CHAPTER 2

Literature Review

This chapter explores the literature on headaches and the implications of age related to change as a foundation for understanding the potential contributions of the cervical musculoskeletal and sensory functions to headache in the elderly. The chapter focuses on changes in the nature of headache as well as changes in the musculoskeletal and sensory system functions with age. The pathophysiology of headache and classification and diagnostic criteria for headache is also discussed. It has been suggested that individuals with headache have dysfunctions of the cervical musculoskeletal and sensory systems; however, these associated dysfunctions may be influenced by age. Thus, this chapter specifically discusses the differences in the cervical musculoskeletal and sensory dysfunctions between younger and older populations with headache. As well, the management of headache was considered. This chapter lays the basis for the hypotheses in this study.

2.1 Headache and the musculoskeletal and sensory systems in the elderly

2.1.1 The prevalence of headache in the elderly

Headache is a common pain symptom in the elderly population. It is more prevalent in women than men (17). Evidence suggests that the prevalence of primary headache (migraine and tension-type headache) declines with increasing age (19, 20), whereas that of secondary headache (cervicogenic headache) increases (21). The onset of migraine and tension-type headache often occurs before the age of 45 and is unusual to occur in persons aged over 65 years. The 1-year prevalence of migraine and tension-type headache reaches a peak in the third and fourth decade of life (19, 22). Estimated prevalence of migraine and tension-type headache in individuals aged $\geq$ 65 years is

3.0%-11% and 33.1%-45%, respectively (17, 23, 24). In Thailand, the reported prevalence of migraine and tension-type headache in Thai elders is 2.9% and 18.3%, respectively (24). The decrease in the prevalence of primary headache in the elderly remains uncertain. However, it has been proposed that it may be associated with changes in structure and function of cerebral blood vessels and decreased work-related factor such as stress (17, 25).

Cervicogenic headache has been suggested to be associated with degenerative changes in the cervical spine and a common of frequent intermittent headache in the otherwise healthy over fifty populations (26, 27). It is thought that 30%-50% of intermittent headaches in the elderly are cervicogenic in origin (26). Lisotto et al (21) reported that the most frequent secondary headache in patients over 65 years of age was headache associated with the cervical spine (50%). Approximately 24% of those cases were diagnosed as cervicogenic headache. Shah and Nafee (28) estimated that the mean age of onset of cervicogenic headache was 62.5 years, which was far later than that of migraine and tension-type headache (17 and 26 years, respectively). In a study conducted by Haldeman and Dagenais (29), the mean age at onset of cervicogenic headache was estimated at 42.9 years.

Furthermore, chronic daily headache (headache $\geq$ 15 per/month and for > 3 months) is likely to be common in the elderly population. The prevalence of chronic daily headache in this age population ranges from 3.9-4.4% (17, 30). Chronic daily headache (CDH) can be subdivided according to the Silberstein and Lipton (S-L) criteria into chronic or transformed migraine (CM/TM), chronic tension-type headache (CTTH), new daily persistent headache (NDPH) and hemicrania continua (31).

2.1.2 Changes in headache characteristics with age

There is evidence suggesting that headache characteristics in particular those of migraine change in older persons. For example, the migraine attacks are often less than 12 hours in duration (2) and lesser intensity (32, 33). However, the frequency of migraine attacks has been reported to be either unchanged (2) or less frequent with age (33). The location of headache is often bilateral and global rather than unilateral (1) and involves the occipital neck area (1, 2, 32). The throbbing quality of pain (1) and

associated symptoms such as vomiting, photophobia and phonophobia are also reported to be less frequent in older persons (1, 2). Additionally, headache is often triggered by neck pain (1).

There is a small number of studies on the changes in characteristics of tension-type headache with age. Clinical features of tension-type headache seem to change with increasing age. There is evidence reporting an increase in headache frequency and duration, as well as frequency of nausea with age (34). It has also been speculated that location of pain is older age than those with constant location (34). In other words, older age with tension-type headache often have diffuse head pain. It has been thought that the presence of primary headache (migraine and tension-type headache) in older persons is associated with neck injury and cervical osteoarthritis (3, 35, 36).

2.1.3 Changes in musculoskeletal system with age

2.1.3.1 Changes in the muscular system

Changes in the neuro-muscular system occur with increasing age. There is a reduction in the number and total size of fast twitch fiber (type II) and a reduction in the number of slow twitch fiber (type I) with age (37, 38). The size of type I fibers is suggested to be less affected by age (9). It has been reported that a decrease in muscle fibers begins at approximately 50 years of age (39). A reduction in both the number and size of muscle fibers leads to a decline in muscle mass and cross-sectional area (CSA) (37, 38). The loss of muscle mass is estimated at a rate of 1-2% per year beyond the age of 50 years (40) and is generally replaced by fat mass (41). Lexell et al (37) investigated a relationship of CSA and muscle fibers and showed that a reduction of muscle CSA in older people was influenced by decrease in total number of muscle fibers, especially type II fibers (37, 38). A decrease in CSA was also found to be related to a reduction in type II muscle fiber size (38). It has been suggested that the CSA of the vastus lateralis decreases by about 40% between ages 20 and 80 years (42). In addition, Kent-Braun et al (41) demonstrated a more than twofold increase in noncontractile contents of locomotor muscle in older adults (65-83 years old) compared to younger subjects (26-44 years old), suggesting that intramuscular fat score accumulates with age.

There is evidence that gender has an effect on a reduction of muscle fibers and muscle mass (43, 44). A rate of decline of type I and II fibers is greater in women than men (type I in men = 15%, in women = 45% and type II in men = 19%, in women = 25%) (43). Janssen et al (44) also reported that men had more total muscle mass than women.

The changes in the muscle fibers with age have been well documented to contribute to a decline in muscle strength, power, endurance and function (9, 45-47). Changes in muscle strength and power with age seem to be in excess of muscle mass loss by about 2-5 fold (9). Muscle strength begins to decline after the age of 50 and at a rate of 12-15% per decade (48). Beyond 60 years, muscle strength declines with an accelerated pace. The decline in muscle strength is not functionally significant until the sixth decade of life (48, 49). A study has shown that the maximal isometric torque for the knee extensors decreases at an average of 20-40% in the seventh and eighth decades (50, 51). Frontera et al (45) demonstrated that older persons (65-78 years) had decrease in strength of both knee extensor and flexor muscles (20% and 22% in men, respectively and 17.6% and 15.5% in women, respectively), compared to younger age (45-54 years). Muscle power begins to decline in the third and fourth decade of life (46, 52) and the decline is found to be more rapidly than muscle strength at a rate of 3-4% per year (a decline in muscle strength = 1-2% per year) (47, 53). There is also evidence of reduction in muscle endurance with age (52, 54). Lindstrom et al (54) investigated the endurance of knee extensor muscle between younger persons (22-34 years) and older persons (70-76 years) and found significantly lower muscle endurance in older persons.

2.1.3.2 Changes in the articular system

Changes also occur in the articular system with age. It has been suggested that cervical range of motion gradually decreases with increasing age, particularly after 30 years (55). Decrease in range of cervical motion is found in all directions approximately 4-5 degrees per decade (56, 57) but it is more pronounced in extension and lateral flexion (58, 59). Youdas et al (60) demonstrated that range of cervical extension in individuals aged 60 years was 20 degrees less than that in healthy persons aged 20 years. Kuhlman (61) reported that range of cervical motion in the elderly (aged 70-90 years) was less than that in younger individuals (aged 20-30 years)

(12% in flexion, 32% in extension, 22% in lateral flexion and 25% in rotation). However, Dvorak et al (55) and Castro (62) demonstrated that rotation of the C1-2 segment did not decrease with age but rather increased slightly to compensate for the reduced range of cervical motion in the lower segments. The effect of gender on cervical range of motion is found to be weak (55, 63). Dvorak et al (55) showed no significant difference in range of cervical motion in all directions between males and females (aged over 60 years). This is also supported by a study of Hole et al (63), which found no effect of gender on range of cervical motion in individuals aged between 20-69 years.

2.1.4 Changes in the sensory system with age

2.1.4.1 Changes in peripheral and central nervous systems

There is evidence for structural and functional changes in the peripheral and central nervous systems with advancing age. It has been suggested that such changes in the nervous system with age can alter perception of pain in the elderly (64, 65). Changes to the peripheral nervous system include loss of myelinated and unmyelinated fibers which a greater changes in myelinated fibers (66, 67), increased axon degeneration, reduced releasing of neurotransmitters and reduction in pain transmission input (66, 68, 69). Changes to the central nervous system include widespread degeneration in the spinal dorsal horn (loss of myeline and axon degeneration) (70) and reduced neurotransmitter (e.g. substance P, calcitonin gene-related peptide (CGRP), β endorphin, gamma amino butyric acid (GABA), catecholamines, serotonin) both in spinal dorsal horn and brain (thalamus, limbic system and cerebral cortex) (71, 72). Additionally, there are smaller proportions of gray matter in anterior cingulate cortex and primary somatosensory cortex (S1) and a deficit of endogenous pain modulation system in healthy older adults. Quiton et al (73) demonstrated age-related changes in cortical processing in responses to painful contact heat, using functional MRI (fMRI). Edwards et al (74, 75) investigated age-related difference in endogenous pain inhibition and demonstrated that older adults required a higher intensity of noxious stimulation in order to first report the presence of pain.

Moreover, older adults demonstrated facilitation rather than inhibition of thermal pain during concurrent noxious cold stimulation.

2.1.4.2 Changes in pain thresholds

Evidence suggests age-associated differences in pain response and pain processing (74, 75). However, the effects of age on pain sensitivity remain unclear and poorly understood. Pain threshold, the minimal amount of stimulus that is perceived as painful is a commonly used measure of pain sensitivity. In a review by Gibson (76), most studies support an increase in pain thresholds to noxious stimuli with advancing age, although decreased or unchanged pain thresholds have been reported in some studies. Increased pain thresholds are found to be more pronounced in females than males (65). Jensen et al (77) investigating age-related changes in pain perception using a pressure algometer in a general population and found that older adults had significantly increased pressure pain thresholds (PPTs) at the temporal muscles compared to healthy younger adults. Likewise, Marini et al (78) investigated age-associated difference in response to noxious stimuli and demonstrated that older subjects had higher pressure pain thresholds than younger persons over the head and neck muscles. There is also evidence of increased heat pain thresholds in older subjects compared to younger persons (65, 79). Lautenbacher and Strain (79) investigated heat pain thresholds over the thenar and the dorsum pedis in healthy person aged 17-63 years and found that pain thresholds were increased significantly with age over the foot but not in the hand, suggesting influence of the length of afferent pathway on the degree of age-related changes in thermal sensitivity. Decreased cold pain thresholds at the dorsal surface of the hand and foot have been also reported in older persons (79).

It has been suggested that suprathreshold response is more sensitive than thresholds to measure generalized increased pain sensitivity. Suprathreshold response is defined as ratings of painful stimulation above threshold (80). Harkins et al (81) assessed age-difference in pain rating to suprathreshold heat pain stimuli over the ventral forearm. The results demonstrated that pain ratings of intensity were lower at a peak temperature of 43°C, 45°C and 48°C, but higher at a peak temperature of 49°C and 51°C in older adults compared to younger controls. Harkins et al's findings are partly

supported by Edward et al's findings (82), which found higher pain ratings of intensity in response to suprathreshold noxious stimuli at a peak temperature of 47°C and 50°C in older adults compared to younger adults. These results may imply that there is the effect of age on suprathreshold response, although the evidence is still inconclusive.

2.2 Symptomatic overlap and pathophysiology of headaches

2.2.1 Symptomatic overlap of headaches

It is well documented that there is an overlap of the clinical features between migraine, tension-type headache and cervicogenic headache (83, 84). For example, pain in migraine is frequently accompanied by nausea, vomiting, sensitive to light and sound but these symptoms can occur in cervicogenic headache and tension-type headache (83). Neck pain is a prominent feature in cervicogenic headache but migraine and tension-type headaches can also present with neck pain (1, 4). The symptomatic overlaps between migraine, tension-type headache and cervicogenic headaches can be explained by convergence of trigeminal and upper cervical (C1-3) afferents within the second-order neurons in the trigeminocervical nucleus (Figure 2.1) (85). The trigeminocervical nucleus extends from the trigeminal nucleus caudalis to the segments of C2-3 (86). The neurons in the trigeminocervical nucleus that receive afferents from both trigeminal and upper cervical nerves mediate inputs to higher center without no determination of a source. Thus, cervical inputs can be interpreted as headache and trigeminal nerve can be interpreted as neck pain (87, 88). In addition, it has been suggested that sensitization of the second-neurons in the trigeminocervical complex is the basic mechanism which underlies the spread of pain and chronicfication of different headache types (89).

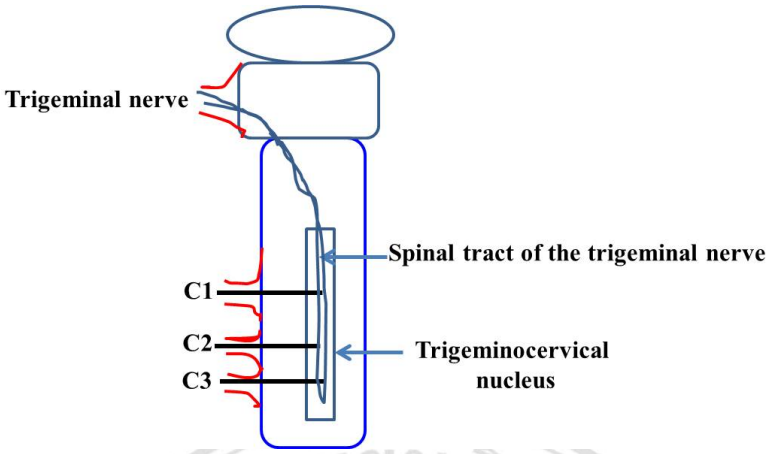

Figure 2.1 Trigeminocervical nucleus (modified from Bogduk, 2009)

2.2.2 Pathophysiology of headaches

Although there is the symptomatic overlap between migraine, tension-type headache and cervicogenic headache, differences in pathogenesis of these headaches have been argued. The pathophysiology of migraine is not well understood, however migraine is regarded as a neurovascular headache (90, 91). It is thought that migraine involves activation of the trigeminovascular pathway through peripheral intracranial nociceptors and central pain facilitation (90). The trigeminovascular system consists of trigeminal neurons (largely from the ophthalmic branch of the trigeminal nerve) and cranial vessels which are innervated by afferent fibers of the trigeminal nerve. Activation of nociceptive of the trigeminal nerve causes the releasing of vasoactive peptides (e.g. SP, CGRP and neurokinin A (NKA)) triggering a neurogenic inflammation characterized by vasodilation, plasma extravasation in meningeal (dural) and mast cell degranulation (90, 92). Then, transmits signals project through the trigeminal ganglion and synapses on the second-order neurons in the trigeminocervical nucleus and further relays to the thalamus and cortex resulting in pain (90). Additionally, abnormal neuronal excitability spreading throughout the cerebral cortex is called cortical spreading depression (CSD) as a result of aura in migraine patients triggering activation of trigeminal nerve, resulting in neurogenic inflammation that then further leads to pain (93). Also, it has been suggested that migraine may involve dysfunction of central modulation of pain. It is possible that the excitability of cerebral cortex might be involved in the modulation of migraine pain through cortico-trigeminal

pathways (94). Descending projections from the cerebral cortex to the spinal trigeminal nucleus can influence meningeal nociception through primary somatosensory (S1) mediated inhibition and insular-mediated facilitation of the excitability of the spinal trigeminal nucleus dura sensitive neurons (94, 95). Moreover, dysfunction of the ventrolateral periaqueductal gray (VlPAG) in the brainstem functions as a descending inhibition system (96), modulation of pain caused by a dysfunction of the descending inhibitory system projecting from the brainstem to the rostral ventromedial medulla (RVM) results in the facilitation of trigeminovascular pain transmission in the spinal and medullary dorsal horn in migraine pain (90). The exact underlying mechanism of tension-type headache is still poorly understood. However, most studies have suggested that tension-type headache is a muscular origin headache (97, 98). A pain model for tension-type headache can involve both peripheral and central sensitization (14, 99). Active myofascial trigger points (TrPs) in the muscles innervated by C1-C3 segments and the trigeminal nerve are suggestive of a possible source responsible for peripheral sensitization in tension-type headache (100). The peripheral nociceptive input from the myofascial tissues is transmitted to the second-neuron in the trigeminocervical nucleus and to higher centers. The peripheral myofascial input can also converge inputs from other afferent sources on the same neurons in the trigeminocervical nucleus complex, resulting in misinterpretation of the origin or source of pain (101). It is believed that prolonged or strong afferent barrage in the periphery (myofascial tissues) is responsible for central sensitization and transmits from episodic to chronic tension-type headache (89). Additionally, there is evidence suggesting that the pathogenesis of chronic tension-type headache may be due to dysfunctions of the endogenous central pain control system (102).

In relation to cervicogenic headache, it is well-documented that cervicogenic headache is a discrete headache that originates from the upper cervical spine (103). Pain is produced by stimulation of nociceptors in any structure which is innervated by the upper cervical nerve roots (C1-3). These include the vessels and dura mater of the posterior fossa, the deep paraspinal and suboccipital neck muscles, zygapophyseal joints, ligaments and intervertebral discs (29, 103). Nociceptive input originating from the cervical structures increases the excitability of the second order neurons in the trigeminocervical nucleus, where there is a convergence of the upper

cervical and trigeminal nerves. The afferent nociceptive input is mediated to higher centers and then perceived as headache and neck pain (29, 85, 103).

2.3 Classification of headache

The International Headache Society (IHS) criteria are universally used to identify all headache types including migraine and tension-type headache. However the IHS criteria are less used to classify cervicogenic headache (104) while the updated criteria proposed by Cervicogenic Headache International Study Group (CHISG) (Sjaastad et al., 1998) (105) are more widely accepted for use in classifying cervicogenic headache. The IHS and CHISG criteria for migraine, tension-type headache and cervicogenic headache are provided below.

2.3.1 Migraine

According to the updated IHS (2004) (104), migraine can be classified into two major subtypes: common migraine (migraine without aura, MWoA) and classic migraine (migraine with aura, MWA). The differential diagnosis criteria for migraine are present in Table 2.1.

Table 2.1 Diagnostic criteria for migraine (104)

Migraine without aura (MWoA)	Migraine with aura (MWA)
A. At least 5 attacks fulfilling criteria B-D.	A. At least 2 attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)	B. Aura consisting of at least one of the following, but no motor weakness 1. Fully reversible visual symptoms including positive features (i.e. flickering, lights, spots or lines), and/or negative features (i.e. loss of vision) 2. Fully reversible sensory symptoms including positive features (i.e. pins
C. Headache has at least two of the following characteristics: 1. Unilateral location 2. Pulsating quality 3. Moderate or severe intensity 4. Aggravation by or causing avoidance of routine physical	

Migraine without aura (MWoA)	Migraine with aura (MWA)
activity (e.g. walking, climbing stairs) D. During headache at least one of following: 1. Nausea and/or vomiting 2. Photophobia and phonophobia E. Not attributed to another disorder	and needles) and/or negative features (i.e. numbness) 3. Fully reversible dysphasic speech disturbances C. At least two of the following: 1. Homonymous visual symptoms and/or unilateral sensory symptoms 2. At least one aura symptom develops gradually $\geq$ 5 minutes and/or different aura symptoms occur in succession $\geq$ 5 minutes 3. Each symptom lasts $\geq$ 5 and $\leq$ 60 minutes D. Headache that meets criteria B-D for 1.1 migraine without aura begins during the aura or follows aura within 60 min. E. Not attributed to another disorder

2.3.2 Tension-type headache

According to the updated IHS criteria (2004) (104), tension-type headache can be divided into three subtypes: infrequent episodic, frequent episodic and chronic tension-type headache. The differential diagnosis criteria for tension-type headache are present in Table 2.2.

Table 2.2 Diagnostic criteria for tension-type headache (104)

Episodic	Chronic
A. <u>Infrequent episode TTH</u> At least 10 episodes occurring < 1 day per month on average (<12 days per year) and fulfilling criteria B-D <u>Frequent episode TTH</u> At least 10 episodes occurring on ≥ 1 but < 15 days per month for at least 3 months B. Headache lasting from 30 minutes to 7 days C. Headache has at least two of the following characteristics: 1. Bilateral location 2. Pressing/tightening quality 3. Mild or moderate intensity 4. Not aggravated by physical activity D. Both of following: 1. No nausea/vomiting (anorexia may occur) 2. No more than one of photophobia and phonophobia E. Not attributed to another disorder	A. Headache occurring on ≥ 15 days per month on average for > 3 months (≥ 180 days per year) and fulfilling criteria B-D B. Headache lasts hours or may be continuous C. Headache has at least two of the following characteristics: 1. Bilateral location 2. Pressing/tightening quality 3. Mild or moderate intensity 4. Not aggravated by physical activity D. Both of the following: 1. No more than one of photophobia, phonophobia or mild nausea 2. Neither moderate or severe nausea nor vomiting E. Not attributed to another disorder

2.3.3 Cervicogenic headache

Cervicogenic headache was first introduced in 1983 by Sjaastad et al (106) to describe headache arising from the upper cervical spine. In 1998, the criteria for cervicogenic headache were updated based on more extensive clinical research by

Cervicogenic Headache International Study Group (CHISG) (105). The CHISG criteria have a high sensitivity and moderate specificity to distinguish cervicogenic headache from migraine and tension-type headache (83). The CHISG criteria for cervicogenic headache are present in Table 2.3.

Table 2.3 Diagnostic criteria for cervicogenic headache (105)

Cervicogenic headache
Major criteria I. Symptoms and signs of neck involvement (a) Precipitation of comparable head pain by: - Neck movement or sustained awkward head posture, and/or - External pressure over the upper cervical or occipital region on the symptomatic side (b) Restriction of range of motion in the neck (c) Ipsilateral neck, shoulder, or arm pain II. Positive response to diagnostic anesthetic blocks III. Unilaterality of head pain, without sideshift <u>Head pain characteristics</u> IV. (a) Moderate to severe, nonthrobbing and non-lancinating pain, usually starting in the neck (b) Episodes of varying duration (c) Fluctuating continuous pain Other features of lesser importance V. (a) Nausea (b) Phonophobia and photophobia (c) Dizziness (d) Ipsilateral blurred vision (e) Difficulties on swallowing (f) Ipsilateral edema, mostly in the periocular area

Given the symptomatic overlap of migraine, tension-type headache and cervicogenic headache, the differential diagnosis between these headaches can be challenging. Vincent and Luna (83) demonstrated that 30% and 3% of patients with cervicogenic headache met the IHS criteria (1988) for migraine and tension-type headache, respectively. In addition, Vincent and Luna (83) demonstrated that symptoms and signs of neck involvement (criteria I) and unilaterality without sideshift (criterion III) of Sjaastad et al's criteria (1998) (105) were important features for differentiating migraine and tension-type headache from cervicogenic headache. None of patients with migraine met any of the cervicogenic criteria in group I (symptoms and signs of neck involvement) and none of patients with tension-type headache met major criterion III (unilateral headache without sideshift). This result is also comparable to other studies (84, 107). D'Amico et al (84) demonstrated that unilateral side pain and pain localization could be used to differentiate migraine, tension-type headache from cervicogenic headache. Sjaastad et al (107) investigated laterality of pain in patients with migraine compared to patients with cervicogenic headache. Unilaterality without side shift of pain was present in only 16% of patients with migraine whereas unilaterality with side alteration of pain was present in 75% of patients with migraine. An anesthetic blockade of the greater occipital nerve is accepted as diagnostic criteria for cervicogenic headache. A study by Bovim et al (108) investigated the response of diagnostic anesthetic blocks of the greater occipital nerve (GON) and supra-orbital nerves and found pain reduction was present in 54.4% of patients with cervicogenic headache. A reduction of pain was present in only 6% of patients with migraine and 14% of patients with tension-type headache after diagnostic anesthetic nerve blocks. A related study by Terzi et al (109) suggested that GON blockage reduced pain in the orbitofrontal region and is a diagnostic tool for distinguishing cervicogenic headache from migraine and tension-type headache patients.

2.4 Cervical musculoskeletal impairments in headache

2.4.1 Cervical musculoskeletal impairments

There is evidence to support that dysfunctions of cervical musculoskeletal system are a clinical feature of cervicogenic headache (6, 110). A restriction in range of cervical motion in extension and rotation is a differential diagnostic criterion for

cervicogenic headache whereas it is not a common feature in migraine or tension-type headache. Zwart (111) investigated range of cervical motion in patients with cervicogenic headache, migraine, tension-type headache and healthy control. The results showed a significant reduction in cervical rotation and flexion/extension in patients with cervicogenic headache compared to patients with other headache types and healthy controls. The similar results are also reported in other studies (6, 110). Also, Hall and Robinson (112) demonstrated reduced cervical rotation in a position of full neck flexion (rotation of C1-C1 segment) in patients with cervicogenic headache compared with asymptomatic subjects. The presence of painful cervical joint dysfunction in the upper cervical segments is regarded as pathogenesis of cervicogenic headache (6, 113). Jull et al (6) investigated cervical symptomatic joint dysfunction in patients with different headaches and found that patients with cervicogenic headache had higher incidence of the upper cervical joint dysfunction (C1-3) compared to patients with migraine and tension-type headache and controls. Zito et al (110) also demonstrated that patients with cervicogenic headache had painful upper cervical joint dysfunction compared with patients with migraine with aura and controls.

Dysfunctions of the muscular system have also been investigated and found to be associated with cervicogenic headache. A number of studies have demonstrated decrease in cervical flexor and extensor muscle strength and endurance in patients with cervicogenic headache compared to healthy controls (6, 114, 115). Jull et al (6) found deficits in the strength of cervical flexor and extensor muscles in patients with cervicogenic headache as compared to patients with other headaches (migraine and tension-type headache) and healthy controls. Deficits in the cervical muscle strength were not found between patients with migraine and tension-type headache compared to healthy controls. Watson and Trott (114) demonstrated that cervicogenic headache had less strength and endurance of the neck flexor muscles than persons who did not have headache. In addition, there is evidence of impaired deep cervical flexor muscles as revealed in the craniocervical flexion test (CCFT) in patients with cervicogenic headache as compared to those with migraine or tension-type headache and as compared to healthy controls (6, 110, 116). The craniocervical flexion test was developed to assess performance of the deep cervical flexor muscles (longus colli and capitis), which have an important role in providing support of the cervical lordosis and motion (117). A

study conducted by Falla et al (118) evaluating an electromyography (EMG) technique for the measurement of muscle activity of the deep cervical flexor muscle found a linear relationship between the amplitude of the deep cervical flexor muscles and the incremental stage of the CCFT (22-30 mmHg). Numerous studies have also suggested that higher EMG activity of the sternocleidomastoid during the CCFT is indicative of impairments of the deep neck flexor muscles (6, 119, 120). In a headache study, Zito et al (110) revealed an increased EMG activity in the SCM during performance of the CCFT (26-30 mmHg) in patients with cervicogenic headache compared to patients with migraine and healthy controls. Similarly, Jull et al (6) demonstrated significantly higher EMG activity of the SCM in the final three stages of the CCFT (26-30 mmHg) in the cervicogenic headache group compared to the migraine, tension-type headache and control groups. These results suggest the impairment in cervical muscle control in cervicogenic headache but not in migraine and tension-type headache.

A reduction in cross-sectional area (CSA) of the cervical extensor muscles has also been reported in patients with headache. Jull et al's study (6) demonstrated that patients with cervicogenic headache had reduced cross-sectional area of the semispinalis capitis muscle on the ipsilateral side of cervicogenic headache compared to migraine, tension-type headache and control. There was one study that investigated changes of the cervical flexor muscles in the cervicogenic headache. A recent study conducted by Abaspour et al (121) has revealed no difference in CSA of the longus colli between the affected and non-affected side in patients with cervicogenic headache. No significant difference was found between subjects with cervicogenic headache and healthy controls. Furthermore, there is evidence suggesting substantial fat infiltration in the suboccipital muscle in patients with neck pain and headache compared with healthy controls (7). Evidence suggests that changes in muscle size are concomitant with an increased amount of fat in chronic musculoskeletal pain (122, 123). Determination of muscle size (CSA) was determined by tracing the fascial muscle borders, however, CSA measured may be distorted by the replacement of muscle with adipose or connective tissue (123). Elliott et al (124) reported on cervical hypertrophy in patients with chronic WAD compared with controls. Later, the same authors further investigated muscle CSA and fatty infiltration of the cervical muscles in WAD and found that increased CSA of the cervical muscle could reflect increased levels of fatty infiltration (123). Likewise,

Danneels et al (122) demonstrated reduced psoas and back muscles (erector spinae and multifidus) and increased fat deposits in the back muscles in patients with chronic low back pain compared with controls.

Some physical impairments have also been found in patients with other headaches like migraine and tension-type headache, albeit the cervical musculoskeletal impairments have been considerably associated with cervicogenic headache. Marcus et al (125) reported that patients with migraine and tension-type headache had a forward head position and the presence of myofascial trigger points in the neck muscles. As well, there was evidence that patients with unilateral migraine and episodic migraine had a forward head posture, presence of active myofascial trigger points in head and neck muscles and lesser cervical range of motion compared with healthy controls (126, 127). The same authors also demonstrated a significant reduction in CSA of the rectus capitis minor and rectus capitis major muscles in patients with tension-type headache (128).

However, while the cervical musculoskeletal dysfunctions are a clinical feature of cervicogenic headache, some dysfunctions can also present in other frequent headache (i.e. migraine and tension-type headache). Thus, isolated features of physical impairment have been suggested not to be useful in headache differential diagnosis (116). Instead, it has been suggested that a pattern of cervical musculoskeletal impairment, taken together with headache classification criteria is helpful in differentiating cervicogenic headache from migraine and tension-type headache. A pattern of cervical musculoskeletal impairment, which has been shown to differentiate cervicogenic headache from migraine and tension-type headache was discussed in the following section.

As mentioned previously, there are age-related changes in the neuro-muscular system. Thus the cervical musculoskeletal impairments revealed in patients with headache can be influenced by age factor. Recently, Uthaikhup et al (5) demonstrated cervical musculoskeletal impairments in elders with various headache types compared with controls. The impairments included reduction in ranges of cervical motion (in rotation, extension and lateral flexion) and increase in the frequency of symptomatic joint dysfunction (C0-1 to C7-T1). However, there were no differences in

cervical muscle control during performance of the CCFT and cranio-cervical muscle strength between the headache and control groups. A discrepancy in the results of muscle control during performance of the CCFT and cervical muscle strength between Uthaikhup et al's study and other studies conducted in younger populations with headache (6, 110) could be influenced by age factors.

In addition to the identified impairments discussed above, there is growing research measuring lipid content in skeletal muscles using magnetic resonance spectroscopy (MRS). Metabolic and structural aspects of muscle can be identified in signals called "resonances" or "peaks" visible in spectra of human muscles in vivo. These include intramyocellular lipids (IMCL), extramyocellular lipids (EMCL), creatine (methylene Cr2, methyl Cr3), trimethylamine (129). Intramyocellular lipids (IMCL) are stored in spheroid droplets in the cytoplasm of muscle cells closed contact with mitochondria and served as energy reserves of skeletal muscles whereas extramyocellular lipids (EMCL) is located outside the muscle cell and defined as compact portion of adipose tissue along fasciae (130, 131). A study demonstrated that an increase in lipid content in the lumbar paravertebral muscles is a sign of muscle degeneration in chronic low back pain (132). At present there is no research investigating lipid content in the cervical muscle in patients with headache. Thus, lipid content in the cervical muscles was investigated in elders with headache in the current study.

2.4.2 A pattern of cervical musculoskeletal impairments

Jull et al (6) demonstrated that a pattern of cervical musculoskeletal impairments has 100% sensitivity and 94% specificity to distinguish cervicogenic headache from migraine and tension-type headache in middle-aged/younger populations. The pattern includes restricted range of cervical motion (extension and rotation), presence of palpably painful upper cervical joint dysfunction, and dysfunction of cervical flexor muscles during performance of the CCFT. These features add to the information gained from the history and symptomatic pattern of headache to enhance accuracy in the differential diagnosis of headache (116). On a contrary, a recent study of Uthaikhup et al (5) revealed that the pattern of cervical musculoskeletal impairment could not differentiate cervicogenic headache from primary headache (migraine and

tension-type headache) in the elderly population. Cervical musculoskeletal impairment was found to be a generic feature of headache in the elderly. However, some distinction could be made based on the magnitude of cervical musculoskeletal impairment. A reduction in cervical extension and rotation, and the presence of symptomatic upper cervical dysfunction at C1-2 could differentiate elders with headache with greater cervical musculoskeletal impairment from elders with headache with lesser cervical musculoskeletal impairment and controls without headache. Not surprisingly, most elders with cervicogenic headache were found in the group with greater cervical musculoskeletal impairment. The authors (5) have proposed that cervical musculoskeletal impairment might be origin of headache or a trigger of headache. Additionally, it may indicate a transition from a primary to a secondary headache (cervicogenic headache). Further research in this area is still required.

2.5 Sensory impairment in headache

Pain threshold, the threshold at which a sensation changes into a sensation of pain is widely used to indicate the underlying mechanism of pain (133). Sensory hypersensitivity (a decrease in pain threshold) found at the site of tissue damage or inflammation suggests peripheral sensitization, whereas that found widespread (local and remote to the site of injury) suggests central sensitization (134). Recently, there is also growing research investigating supra-threshold responses, rating of painful stimulus above threshold, as they are believed to be representative of A-delta fiber mediated pain sensitivity and more sensitive for evaluation of generalized pain perception (80).

2.5.1 Pressure pain threshold (PPT)

Increased pain sensitivity (decreased PPT) has been considerably identified in patients with different type of headaches. In migraine, most studies have demonstrated that patients with migraine had lowered pain thresholds compared to healthy controls (135-137). Fernández-de-las-Peñas et al (136) investigated mechanical pain sensitivity and pericranial muscle tenderness between patients with unilateral migraine and healthy controls. The results revealed that patients with migraine had lowered PPTs over the upper trapezius muscle on the symptomatic side compared to the

non-symptomatic side and either side compared to controls. There were also significant differences in PPTs over the temporalis muscle both sides between the migraine and control groups. Later, the same authors investigated the mechanical pain sensitivity over specific nerve in patients with unilateral migraine and found an increased mechanical sensitivity of the supra-orbital nerve on the symptomatic side of the head and also on the main peripheral nerves of both upper limbs (135). Recently, Grossi et al (12) determined mechanical pain sensitivity over the craniocervical muscles and showed lowered PPTs over the frontalis and upper trapezius muscles in patients with migraine (both episodic and chronic) compared to controls. However, differences in PPTs between episodic and chronic migraine were not found. Palacios-Ceña et al (137) showed lowered pain thresholds over trigeminal and extra-trigeminal points in migraine patients compared to controls. No differences between episodic and chronic migraine were observed in both trigeminal and extra-trigeminal areas. Furthermore, Jensen et al (138) revealed no differences in PPTs over pericranial muscles between migraine, tension-type headache and no headache. There were no differences in PPTs over the temporal regions between periods during a migraine attack and non-migraine attack periods (139). Reduced mechanical pain thresholds both locally and remotely from the site of reported pain may suggest the presence of localized and generalized hypersensitivity in patients with migraine.

There is also evidence of decrease in pressure pain threshold in patients with both episodic and chronic tension-type headache. Mork et al (140) found decreased pressure pain thresholds over the temporal region and finger in patients with frequent episodic tension-type headache compared to controls. Schmidt-Hansen et al (13) reported increased mechanical sensitivity over the temporalis and masseter muscles as well as tibialis anterior, a remote site in patients with frequent episodic and chronic tension-type headache compared with controls. These results are comparable to other studies demonstrating lowered pressure pain thresholds in both cephalic and extracephalic regions in patients with chronic tension-type headache (141-143). The widespread pressure pain hypersensitivity suggests the presence of peripheral and central sensitization in patients with tension-type headache. In addition, there is evidence of a negative correlation of PPTs and severity of headache in the day of measurement in patients with tension-type headache (143). Differences in PPTs are also

suggested to be associated with headache frequency and the length of headache history (144).

Only few studies have investigated mechanical pain sensitivity in patients with cervicogenic headache (110, 145, 146). Altered mechanical pain sensitivity has been identified over the occipital and upper cervical regions in patients with cervicogenic headache (110, 145, 146). Chua et al (146) investigating PPTs over the cervical zygapophyseal joint and the greater occipital nerve in patients with chronic cervical zygapophyseal joint pain with cervicogenic headache compared with those with non-cervicogenic headache and healthy controls. Patients with cervicogenic headache had decreased PPT over the greater occipital nerve and cervical zygapophyseal joint on the ipsilateral side of headache. The authors suggested that rostal neuraxial spread of central sensitization, probably to the trigeminal spinal nucleus may play a major role in the development of cervicogenic headache.

Bovim (145) assessed PPTs over the 11 points of the head bilaterally in patients with cervicogenic headache, migraine, tension-type headache and healthy controls. The results showed that patients with cervicogenic headache had lowered PPTs over the whole head compared to patients with migraine and tension type and healthy controls. The lowest PPT was found in the occipital area of the head on the symptomatic side. This may suggest that etiology of cervicogenic headache has involved the C2 fiber, which innervates the occipital part of the head. Bovim's results are also supported by results of Anthony's study (147), which reported decreased PPTs over the greater occipital nerve ipsilateral to headache in patients with cervicogenic headache compared to patients with migraine.

As mentioned earlier, there are age-related changes in the sensory system. A recent study has investigated PPTs in elder with chronic frequent headache (cervicogenic headache, migraine and TTH) and revealed no presence of mechanical sensory hypersensitivity over the forehead, upper neck and tibialis anterior in all types of headaches compared to healthy older subjects. Correlations between PPTs and headache features (headache intensity and frequency, length of headache history, the presence of headache on the testing day) were also not found. Also, psychological factors did not seem to have an effect on pain perception in elder with headache. The

authors proposed that any changes in nociceptive fiber may be offset by a commensurate reduction in the endogenous inhibitory mechanism of older persons (11).

Overall, increased mechanical pain sensitivity has been demonstrated in patients with any headache type. However, the presence of localized mechanical hypersensitivity over the upper cervical nerve root is more pronounced in patients with cervicogenic headache whereas that over the cephalic region is more pronounced in patients with migraine and tension-type headache. The presence of generalized mechanical hypersensitivity is commonly found in patients with migraine and tension-type headache both episodic and chronic conditions. Nevertheless, the presence of localized and generalized mechanical hypersensitivity in headache seems to be influenced by a factor of age. Further research in this area is still required.

2.5.2 Thermal pain threshold (TPT)

Investigation of pain sensitivity to thermal stimuli has also been conducted in patients with headache. Sand et al (148) revealed decreased heat pain thresholds (HPTs) and cold pain thresholds (CPTs) over the forehead, neck and hands in patients with migraine during a pre-attack phase. Schwedt et al (149) reported decreased HPTs and CPTs over the forehead and forearm between migraine attack phase in patients with episodic and chronic migraine compared to controls. Later, the same authors investigated heat pain sensitivity over the head and arm in patients with migraine (episodic and chronic migraine) and found lower heat pain thresholds over the head and arm between migraine attacks (150). There is also evidence of decreased HPT and CPT over the neck and arm in patients with transformed migraine compared to those with episodic migraine during pre-attack phase and over the ophthalmic nerve during migraine attack phase (151).

In tension-type headache patients, Jensen (152) demonstrated that patients with chronic tension-type headache had decreased HPT in the temporal region compared to individuals who did not have headache. Similarly, Langemark et al (143) found lowered HPTs in both temporal region and hands in patients with chronic tension-type headache compared with asymptomatic subjects.

Investigation of increased thermal pain sensitivity in patients with cervicogenic headache is still sparse. Chu et al (146) investigated thermal detection threshold and demonstrated warm and cold hyperalgesia over the ophthalmic division of the trigeminal nerve on the symptomatic side in patients with chronic cervical zygapophyseal joint pain with cervicogenic headache in comparison with patients with chronic cervical zygapophyseal joint pain but without cervicogenic headache. Again, the author suggested that rostral neuraxial spread of central sensitization may be linked to the development of cervicogenic headache.

Given age-related changes in the sensory system, pain sensitivity to thermal stimuli in older persons with headache may differ from the findings which have been reported in the middle-aged/younger populations. Uthaikhup et al (11) demonstrated lowered heat pain threshold over the upper cervical region in the headache groups (migraine, tension-type headache, cervicogenic headache and unclassified headache) compared with a control group. There were no differences in CPTs between the headache and control groups. Again, the authors discussed that the results may be influenced by age-related changes in the sensory system. Also there may be a selective alteration fibers mediating pain perception with age. However, it is noted that thermal pain sensitivity in Uthaikhup et al's study was investigated over the upper cervical region only. Thus, further investigation of sensory hypersensitivity to thermal (heat and cold) stimuli is still needed to be conducted in elders with headache.

2.5.3 Supra-threshold pain ratings

Only a few studies have investigated suprathreshold testing to determine the presence of the central sensitization in patients with headache (153-155). Gierse-Plogmeier et al (154) investigated pain perception and demonstrated that patients with migraine had higher pain rating (0-100) after repeated suprathreshold stimulation over the trigeminal region but not in the peripheral region as compared to healthy controls. Ashina et al (153) also investigated pain rating to suprathreshold single and repetitive (2 Hz) electrical stimulation of muscle and skin in cephalic (temporal and trapezius) and extracephalic (tibialis anterior) regions in patients with chronic tension-type headache compared to controls. Pain ratings to both single and repetitive were significantly higher in patients with chronic tension-type headache in both skin and muscle all examined

cephalic and extracephalic regions. Additionally, the pain ratings were significantly higher in females compared to males. These results are also in agreement with findings of a study by Lindelof et al (155).

Yet, there is no evidence of suprathreshold pain ratings in patients with cervicogenic headache. Also, suprathreshold pain ratings in elders with headache have not been investigated previously. Thus, the presence of central sensitization using suprathreshold pain ratings was investigated in elders with different types of headache in this study.

2.6 Management of headache

Pharmacological treatment is generally used to treat migraine and tension type whereas physiotherapy including manual therapy and therapeutic exercise is recommended as the first line treatment for cervicogenic headache (15, 16, 156). It has been reported that medications can help to relieve pain in migraine and tension-type headache (91, 157, 158). Some medications are used to stop migraine attacks (abortive treatment) whilst some are taken on a daily basis in order to reduce the severity, duration and frequency of migraine attacks (prophylactic or preventive therapy) (158). Common medications used for treating migraine include nonspecific drugs (e.g. paracetamol and aspirin) and specific drugs (i.e. ergot, dihydroergotamine and triptans) (158). For prophylactic therapy, medications commonly used include propranolol, metoprolol, amitriptyline, divalproex, flunarizine, pizotyline and methysergide (91). Non-steroidal anti-inflammatory (NSAID) drugs are often used to relieve acute pain in patients with tension-type headache (157), whereas, tricyclic antidepressant is recommended for chronic tension type headache and frequent episodic tension type headache (157). There is also a study suggesting that antidepressant medication and stress management therapy are each modestly effective in treating chronic tension-type headache (159).

Physiotherapy treatment is advocated as the most appropriate treatment for cervicogenic headache. In a high-quality study design, Jull et al (15) investigated the effectiveness of manipulative therapy and a specific therapeutic exercise program for cervicogenic headache when used alone and in combination as compared with a control

group. The manipulative therapy intervention included both low-velocity cervical joint mobilization and high-velocity manipulative techniques. The therapeutic exercise intervention included the use of low load endurance exercises to train muscle control of the cervicoscapular regions, with the first stage consisting of specific exercise to address the impairment in neck flexor synergy. The interventions were given over a period of 6 weeks (8-12 treatments). The control group received no physiotherapy treatment. The results demonstrated that both manipulative therapy and specific therapeutic exercise therapy used alone and in combination were effective for patients with cervicogenic headache. Headache frequency and intensity as well as neck pain and disability were reduced in all intervention groups. Headache relief was also maintained over the 12-months follow-up period. In addition, the results demonstrated that medication intake as well as the pain associated with neck movement and joint palpation were reduced in all treatment groups. Improved performance in the muscle test of craniocervical flexion was found in the therapeutic exercise therapy used alone and in the combination of therapies groups, but not in the manipulative therapy group. This may allow the authors to conclude that there was no spontaneous return of the neck flexor muscle function without the use of exercise, although the pain was relieved. The findings of Jull et al (15) are in accordance with previous findings in a study by Nilsson (16) demonstrating that manipulation treatment could reduce headache intensity, headache duration as well as analgesic use in patients with cervicogenic headache.

The effectiveness of physiotherapy treatment has also been demonstrated in patients with migraine and tension-type headache. Bevilaqua-Grossi et al (160) investigated the efficacy of medication and combination of physiotherapy and medication in patients with migraine and found that physiotherapy plus medication seemed to be as effective as medication. A systematic review in 2011 suggested that current evidence does not support the use of spinal manipulation for the treatment for migraine patients (161). Additionally, in a review by Biondi (162), it has been suggested that physiotherapy treatment is effective for treatment of migraine when combined with other treatments such as thermal biofeedback, relaxation training and exercise and also is more effective than massage therapy and acupuncture for treatment of tension-type headache. However, the author has warranted that further studies of improved quality are necessary to confirm the effectiveness of physical therapy

treatment in primary headache. Bove and Nilsson (163) investigated the effectiveness of spinal manipulation combined with soft tissue therapy in patients with episodic tension-type headache as compared with laser with soft tissue therapy (the control group). The results demonstrated no differences in the number of headache hours per day, the mean headache intensity per headache episodes and consumption of analgesics per day between the spinal manipulation and control groups. These results are also similar to findings of Boline's study (164). It appears, from the previous findings, that spinal manipulation has an effect comparable to commonly used first-line prescription. However, it is difficult to draw a conclusion as high methodological quality of those studies is not yet to be achieved.

Yet, there is no study of the effectiveness of physiotherapy in elders with frequent intermittent headache. While headache in the elders is more often associated with neck pain and impairment, regardless of headache type (5), physiotherapy treatment (i.e. manual therapy and specific therapeutic exercise) is undoubtedly indicated in elders with headache diagnosed with cervicogenic headache. Additionally, it could be an adjunct treatment for those elders who have other headaches associated with neck pain and impairment.

2.7 Summary statement

The frequent intermittent headache is a common health problem in the elderly population. Alteration of the muscular and sensory systems with increasing age may result in changes in nature of headache in this age group. Previous studies have investigated cervical musculoskeletal impairments in elders with headache but changes in other features of the cervical muscles (i.e. morphology, fat infiltration and lipid content) have not yet been investigated. Besides, there is no comprehensive study of sensory hypersensitivity in elders with headache. Thus, investigations of changes in the cervical muscle structures (morphology, fat infiltration and lipid content) and the presence of sensory hypersensitivity are still required. Treatment method such as manual therapy and therapeutic exercise are appropriate management strategies for cervicogenic headache (15, 16). However, in the elderly, it may also be a treatment option for those who have suffered from other headaches associated with cervical musculoskeletal signs. Thus, investigation of the effectiveness of physiotherapy

treatment in elders with headache associated with cervical musculoskeletal impairment would be helpful in determining the contribution of the neck and headache in the elderly population.

This present study has therefore aimed to evaluate the cervical musculature, pain sensitivity and effectiveness of physiotherapy treatment in the elderly (aged between 60 and 75 years) with frequent intermittent headaches. A small number of participants with primary headache (migraine, tension-type headache) were recruited for investigation of cervical musculature and pain sensitivity in this study, thus, this study explored the extent of the impairments of cervical muscles (morphology, fat infiltration, lipid content) and pain sensitivity in elders with cervicogenic headache.

2.8 Aims and hypotheses of the study

2.8.1 Aims of the study

- To investigate rCSAs, fat infiltration and lipid content of the cervical muscles in elders with cervicogenic headache compared to controls (study I)

- To investigate the presence of pain sensitivity in elders with cervicogenic headache compared to controls (study II)

- To investigate the effectiveness of physiotherapy treatment in elders with headache associated with neck pain and concomitant cervical musculoskeletal impairment (study III)

2.8.2 Hypotheses of the study

- Elder women with cervicogenic headache would have decreased rCSAs of the cervical muscles and increased fat structure (fat infiltration and lipid content) compared to those without headache (Study I).

- Sensory hypersensitivity at the periphery (the upper cervical spine) would be present in elders with cervicogenic headache compared to those without headache (Study II).

- Physiotherapy treatment would be more effective than usual care for reducing headache and neck symptoms in the elders with headache associated with neck pain and concomitant cervical musculoskeletal impairment (Study III).