Special Article

Chronic Kidney Disease and Pain Perception

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Abstract

Background: Pain is considered to be a challenge for healthcare professionals. It is a multidimensional phenomenon affecting everyday life and functionality. People with renal problems, acute or chronic, are experiencing various types of pain either due the illness itself, adverse effects or due to clinical interventions.
Objectives: The aim of the present study was to present the different theories regarding pain and to familiarize readers with the various types of pain experienced by patients and in particular patients with renal problems.
Methods: A comprehensive literature search was undertaken regarding pain, particular in pain experienced by patients on different stages of Kidney Disease and on various types of Renal Replacement Therapies.
Results: Several explanatory theories regarding pain have been published by scholars since the mid-1960s. According to researchers brain is dictating how much pain a person feels caused by a harmful stimulus. In other words, if the route from peripheral nerves to the central nervous system is occupied by positive and relaxing thoughts pain could not be experienced, as only one impulse can travel at a time. In renal patients pain can be attributed to the primary kidney disease or comorbidities, such as Diabetes Mellitus and Cardiovascular Disease, and/or dialysis.
Conclusion: Renal patient's high levels of pain could be effectively and individually assessed and managed if healthcare professionals are more familiarized with different types and aetiology of pain, as well as the current ways of treatment. Through curriculum and continuous education, clinicians can choose from a cascade of treatments aiming at maintaining the quality of life of renal population.

Key words: Chronic Kidney Disease, Theories of Pain, Aetiology of Pain

Background

Despite the advances in the medical and health-related sciences over the last century, pain continues to be seen as an "intriguing puzzle" and a challenge for healthcare professionals (Madjar 1998, Greek Nurses Code of Ethics 2001, Ferrell & Coyle 2008, IOM 2011). Pain is a multidimensional phenomenon with physical, psychological as well as social components often determined by personal beliefs and cultural values (Turk & Okifuji 2002, IOM 2011, Vaajoki et al. 2013). It is a subjective bodily response to physical and psychological stressors imposed to the individual by his/her health status and the clinical environment (Mann & Carr 2008, Wilkstrom et al. 2014). It is associated with problematic interpersonal relationships, psychological distress and depression, activity limitations in work, family and social life and, quite often, excessive use of health care services (Dysvik et al. 2004, Davison 2007a, Heiwe & Bjuke 2009, Hogan & Norby 2010). Pain warns the human body for any health-threatening situations and is considered to be a major defense mechanism of the body. Furthermore, it is

recognised as an important part of the psychosocial impact of illness and the adoption to the chronic sick role.

Kidney Disease can be manifested either as an acute health problem (Acute Renal Failure, ARF) or as a result of a long procedure of deterioration of renal function (Chronic Kidney Disease, CKD). To the best of our knowledge, in the literature there is limited information on renal patient's pain perception and management. Thus, the aim of the present paper was to present the different theories regarding pain and to familiarize readers with the various types of pain experienced by patients and in particular patients with renal problems.

Definitions

McCaffery in the late 1960s was the first to describe pain as "whatever the experiencing person says it is, existing whenever she/he says it does". This early definition emphasizes in the subjective nature of pain. The patient, not the healthcare professional, is the authority on pain and her/his self-report is the most reliable indicator. A decade later, in 1979, the International Association for the Study of Pain (IASP) stated that "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey & Bugduk 1994). Localisation, type and intensity of pain vary greatly from person to person.

Theories of pain

Several explanatory theories regarding pain have been published by scholars. In 1965, an innovative theory about pain was proposed by Melzack and Wall, which is still updated by further research (Wall & Melzack 1994, McMahon et al. 2013). According to this theory, only one impulse (signal) can travel up the spinal cord to the central nervous system at a time. If positive and relaxing thoughts are occupying the route, then the sensations that activate pain cannot reach the brain to trigger a perception of pain. Another significant theory is the Gate Control Theory, which states that in substantia gelatinosa (dorsal horn of the spinal cord) pain can be modified by the stimulation of non-pain ascending or descending fibres. Substantia gelatinosa plays the role of a "gate" modulating the afferent signals before they ascend to the cerebral cortex. On the other hand, feelings like anxiety, excitement and anticipation may open the gate, increasing the perception of pain (Wall & Melzack 1994, Jurf & Nirschl 1993, Ackerman & Turkoski 2000, Chang et al. 2015).

Furthermore, during tissue damage, cells are breaking down, resulting in the release or production of chemicals-mediators (bradykinin, histamine, serotonin, prostaglandins and cytokines), which react with each other and on nerve endings, sending signals from there to the dorsal horn of the spinal cord and up the cortex of the brain, where the perception of pain takes place (Pham et al. 2009).

Another theory coming from Melzack (1999), proposes that a neural network, "the body-self neuromatrix", is included in the brain translating painful stimuli. Although genetically determined, it accepts cognitive, emotional, sensory and visual inputs during a persons' life in order to create the specific pattern of individual's pain perception (the neurosignature). Neuromatrix Theory is used to explain why some individuals develop chronic pain, while others do not (Melzack & Wall 2003).

In conclusion, all the different theories stress that the brain is dictating how much, if any, pain a person feels from a potentially harmful stimulus. Acute, as well as chronic pain is addressed in the context of Gate Control Theory.

Classification of Pain

Pain can be encountered in many types. The most common types of pain are presented in Figure 1. Acute pain is considered to be the pain of recent onset, usually transient in nature. It is viewed as a "complex, unpleasant, experience with emotional and cognitive, as well as sensory, features that occur in response to tissue trauma" (Chapman & Nakamura 1999). Acute pain is caused by tissue damage and is often associated with some degree of inflammation. Generally, it warns the body of the likelihood or the extent of injury, and it subsides as the healing process moves forward.

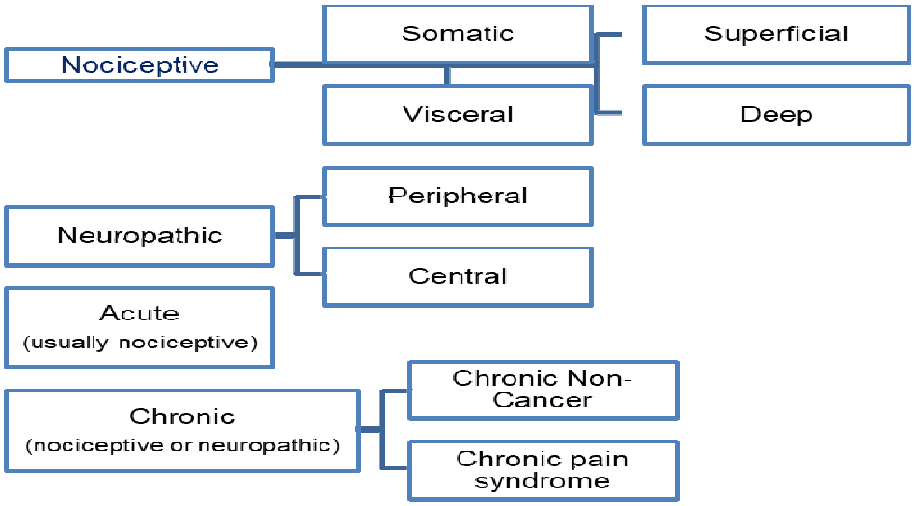

Figure 1. Pain classification.

Chronic pain is defined as "pain that has lasted six months or longer, is ongoing, is due to non-life-threatening causes, has not responded to currently available treatment methods, and may continue for the remainder of the patient's life" (Merskey & Bogduk 1994). Usually, it persists beyond the course of an acute illness/injury and lasts beyond the healing process. It is associated with a pattern of recurrence over months or years (Thienhaus & Cole 2002, Turk & Okifuji 2001) and excessive use of health care services (Davison 2005).

In addition, chronic pain can be described as a persistent feeling that "disrupts sleep and normal living, ceases to serve as a protective function, and instead degrades health and functional capability" (Chapman & Stillman 1999). Moreover, chronic pain can be caused by injury, malignancy, or other non-life-threatening conditions, such as arthritis or neuropathies, and can be neuropathic and/or nociceptive. It can also be of unknown cause, idiopathic pain.

As presented in the figure 1, another type of pain is Neuropathic pain which has been defined as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system" (Treede et al. 2008). It can be attributed to autonomic dysfunction or associated with vascular occlusion or nerve involvement either in the central or the peripheral nervous system, and it is characterised as burning or lancinating (Turner et al. 2007, Pham et al. 2009). Alas, this type of pain does not provide a protective benefit, but instead precipitates ongoing suffering.

Direct stimulation of peripheral sensory neurons called nociceptors (A-δ and C), cause Nociceptive pain. A type of pain associated with tissue injury or inflammation, and excited by endogenous chemical substances. Nociceptors receiving input of pain from internal organs are responsible for visceral pain which is deep, dull and of vague localisation, whereas those receiving input from outer body tissues are responsible for somatic pain. Somatic pain according to its origin can be further categorised as superficial (cutaneous) or deep (Kurella et al 2003).

Life-threatening conditions, such as cancer, can produce malignant or cancer pain. This form of pain can be caused either by the disease itself (tumor compressing nerves, blood vessels or organs) and/or by painful diagnostic procedures, such as biopsies, chemotherapy or radiation. For some researchers, however, malignant pain is included in acute or chronic pain (Turk & Okifuji 2001).

Finally, psychogenic pain is caused by emotional, psychological or behavioral factors. Headache, back pain and stomachache can be regarded as psychogenic. A kind of pain which cannot be attributed to any known cause can be characterised as psychogenic. Most of the times, it reflects inability to diagnose a medical situation or it is due to inadequate analgesic management (Melzack & Wall 2008).

Chronic Kidney Disease and pain perception

Patients with renal problems experience pain, acute and chronic, quite often. Irrespective of its

aetiology, renal pain is a debilitating condition and often leads to avoidable over-investigation, suboptimal management and poor quality of life, as well as morbidity (Binik et al. 1982, Bailie et al. 2004, Cohen et al. 2007, Davison & Jhangri 2010, Davison et al. 2014).

The prevalence of symptoms such as pain, sleep disturbance, fatigue, and abnormal psychosocial status may be similar to that of diabetes and other chronic medical illnesses such as cancer or Human Immunodeficiency Virus (HIV) (Davison & Jhangri 2005, Murtagh et al. 2007a, Murtagh et al. 2007b, Bouattar et al. 2009, Harris et al. 2012, Gamondi et al. 2013, Cohen & Davison 2015, Zyga et al. 2015). Although patients with Chronic Kidney Disease experience severe disease burden, denial is quite often used as a coping strategy to deny the severity of their illness and its symptoms or adverse effects (Shayamsunder et al. 2005, Weisbord et al. 2005, Cohen et al. 2007, Salisbury et al. 2009).

Renal patients experience pathological pain due to their disease, but also pain generated by diagnostic and treatment procedures or interventions carried out by renal nurses. Such pain is often seen as a side-effect and not a result of insensitive and uncaring staff. Inflicted pain is often both inevitable and necessary in order to provide an accurate diagnosis and appropriate treatment (Madjar 1998, Aitken et al. 2013) and can be affected by the physical and social environment of the hospital, the stage of Chronic Kidney Disease, the impact of treatment (pre-dialysis or dialysis), and the concerns about rehabilitation and returning to a prior status. Nephrologists and renal nurses play an important role in emotional, social, and spiritual support of their patients (Davison 2007a).

Research on Chronic Kidney Disease suggests that patient's perceptions of physical symptoms, such as pain, are associated with depression and insomnia, which are more important than objective assessments in determining the health-related quality of life of patients with Chronic Kidney Disease and their families (Lindqvist et al. 2000, Shayamsunder et al. 2005, Weisbord et al. 2005, Gamondi et al. 2013, Minasidou et al. 2016, Kafkia et al. 2017). Chronic Dialysis patients are presenting a number of physical and emotional symptoms, including pain, fatigue, anorexia, nausea, pruritus, shortness of breath, muscle cramps, paresthesias, depression, sexual difficulty and sleep disturbance (Mercadante et al. 2005, Yamamoto et al. 2009, Harris et al. 2012, Zyga et al. 2015).

Researchers have reported that the severity of pain is often at the same magnitude to pain experienced by cancer and HIV positive patients, alas moderate to severe in intensity in 50-80% of haemodialysis patients (Davison 2003, Gamondi et al. 2013, Wu et al. 2015). Furthermore, joint and bone pain secondary to arthritis or renal osteodystrophy was the main cause of pain in long-term haemodialysis patients (Davison 2003, Gamondi et al. 2013). In the cases of Polycystic Kidney Disease (PKD), flank or abdominal pain, acute or chronic, affects almost 60% of the patients and is accompanying renal infection, cyst haemorrhage, renal stone, traction of the kidney pedicle or compression of surrounding structures (Bajwa et al. 2004, Torres et al. 2007, Tellman et al. 2015). Almost half of the Chronic Kidney Disease population (Atalay et al. 2013, Santoro et al. 2013) report Neuropathic pain compared to 7-8% of the general population (Smith et al. 2007, Bouhassira et al. 2008).

A major problem regarding Chronic Kidney Disease patients' pain is that it is undertreated. Davison (2005) reports that 74% of patients with pain negatively affecting their work had no analgesic prescribed to them. The same researcher in a previous study (Davison 2003) found that 35% of haemodialysis patients with chronic pain were not prescribed any analgesics and less than 10% were prescribed strong opioids. Furthermore, 74% of Chronic Kidney Disease stages 4-5 patients with moderate to severe pain or pain that interfered with their work were undertreated (Bailie et al. 2004, Bulter et al. 2014, Wu et al. 2015).

Aetiology of Pain in Chronic Kidney Disease Patients

There are numerous causes of pain in Chronic Kidney Disease and their manifestations vary. Pain may result from the primary kidney disease, such as Polycystic Kidney Disease (PKD) or Systemic Lupus Erythematous (SLE), or comorbid situations, such as Diabetes Mellitus (DM), Peripheral Vascular Disease (PVD), and Cardiovascular Disease (CVD). There are, also, several other conditions that produce pain and are associated with renal disease (nephrogenic fibrosing dermopathy, secondary hyperparathyroidism, calcific uremic arteriolopathy), or RRT (abdominal distension from PD, steal syndrome from an arteriovenous

fistula for HD, needle insertion, and muscle cramps) (Davison 2007a, Salisbury et al. 2009, Bagheri-Nesami et al. 2014, Moss & Davison 2015). Furthermore, painful ischaemic neuropathies can be caused by chronic infections, such as osteomyelitis or discitis; complications from central venous catheters used for dialysis or infected arteriovenous fistulas. Finally, pain between the twelfth thoracic (T_{12}) and the third lumbar (L_3) vertebra can be caused either by injury to back muscles or the spine, or by renal problems (Manias & Williams 2007, Heiwe & Bjuke 2009).

Polycystic Kidney Disease (PKD) is the most common renal hereditary disease, which can be found either as autosomal dominant or autosomal recessive PKD, due to a gene mutation or defect. The prevalence of PKD in Europe and USA is ranging from 1/200 to 1/1000 individuals. PKD is characterised by kidney cyst development and growth resulting in progressive enlargement of them. Pain in patients with PKD can either begin with an acute episode and persist as chronic, or develop gradually and become more severe over time. Either type of pain (acute or chronic) is the source of great frustration and distress for PKD patients (Steinman 2000, Bajwa et al. 2004, Rizk & Chapman 2003, Torres et al. 2007, Shetty et al. 2012, Walsh & Sarria 2012, Savige et al. 2015). During cyst formation or enlargement, the surrounding tissues are compressed, the pedicle of the kidney is pulled and renal capsule becomes swollen (Steinman 2000, Cohen et al. 2006, Torres et al. 2011, Shetty et al. 2012). These mechanisms are the source of chronic and localised pain, usually in the anterior abdominal area (Walsh & Sarria 2012). According to the researchers, afferent fibers from the renal capsule, parenchyma, and vasculature go to neuraxis, passing through sympathetic nerves and prevertebral ganglia, and join the lesser and least splanchnic nerves. These nerves then travel cranially along the retrocrural space to the T_{10}-T_{12} and L_1 spinal levels through the respective paravertebral ganglia and rami communicans. Intercostal somatic nerves are nerving part of the renal capsule and nearby musculoskeletal structures, corresponding to T_7-T_{12} dermatomal levels. Large cysts result in bigger pelvic angle and lumbar lordosis causing mechanical low back pain, as the abdomen projects, more strain is forced to lower back muscles and disc disease is established in the lumbosacral area (Steinman 2000, Bajwa et al. 2004, Tozzi et al. 2012).

Infected renal cysts can cause diffuse, generalised unilateral or bilateral pain accompanied by fever, unrelieved by position change. This type of pain is similar to pyelonephritis in general population. Raptured cysts, on the other hand, manifested by haematuria, are the cause of acute flank pain which is, usually, localised and finger pointed by patients. It can, also, reflect to anterior abdominal area (Hogan & Norby 2010, Haseebuddin et al. 2012) or even the shoulder if the cysts are larger and compressing the surrounding tissues (Bajwa 2001). In case of ruptured cysts which are on the surface of the kidney, sub-capsular hematoma is caused, resulting in mild and steady pain persisting until it is absorbed (Steinman 2000). Clots within the renal cysts can lead to urinary tract obstruction, like the one caused by kidney stones, and renal colic. The actual renal colic caused by kidney stones (calcium oxalate, calcium phosphate, calcium carbonate or uric acid) can be found in almost 20% of patients with PKD. Anatomic deformity caused by the cysts may contribute to the formation of kidney stones, possibly due to increased urinary stasis (Grampsas et al. 2000). Liver cysts, found in 85% of the individuals in Bae et al (2006) CRISP study are associated with more severe pain and abdominal distension while in standing position.

It is worth mentioning the in the PKD population persisting headache or migraine could be an early sign of cerebral aneurysm, even though its prevalence is between 4%-6% of the total ADPKD group (Bajwa et al. 2001).

Secondary hyperparathyroidism, a serious complication of Chronic Kidney Disease, originates from deregulation of serum calcium, phosphorus and vitamin D, resulting in elevated levels of parathyroid hormone and, furthermore, in abnormal bone metabolism and muscle weakness, skeletal deformities and bone pain, called renal osteodystrophy. Ergocalciferol (vitamin D_2), cholecalciferol (vitamin D_3), and their metabolites and derivatives are involved in this process. Vitamin D_3 is produced after the conversion of skin's 7-Dehydrocholesterol in the presence of sunlight. As it is not active, it has to be hydroxylated in the liver to produce 25-hydroxyvitamin D_3. Then in the normal kidney it is converted into calcitriol (1.25 dihydroxyvitamin D_3). The same process happens with vitamin D_2, which comes from plants and fungus, producing 1.25

dihydroxyergocalciferol. Both of them maintain normal calcium homeostasis via the vitamin D receptor to increase intestinal calcium absorption and to modulate mineral mobilization from bone (Palmer et al. 2009). These mineral and hormonal abnormalities start early in Chronic Kidney Disease process, usually in Stage 3, when GFR is <60mL/min/1.73m^2. If left untreated, hyperparathyroidism can lead to onset of purpuric plagues, discolored skin and nodules, signs of calciphylaxis, and could evolve in necrotic ulcers, gangrene, and amputation. Painful proximal myopathy can accompany the skin manifestations, resembling dermatomyositis. Biopsy findings show varying degrees of calcification of the media layer of the blood vessel walls of subcutaneous or digital arteries causing ischaemic necrosis of the skin and other organs (Rich et al. 2001, Perlman 2005, Terzibasioglu et al. 2005, Schlosser et al. 2008, Strippoli et al. 2010).

In addition to the pain caused by the disease itself, HD patients are exposed to clinically inflicted pain, such as insertion of Central Venous Catheters (CVC) for HD or cannulation of vascular access (Arteriovenous fistula or graft). Haemodialysis sessions are held, usually, three times a week and involve at least one puncture at the arterial and one at the venous part of the vascular access for every session, a total of at least 320 punctures each year. This repeated puncturing leads to a considerable pain, due to the tearing of the skin, and the punch in the walls of the vessels (Montero et al. 2004, Verhallen et al. 2007, Figueiredo et al. 2008). Due to irritation of the skin's nerve endings, pain perception mechanism is triggered and pain is experienced.

Another problem common among patients on dialysis, HD or PD, for more than 5 years is Dialysis-related amyloidosis (DRA) (Moss et a 2004). B_2-microglobulin deposits in bone, synovium, tendons and peripheral nerves and causing bone cysts, fractures, arthritis, and carpal tunnel syndrome accompanied by pain (Kelly et al. 2007). It is a cause of musculoskeletal pain in 51% of dialysis patients, as described by Davison (2003) and 37% of another HD population studied by Carreon et al. (2008).

Last by not least, diabetic peripheral neuropathy, affecting large and small fibres, is another cause of pain in Chronic Kidney Disease patients and is correlated with duration of Diabetes Mellitus (DM), degree of glycaemic control and level of uraemia (Edwards et al. 2008). Sensory deficits overshadow motor nerve dysfunction and appear first in the distal portions of the extremities and progress proximally in a "stocking-glove" distribution (Pop-Busui et al. 2010).

Conclusion

Renal patients experience high levels of pain due to nature of their disease or painful interventions, such as vascular access cannulation, insertion of peritoneal dialysis catheter or examinations. In order to effectively and individually assess and manage pain healthcare professionals need to be familiar with different types and aetiology of pain, as well as the current ways of treatment. Through curriculum and continuous education clinicians can choose from a cascade of treatments aiming at maintaining the quality of life of renal population.

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