
<td>• Consumption of alcohol within 24 hours</td>
</tr>
<tr>
<td></td>
<td>• Present or previous substance abuse</td>
</tr>
<tr>
<td></td>
<td>• Pregnant</td>
</tr>
</tbody>
</table>

#### Design and Methods

The subjects are to take part in one experimental session lasting approx. 1 hour. The experimental session will take place at the institution where the participant attends school, in order to lessen the travel burden (time/cost) and facilitate participation. In the event that this is not possible, the experimental session will take place at Aalborg University.

The below is a description of the effect parameters, assessment tools, test procedures and statistical methods. Effect parameters are divided into four main areas:

1. Psychosocial factors
2. Pain perception
3. Muscle tonus
4. Posture

#### Psychosocial Factors

**Demographic Data**

Data regarding the participants’ age, height, weight, physical activity, menstruation cycle, medicine, duration of back pain will be recorded. The questionnaire can be found in Appendix A.

**EQ-5D**

This questionnaire measures health-related quality of life based on the participants’ own evaluation. It consists of 5 questions from which an index for the quality of life can be obtained. The index can be used to compare the participant with other participants with or without pain. This questionnaire has been defined by Danske Fysioterapeuter as suitable for clinical research, and no previous experience is required to evaluate the data. The
questionnaire takes approximately 5 minutes to complete. The questionnaire has been translated from English to Danish and has been validated and found reliable. (Wesselhoff 2013) EQ-5D will be used to find possible links between self-reported health-related quality of life and LBP. The questionnaire can be found in Appendix B (Appendix B_v1_27102014).

Pain Catastrophizing Scale (PCS)
Pain catastrophizing is an important cognitive factor that can have influence on the participants’ pain perception. (Sullivan, Bishop et al. 1995) The Pain Catastrophizing Scale is originally an English questionnaire, which has been translated to Danish. This questionnaire will be used to measure risk factors for developing chronic pain. It is not a prerequisite that the participant needs to be in pain while completing the questionnaire. The three main sections are: helplessness, magnification and rumination (Vase, Nikolajsen et al. 2010). The questionnaire can be found in Appendix C (Appendix C_v1_27102014).

DASS21
A self-reported questionnaire designed to measure the severity of depression and anxiety and stress. LBP is commonly known to be associated with mood disorders such as depression which influence on pain intensity, physical and psychosocial disability, increased medication use, and increased likelihood of unemployment. This questionnaire will be used to investigate possible links between anxiety, depression, and pain mechanisms (Haggman, Maher et al. 2004). The questionnaire can be found in Appendix D (Appendix D_v1_27102014).

Pittsburgh Sleep Quality Index
The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep. It differentiates “poor” from “good” sleep by measuring seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction over the last month. The subject self-rates each of these seven areas of sleep. This questionnaire will be used to estimate the impact of sleep quality on pain mechanisms and psychosocial factors. The questionnaire can be found in Appendix E (Appendix E_v1_27102014).

Follow-up Questionnaires
- The questionnaires described above will be sent to all participants again one year after inclusion in the study in order to investigate possible changes and developments in their pain.

- Pain Perception
  Pressure Pain Thresholds (PPT)
  Equipment: Algometer Type II, Somedic AB, Sweden, with a 1cm² probe.

The participant’s pressure pain threshold (PPT) will be measured using a handheld pressure algometer while lying on an examination couch facing down. Pressure will be applied at a rate
of 30 kPa per second. The participant is given a stop button and is told to push the button as soon as the applied pressure becomes painful. When the button is pushed, the pressure is stopped and the pain pressure threshold is noted. Pain pressure threshold (PPT) is measured bilaterally in four locations on the lower back and one reference point on the shoulder. These locations are (see figure 1):

1. The muscle belly of m.deltoideus
2. 3cm lateral to the spinous processes of thoracic vertebrae 12 and lumbar vertebrae 1 (T12/L1)
3. 3cm lateral to the spinous processes of lumbar vertebrae 2 and 3 (L2/L3)
4. 3cm lateral to the spinous processes of lumbar vertebrae 4 and lumbar vertebrae 5 (L4/L5)
5. Muscle belly of m. gluteus medius.

PPTs will be measured three times for each location. The PPTs will be measured in randomized order. There will be a 30-second break between each measurement. The average of the three points will be used for statistical analysis.

![Figure 3: The five points for measuring PPT on the back. PPTs will be measured bilaterally.](image)

Central Pain Mechanisms

Equipment:

1. A double chambered pneumatic tourniquet cuff, with a length of 61cm and a width of 13cm. The cuff is produced by VBM Medizintechnik GmbH, Sulz, Germany.
2. A computerized air compressor produced by Condor MDR2, JUN-AIR International A/S, Nørresundby, DK, connected to an electric pneumatic converter (ITV2030, SMC Corp., Tokyo, Japan) which is controlled by a computer.

3. A 10cm long electronic visual analog scale.

The primary pain mechanisms to be investigated are Temporal Summation (TS) and Conditioned Pain Modulation (CPM). Each of the following three tests will be performed once.

1. Pain Tolerance Threshold: The cuff will be placed on the participant’s non-dominant lower leg. The cuff will be slowly inflated (1 kPa/second) until the pain tolerance threshold is reached (PTT). PTT is reached when the participant presses the stop button, or if the upper limit (maximum) for pressure is reached. The upper limit will be set to 100 kPa. The participant will be asked to evaluate the pain during the inflation on an electronic VAS scale and are instructed to push the stop button when the pain becomes intolerable.

2. Temporal summation: The cuff remains on the participant’s non-dominant leg and will then be inflated and deflated 10 times using the intensity found during the PTT measurement. Inflation and deflation each have a duration of 1 second (Inter Stimulus Interval: 1 second) and the total duration of the test is 20 seconds. The participant will evaluate the pain during the 10 inflations, and if the pain becomes unbearable, the participant can disconnect the test by pressing the stop button.

3. Conditioned pain modulation: A second cuff will be placed around the participant’s dominant arm, in addition to the cuff placed around the participant’s non-dominant leg. The cuff around the arm will be inflated to 60 kPa, which is the pre-set limit. If the participant cannot tolerate this pressure, the pressure will be reduced to 30 kPa. The first test is then repeated (see item 1 above) while the pressure stimulation on the arm is maintained. The participant will be asked to concentrate on the pressure applied to the leg and to try to ignore the pain in the arm. The participant will then evaluate the leg pain as per the first test. If the pain becomes unbearable, the participant will have the option to disconnect the test.

Digital Body Schema

Digital body schema is a computer application downloaded onto a Personal Computer Tablet (PCT, android operating system). It is an assessment tool currently used for research purposes in order to quantify areas in which a patient has pain.

The participants are requested to draw and fill in their pain on a 3D body schema of a female body. These areas will then be quantified offline according to area, circumference, centroid, shape, and location.

- Muscle Tonus

The muscle tonus will be measured with a myotonometer. A myotonometer measurement device contains a linear array of transducers that measure: 1) the amount of displacement of
a probe as it is pushed onto the skin overlying the tested muscle and 2) the amount of force required per millimeter of tissue displacement. The myotonometer measurements are very sensitive to small changes in muscle tonus. Myoton measures will be made over muscles on the back and abdomen (see figure 2). The myoton measurements will be measured once in each location in randomized order.

The locations on the back are:

1. The muscle belly of m.deltoides
2. 3cm lateral to the spinous processes of thoracic vertebrae 12 and lumbar vertebrae 1 (T12/L1)
3. 3cm lateral to the spinous processes of lumbar vertebrae 2 and 3 (L2/L3)
4. 3cm lateral to the spinous processes of lumbar vertebrae 4 and lumbar vertebrae 5 (L4/L5)
5. Muscle belly of m. gluteus medius.
6. 3 cm lateral to the origin of the lower part of m. trapezius
7. The muscle belly of infraspinatus
8. 3cm lateral to the C7 vertebrae on the upper part of m. trapezius

The locations on the front are:

1. 2cm medial to anterior superior iliac spine (ASIS)
2. 8-10cm lateral to the midline of the waist
3. The lower part of m. rectus abdominis
4. The upper part of m. rectus abdominis

Figure 4: LEFT: the 8 points for myoton measurement on the back. RIGHT: the locations of myoton measurements on the front. All measurements are performed bilaterally.
Posture

Posture of the spine will be measured using two different methods to estimate the spinal curvature and spinal rotation. The length of the spine will also be measured using a standard measuring tape.

Spinal Curvature

Equipment: Standard goniometer

The spinal curvature can be measured with a standard goniometer. Spinal curvature is measured while the test subject is standing erect facing directly forward, feet pointed forward and slightly apart, and arms hanging down at the sides. A goniometer is an instrument that measures an angle or a range of motion. A goniometer consists of two arms and it is the angle between these two arms which is measured. The arms can be placed on the spine to measure the spinal curvature. There are four natural variations in spinal posture (see table 1). The spinal posture will be measured by goniometer assessment in four locations as described in Table 1. All measurements in Table 1 will be measured once for each test subject.

<table>
<thead>
<tr>
<th>Spinal curvature</th>
<th>Normal range</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical Lordosis</td>
<td>20 to 40 degrees</td>
<td>Between C2 and C7</td>
</tr>
<tr>
<td>Thoracic Kyphosis</td>
<td>20 to 40 degrees</td>
<td>Between T1 and T6, Between T7 and T12</td>
</tr>
<tr>
<td>Lumbar Lordosis</td>
<td>40 to 60 degrees</td>
<td>Between L1 and L5</td>
</tr>
<tr>
<td>Sacral Kyphosis</td>
<td>Sacrum fused in a kyphotic curve</td>
<td>Between S1 and S5</td>
</tr>
</tbody>
</table>

Table 8: Spinal curvature variations, normal ranges and measurement locations.

Spinal Rotation

Equipment: Incliniometer (scoliometer)

Distortions of the torso (rotation) can be measured with an inclinometer (scoliometer). The test subject is asked to bend over, with arms dangling and palms pressed together, until a curve can be observed in the thoracic area (the upper back). The scoliometer is placed on the back and used to measure the apex (the highest point) of the curve. The patient is then asked to continue bending until the curve in the lower back can be seen; the apex of this curve is then measured. The measurements are repeated twice, with the test subject returning to a standing position between repetitions.

Risks, Side Effects and Disadvantages

All the applied methods in this research proposal have previously been approved by The North Denmark Region Committee on Health Research Ethics and are well investigated. Cuff
and pressure algometry have been used in several other studies with no prolonged effects. The procedures will induce a short lasting pain, which will disappear within a short time period after the experiment has been completed. Further, bruises and soreness may arise following the measurements. However, this will disappear within a few days.

- **Statistics**
  The number of participants to be included in the study in order to produce the desired effect size has been calculated to be 46 per group and/or incomplete data taken into consideration, 50 adolescent females will be included in the back pain group and 50 adolescent females in the healthy control group. The two groups will be age matched.

  All data will be analyzed for their distributions properties. Paired t-tests (parametric or non-parametric where appropriate) will be used to identify differences in self-reported questionnaire data, pain perception, muscle tonus and posture between the two groups. Correlation analyses will be used to examine the relationship between psychosocial factors and pain perception measures. Follow-up analyses will be performed with a one way or two way repeated measures ANOVA (parametric or non-parametric where appropriate). The Bonferroni post hoc test will be used to correct for multiple comparisons. Significance will be accepted as P<0.05.

- **Ethical Considerations**
  All the applied methods in this research proposal have previously been approved by the regional ethical committee and are well investigated. Cuff and pressure algometry have been used in several other studies (e.g., Jespersen et al., 2006, O'Neill et al., 2006, Neziri et al., 2012, Rolke et al., 2006, Olesen et al., 2013, Rolke et al., 2005) with no prolonged effects. The procedures will induce a short lasting pain, which will disappear within a short time period after the experiment has been completed. Further, the procedures can leave bruises in the locations where they were applied which will disappear within a few days. Cuff algometry has several inbuilt safety mechanisms to ensure that the pressure applied does not induce lasting effects. The maximal amount of pressure is set to 100 kPa. The pressure is increased by 1 kPa per second, and therefore, the participant will not receive pressure for longer than a maximum of 100 seconds. The participant will be given a stop button which will release the pressure when pushed. The computer is also equipped with a safety button which enables the investigator to release the pressure in case of malfunction.
  The pain experienced by the participant is short-lived. Thus, the risks involved in this study are minimal compared to the potential benefits.

  Under normal circumstances, the healthy control group would often be offered compensation for their participation. However after due consideration, it has been decided that offering compensation to one group and not the other could create problems of “unfair treatment.” The participants are adolescents and will likely talk to each other about their experience of
participation in the study. Therefore, neither group will receive compensation for their participation.

The study population of this project includes minors. Lower back pain is a common problem in adolescents and most prevalent in the female population as previously described in the Background section. Further, present lower back pain increases in severity until the age of 18. Using female minors is therefore a necessity to investigate the development and risk factors of lower back pain. Minors are unable to provide full consent themselves and therefore the responsibility for consent for participation of minors (15-17 years old) in this study is vested in parents or guardians. For minors, informed consent will be obtained (S5) from both parents or guardians, prior to study participation, where both parents or guardians have legal custody. Alternatively, one parent or guardian may authorize the other parent or guardian to give informed consent on their behalf. Single parents or guardians with full legal custody may give informed consent, without the involvement of a parent without legal custody. In the event that a minor becomes of legal age, a new informed consent (S1) will be obtained. Further, the parents or guardians are encouraged to accompany the participant during study participation. The study will be conducted in accordance with national regulations and the Helsinki Declaration.

After oral information is given, the participants, and the parents or guardians of those participant not of legal age, will have a deliberation time of at least 24 hours prior to giving informed consent. A written consent form will be obtained from all participants prior to participation. Data will not be collected before informed consent has been obtained. This includes the questionnaire in appendix A.

The investigator will ensure that participants will be anonymized by way of ID number coding and data will be stored in a locked room.

- **Significance/Justification for the Study**
  
  This research proposal is justified by two main factors. Firstly, there is a need for better tools for diagnosing chronic pain, and the risk factors for developing chronic pain. Secondly, more and more focus has been placed on Quantitative Sensory Testing (QST) in order to meet this need. This research proposal utilizes several reliable QST methods; cuff algometry, pain pressure algometry, myoton for investigation of muscle tone, and a digital body schema in order to quantify painful areas. Some of these methods are new and research is necessary to investigate their potential contribution to the understanding of chronic pain.

  This study will generate a broad spectrum of data that are expected to make a significant contribution to the understanding of the development of chronic non-specific low back pain in female adolescents, which currently is poorly understood.

  The possible risks involved in this study are minimal compared to the potential benefits to the general and clinical population. The expected results are considered to have an impact on future research regarding the study of female adolescent LBP and may contribute to better diagnosis and treatment.
• **Risk/benefit Assessment**
If it becomes evident at inclusion or during the study that the subject meets some of the exclusion criteria or suffers from known physiological/psychiatric disorders, which might require medical attention, the data collection for the respective subject is terminated. Furthermore, the subject will be encouraged to seek medical attention.

• **Expected and Unexpected Side Effects from the Study**
All serious side effects (expected and unexpected) will be reported to The North Denmark Region Committee on Health Research Ethics by the study responsible person. The study responsible and the project group have extensive experience in working with people with problems related to the musculoskeletal system and are considered qualified to make decisions regarding management of any side effects resulting from the study.

• **Insurance**
The subjects are covered by the Danish Patient Compensation Association (Patient-erstatningen).

• **Placebo/Control Treatment**
  • This research project does not contain any treatments; however, a control group is included for comparison.

• **Personal Data**
Data will be stored after termination of the project. These data can only be used for the interpretation of this project and will therefore not be of interest to third party.

Data are stored in accordance with the stipulations in The Danish Personal Data Protection Act (Persondataloven) and other relevant Danish legislation.

The project is not reported to The Danish Data Protection Agency cf “Bekendtgørelse om ændring af bekendtgørelse om undtagelse fra pligten til anmeldelse af visse behandlinger, som foretages for en privat dataansvarlig”.

• **Project Economy**
The project has been initiated by Assistant Professor Line Lindhardt Egsgaard, Center for Sensory-Motor Interaction, Aalborg University.
The project is financed by Center of Sensory-Motor Interaction with DKK 10,000. Applications for additional financial support have been submitted to Siemens Fonden and Danske Fysioterapeuter.
The researchers are independent of third-party interests.
• 

**Compensation to Subjects**
The subjects will not receive compensation for their participation in the study (see Ethical Considerations for justification).

•  

**Publishing of Results**
The results of the study, be they positive, negative or inconclusive, will be published in international peer reviewed journals. Further, it is intended that the results will be published in Danish journals for health care professionals as well (e.g., Ugeskrift for Læger, Forskning i Fysioterapi, Sypeplejersken) to ensure exposure of the results to health care professionals working within the area.

•  

**Time Schedule**
This research project will be initiated the 2\textsuperscript{nd} of February 2015 and completed in December 2017.
Guidelines for Oral Information and Informed Consent

Summoning Potential Subjects

When potential subjects address the contact person, the following should be stated:

- Oral information is given to participants of legal age and the parents of participants who are not of legal age, either in person, or in the event that this is not possible, by telephone.
- That it is a request for participation in a scientific research project
- The purpose of the project
- That participation is voluntary and that the subject can withdraw from the project at any time without consequences
- That the potential subject has time to consider her participation before giving consent to participation in the project
- That potential subjects aged 18-19 are recommended to bring a family member or a friend to the information meeting. Potential subjects aged 15-17 are to bring one of their parents.
- The potential volunteer will receive the leaflet “The Rights of a Trial Subject in a Health Scientific Research Project”/ "Forsøgspersonens rettigheder i et sundhedsvidenskabeligt forskningsprojekt" which includes information on confidentiality, right of access to documents and right to complain.
- That the material “Information for Participants”/”Deltagerinformation” will be forwarded by mail/e-mail to the potential subject in order for him/her to know more about the project before the information meeting.
- Finally, time for the information meeting is arranged

The Information Meeting

The information meeting is held in a quiet room where it is possible to have an uninterrupted conversation. Coffee/tea/soft drink may be served. The information meeting is held by the person responsible for the project or a senior researcher who has been authorized to do the information.

The meeting is to include the following information/questions:

- Participation is voluntary and the subject can withdraw from the project at any time without consequences
- The subject has time to consider her participation before giving consent to participation in the project. The purpose of the experiment is presented, and it is explained how the experiment is performed. The “Information for Participants”/”Deltagerinformation”, which has been sent to the potential subject in advance, is the starting point for the information meeting.
- The subject is asked if she is healthy or whether he/she has an infectious disease.
• The leaflet “The Rights of a Trial Subject in a Health Scientific Research Project”/"Forsøgspersonens rettigheder i et sundhedsvidenskabeligt forskningsprojekt” is handed over. It is explained that it includes information on confidentiality, right of access to documents and right to complain.

• The subject is asked whether she has read “Information for Participants”/"Deltagerinformation”. If this is not the case, we will ask the subject to read it.

• When it has been ensured that the subject has read the “Information for Participants”/"Deltagerinformation”, she is asked whether he/she has questions about the experiment.

• After this a demonstration is given in the lab; measuring equipment and its use is presented to the subject.

• It is underlined that participation is voluntary, and that the subject has time to consider her participation (please note that The National Committee on Health Research Ethics recommends 24 hours of deliberation time)

• Again it is underlined that participation is voluntary and that the subject can withdraw her consent at any time without consequences.

• The subject is informed that if she does not need time to consider the participation, the consent can be given at the information meeting (either by the subject herself (age 18-19) or by one of the parents (age 15-17).

• Time/place for the experiment is agreed.

• Finally, information about the contact person of the experiment is given (it is shown to the subject that the name and contact details appear from the “Information for Participants”/"Deltagerinformation”) and it is informed that this person can be contacted at any time if further questions should arise.
List of References


Appendix 5 – Informed Consent – 15-17 year olds

Deltagere 15-17 år

(S5)

Samtykke fra forældremyndighedens indehaver til deres barns deltagelse i et sundhedsvidenskabeligt forskningsprojekt.

Forskningsprojektets titel:
Ændringer i smertemekanismer hos unge piger mellem 15-19 år med kroniske uspecifikke lænderygsmerter

Erklæring fra indehaveren af forældremyndigheden:

Jeg/vi har fået skriftlig og mundtlig information og jeg/vi ved nok om formål, metode, fordele og ulemper til at give mit/vores samtykke.

Jeg/vi ved, at det er frivilligt at deltage, og at jeg/vi altid kan trække mit/vores samtykke tilbage uden, at min/vores datter/søn mister sine nuværende eller fremtidige rettigheder til behandling.

Jeg/vi giver samtykke til, at _____________________________________________ (barnets navn) deltager i forskningsprojektet. Jeg/vi har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Navnet eller navnene på forældremyndighedens indehaver(e):

Dato: _______________ Underskrift: _______________________________________

Dato: _______________ Underskrift: _______________________________________

Ønsker du/I at blive informeret om forskningsprojektets resultat samt eventuelle konsekvenser for dit/jeres barn?:

Ja _____ (sæt x)   Nej _____ (sæt x)

Erklæring fra den, der afgiver information:

Jeg erklærer, at forældrene/barnet har modtaget mundtlig og skriftlig information om forsøget.
Efter min overbevisning er der givet tilstrækkelig information til, at forældrene kan træffe beslutning om barnets deltagelse i forsøget.

Navnet på den, der har afgivet information:

Dato: _______________ Underskrift: ______________________________________

Projektidentifikation: (Fx komiteens Projekt-ID, EudraCT nr., versions nr./dato eller lign.)

N - 20140082

Appendix 6 – Informed Consent 18-19 year olds

Deltagere 18-19 år

(S1)

Informert samtykke til deltagelse i et sundhedsvidenskabeligt forskningsprojekt.

Forskningsprojektets titel: Ændringer i smertemekanismer hos unge piger mellem 15-19 år med kroniske uspecifikke lænderygsmørter

Erklæring fra forsøgspersonen:
Jeg har fået skriftlig og mundtlig information og jeg ved nok om formål, metode, fordele og ulemper til at sige ja til at deltage.

Jeg ved, at det er frivilligt at deltage, og at jeg altid kan trække mit samtykke tilbage uden at miste mine nuværende eller fremtidige rettigheder til behandling.

Jeg giver samtykke til, at deltage i forskningsprojektet og har fået en kopi af dette samtykkeark samt en kopi af den skriftlige information om projektet til eget brug.

Forsøgspersonens navn: ________________________________________________________

Dato: _______________  Underskrift: ___________________________________________

Ønsker du at blive informeret om forskningsprojektets resultat samt eventuelle konsekvenser for dig?:

Ja _____ (sæt x)  Nej _____ (sæt x)

Erklæring fra den, der afgiver information:
Jeg erklærer, at forsøgspersonen har modtaget mundtlig og skriftlig information om forsøget.

Efter min overbevisning er der givet tilstrækkelig information til, at der kan træffes beslutning om deltagelse i forsøget.

Navnet på den, der har afgivet information:
Dato: _______________ Underskrift: ________________________________

Projektidentifikation: (Fx komiteens Projekt-ID, EudraCT nr., versions nr./dato eller lign.)

N - 20140082