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Sleep Disturbances Among Dialysis Patients

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1. Introduction

Sleep disturbances are extremely common among dialysis patients. Subjective sleep complaints are reported in up to 80% of patients and are characterized by difficulty in initiating and maintaining sleep, problems with restlessness, jerking legs, snoring, choking sensations and/or daytime sleepiness (Holley et al., 1992; Walker et al., 1995; Veiga et al., 1997). Epidemiological studies have found how sleep apnea syndrome (SAS), restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) are much more prevalent than in the general population. These sleep problems appear to have significant negative effects on the quality of life as they are often cited as major sources of stress. Indeed, interviews of patients on hemodialysis and on peritoneal dialysis have found that sleep disturbances are one of the seven most distressing symptoms experienced (Eichel et al., 1986; Bass et al., 1999). Half of patients complaining of sleep disturbances feel that these problems affect their daily living and activity, and 21% consider that relief of this symptom would improve significantly their subjective quality of life (Parfrey et al., 1988; Iliescu et al., 2003).
In the following sections two major sleep disturbances associated with Insomnia, Restless Legs Syndrome and Sleep Apnea Syndrome, will be reviewed in detail.

2. Sleep disturbances among dialysis patients

2.1 Insomnia

Insomnia, one of the major causes of sleep disturbances, is defined by the presence of difficulty in falling asleep, frequent awakenings with difficulty in falling asleep again and early morning awakenings. In order to be considered an insomniac, these symptoms should be reported at least 3 times per week and the presence of resultant daytime dysfunction should be investigated in order to distinguish two levels of insomnia (level 1, without daytime dysfunction, and level 2, with daytime dysfunction) (Ohayon et al., 1996). Insomnia should be distinguished in primary and secondary insomnia. Secondary forms of insomnia can be the consequence of internal medical disturbances but also of other sleep disturbances such as RLS and SAS, which will be further reviewed in detail. Insomnia is primarily a clinical diagnosis and is most frequently diagnosed using data obtained from patient histories and sleep diaries. The prevalence estimates of insomnia vary because of differences in definition, diagnosis, population characteristics, and research methodologies. Its prevalence in the general population ranges from 4% to 64% (Ohayon et al., 2002, Chevalier et al., 1999).

The assessment of sleep disturbances can be done through sleep questionnaires (i.e. Pittsburgh Quality Index– PSQI) aimed to evaluate subjectively these disorders, or through polysomnographic measures, able to offer an objective analysis of sleep disturbances. The latter would also have a role in the diagnosis of SAS or periodic limbs movements and for the objective characterization of macro or micro alterations of sleep architecture in insomnia.
Many studies have been conducted up to now in order to assess the prevalence of sleep complaints among dialysis patients. Prevalence rates of subjective sleep complaints vary among studies due to the different methodological approaches (e.g. modalities of interview, type of questionnaires, definition of inclusion criteria, etc.) and sample sizes.
The prevalence of insomnia among dialysis patients is greater than the general population, rates up to 70% have been reported (Sabbatini et al., 2002; Iliescu et al., 2003; Merlino et al., 2006). The earliest study to have evaluated the prevalence of subjective sleep complaints among dialysis patients was conducted in 1982 (Strub et al., 1982). They found that 63% of patients reported sleep disturbances characterized by diminished, fragmented sleep and increased wake time after sleep onset. Similar data were found by a study of Holley et al. in which the most common complaints included trouble falling asleep (67%), nighttime awaking (80%), early morning awaking (72%), restless legs (83%), and jerking legs (28%). Daytime sleepiness was common and dialysis patients reported napping for periods averaging 1.1+1.3 h per day (Holley et al., 1992). After these pioneer studies many others have addressed on this topic and have found similar prevalence rates. A recent study from 20 Italian dialysis centers, showed the prevalence of insomnia, RLS, and symptoms suggestive of SAS to be 69.3%, 18%, and 27%, respectively (higher than in the general non-renal population) (Merlino et al., 2006).
Most of these studies have also looked for a correlation between sleep complaints and numerous demographic, clinical, and laboratory data. Sleep complaints seem to be more common in elderly patients on dialysis than in younger patients (Kutner et al., 2001; Walker et al., 1995). It has been reported that each decade of age increases the risk of insomnia (subclinical and clinical) by 239% and the risk of overt clinical insomnia by 51% (De Santo et al., 2005). The effect of gender on sleep quality is controversial. It has been found that male patients are more likely to have sleep complaints than female patients, even though women report using more sleep medications than men (Kutner et al., 2001; Walker et al., 1995). White patients have a higher prevalence of restless sleep than blacks (Walker et al., 1995). Positive relationship between subjective sleep complaints and caffeine intake and cigarette use has also been reported (Holley et al., 1992). Increased stress, anxiety, depression and worry, as observed also in the general population, are associated with poor subjective sleep quality in dialysis patients (Holley et al., 1992; Kutner et al., 2001; Parker et al., 1996). Depression seems to be the primary mental health problem in this group of patients. Dialysis patients with sleep disturbances have a prevalence of depression of 20% (Iliescu et al., 2003). The use of sleep ipnotic medications among dialysis patients is about 8-10% (De Santo et al., 2001; 2005).
Concerning laboratory data, one study has reported that improvement of anemia leads to amelioration of sleep quality, reduction of nighttime awakenings and reduction of sleep fragmentation. Thus, a more efficient sleep is obtained, leading to a decreased daytime somnolence (Ohayon et al., 1997). Other previous studies have shown how low levels of Hb are associated with a deteriorated sleep quality (Kusleikaite et al., 2005; Iliescu et al., 2003; Benz et al., 1999). However, this situation is controversial and is not confirmed by all studies. Other studies assessing an association between sleep disturbances in peritoneal

dialysis patients and Hb levels have failed to show such an association (Walker et al., 1995; Holley et al., 1992; Stepanski et al., 1995). No consistent relationships have been found between subjective sleep complaints and laboratory measures of renal failure (blood urea nitrogen-BUN, creatinine) and parameters of dialysis efficacy (Kt/V) (Puntriano et al., 1999; Holley et al., 1992; Walker et al., 1995). Only a small study by Millman et al., has reported a significant relationship between sleep apnea and azotemia (Millman et al., 1985).

A correlation between the type and the duration of dialysis has also been searched. No difference has been found between hemo (HD) and peritoneal dialysis (PD). Both of them, indeed, are associated with a high rate of poor sleep quality (Eryavus et al., 2008). A relationship with the dialysis vintage has been found. It appears that, the longer the dialysis vintage, the higher the prevalence of sleep disturbances. In an Italian study, those patients on dialysis who presented sleep disturbances had a double dialysis vintage when compared to those on dialysis who did not have sleep problems (De Santo et al., 2005). When analyzing the timing of dialysis shifts, a higher rate of insomnia has been reported among patients on the morning dialysis shift. In fact, compared to patients receiving their dialysis in the afternoon, subjects treated in the morning show a significantly higher risk of being affected by insomnia ($p<0.001$) (Merlino et al., 2006). However these results have not been confirmed. In fact, a later study by Eryavuz et al. has found a higher rate of insomnia among patients on the afternoon shift. Regarding dialysis duration, results seem to be controversial as well. Only some studies have reported an association between longer dialysis duration and insomnia (Sabbatini et al., 2001; Veiga et al., 1997). In particular, higher PSQI scores have been found among patients who have received HD for a long period of time. Whereas, a positive correlation has also been found with a premature discontinuation of dialysis.

Recently literature has focused the attention on inflammatory markers. It has been demonstrated indeed, how they can be increased in sleep disorders with normal renal function or in end stage renal disease (ESRD) patients. Subsequently persistent elevation of these markers is associated with many clinically important complications, including atherosclerosis and cardiovascular mortality. These findings, together with the finding of a poorer sleep quality independently linked to higher mortality rate among ESRD patients, has led to the search of an association between inflammatory markers in ESRD and poor sleep quality. A recent study has shown that higher systemic inflammation, as demonstrated by serum hsCRP and IL-1β levels, is associated with poorer sleep quality in stable HD patients. Other inflammatory markers, such as IL-6 and TNF-α, are also positively correlated with poorer sleep quality; even though these results did not reach statistical significance (Yen-Ling Chiu et al., 2009).

Polysomnographic studies of this population have found how sleep macrostructure can be altered. The earliest studies are reported in the late 1960s and early 1970s. These reports described sleep as being characterized by decreased total sleep time, irregular sleep cycles, and long periods of interspersed waking (Reichenmiller et al., 1971; Passouant et al., 1970). Recent studies have confirmed a sleep characterized by short duration and fragmentation with sleep efficiencies ranging between 66% and 85%, long periods of wake time after sleep onset (77±135 min), and frequent arousals (25±30/h of sleep) (Parker et al., 2003). The macrostructural analysis has shown an increase of Stage 1 and 2 and a decrease of slow wave sleep (SWS) and REM sleep (Wadhwa et al., 1992; Parker et al., 2003; Stepanski et al., 1995). Parker et al has conducted a polysomnographic study on HD patients and has observed that these patients have a total sleep time and sleep efficiency significantly reduced compared to the general population, while, in comparison with patients affected by

chronic kidney disease but not undergoing dialysis therapy, they have a significantly higher brief arousal index (Parker et al., 2005).
The presence of insomnia among dialysis patients has led to the hypothesis that kidney transplant, by restoring renal function and alleviating many uremic symptoms, might also reduce sleep complaints. A cross sectional study, has used the Athens Insomnia Scale to assess the prevalence of insomnia in a large sample of kidney transplant recipients compared with wait-listed dialysis patients and also a matched group obtained from a nationally representative sample of the Hungarian population. Authors found that the prevalence of insomnia was lower among kidney transplant patients than among those on dialysis (Novak et al., 2006).

2.2 Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS), the major daytime consequence of sleep disturbances, has also been assessed among dialysis patients. EDS is defined by the inability to stay awake and alert during the major waking periods of the day, resulting in unintended lapses into drowsiness or sleep. Prevalence of EDS can be assessed subjectively, by standardized questionnaires, or objectively, by Multi Sleep Latency Test (MSLT). Most studies prefer to use subjective scales. Prevalence of EDS in patients ongoing dialysis therapy varies between 12% and 67% (Mucsi et al 2004, Merlino et al 2006, Hanly et al, American Accademy of sleep medicine). This large variability may be explained by different sample size and cut-off scores to indicate pathological sleepiness.
Parker et al. showed that 32,6 % of hemodialyzed patients had MSLT score < 8 minute and 13% < 5 minutes. MSLT scores were negatively correlated with respiratory disturbances (P= 0,028) and brief arousals (p=0,009). Metabolic parameters and sleep apnea seemed to directly or indirectly influence daytime sleepiness (Parker et al. 2003). Hanly et al. reported that MSLT score was negatively correlated to blood urea nitrogen, a marker of renal function, (r= -0,58; p=0,008. These studies hypothesized some possible mechanisms able to explain the presence of EDS. First, dialyzed patients frequently receive multiple medications, some of which can have sedative effects. Second, sleep apnea and sleep fragmentation, typical among dialyzed patients, can be associated with EDS. Third, renal function might affect the ability to stay awake, due to uremic encephalopathy, elevations of parathyroid hormone and abnormalities in neurotransmitter synthesis. Fourth, inflammatory cytokines may be released following stimulation of neutrophiles by the dialyzing membrane, which may have sleep inducing properties.

2.3 Restless legs syndrome

Restless legs syndrome is a common neurological disorder that is characterized by an urge to move the legs (rarely also the arms) and peculiar unpleasant sensations deep in the legs. Sensations appear during periods of rest or inactivity , particularly in the evening and at the night , and are tipically relieved by movements. Prevalence of RLS in general population ranges between 3 and 5%; RLS may occur as an idiopathic form or secondary to other conditions; the main secondary forms are iron deficiency, pregnancy , use of drugs and kidney disease. The association has been described for other diseases, among them, for diabetes (Merlino et al., 2007; Lopes et al., 2005) and multiple sclerosis (Italian REMS Study Group). RLS secondary to end stage renal disease is one of the most important secondary forms. In the past most of the studies have analyzed only hemodialysis. However, recently

there is an increasing interest on the pre-dialytic phase of kidney disease and on the peritoneal dialysis.

The prevalence of RLS in patients undergoing dialysis varies widely, from 12% to 57,4% (Takaki et al., 2003; Walker et al., 1995). This large variability is due to the heterogeneity of the study population and to the different criteria used to diagnose RLS. Pathophysiology of RLS in ESRD is still unclear. Some studies have suggested a possible role of anemia. In a study with 55 dialyzed patients, authors found RLS's symptoms in 40 % of patients and showed that RLS's patients had lower hemoglobin values compared to others dialyzed patients (P=0,03). Same authors subsequently demonstrated that symptoms in this group of patients improved with the correction of anemia with epoetin alfa (Roger et al., 1991). The role of calcium/phosphate in the pathogenesis of RLS has also been hypothesized. In a study with 136 dialyzed patients, with a prevalence of RLS of 23%, there were no significant differences between the two groups, except for intact parathyroid hormone (iPTH). Uremic patients with RLS showed a significantly lower iPTH ($p< 0,01$) concentration (Collado Seidel V et al., 1998). However, this hypothesis has not been confirmed by other studies. Successful renal transplantation has immediate dramatic effects on uremic RLS. In a study including 11 patients with a long term course of RLS symptoms, they all had a complete recovery within 1 to 21 days after a kidney transplantation. Whereas, among those patients who again became dependent on dialysis due to a chronic transplant failure, RLS symptoms reoccurred within a few days after restarting hemodialysis. (Wilkelmann et al., 2002). In 2005 Molnar et al showed that RLS's symptoms were less frequent in patients after kidney transplantation than in patients undergoing dialysis therapy. Thus, authors suggested that "uremic factors ", responsible for the higher prevalence of RLS in dialysis patients, are largely eliminated after a successful kidney transplantation (Molnar et al., 2005). Differently from transplantation, dialysis did not show any positive effect on RLS. Indeed, studies reported that frequency of dialysis session per week and dialysis dependency, are higher in uremic patients with RLS than in those without it (Gigli et al., 2004; Huiqi et al., 2000). Several observations have suggested an association between RLS and neuropathy, especially with involvement of small sensory fibers. In fact, abnormal hyperexcitability of spinal circuits in RLS could be induced not only by impaired descending dopaminergic modulation, but also by changes in the spinal cord itself (Paulus et al., 2007) or by abnormal inputs as found in peripheral nervous system (PNS) diseases (Gemignani et al., 2006). In general, prevalence estimates of RLS in neuropathy of any kind are extremely variable, ranging from 5.2% to 54% (Rutkove et al., 1996; Nineb et al., 2007). The occurrence of symptoms of burning feet suggested a prominent role of C fibers, assuming that receptors are hyperexcitable due to irritative changes in unmyelinated fibers conveying hot sense (Lacomis, 2002; Ochoa et al., 2005; Ørstavik et al., 2006). Alternatively, abnormal thermal sensations may be produced by impaired central integration of information from nociceptive and thermal channels, as suggested by paradoxical heat sensation produced by A-delta fiber deafferentation (Susser et al., 1999). In accordance with previous data suggesting that RLS occurs preferentially in sensory polyneuropathy of mild to moderate degree and/or in early phase (Iannaccone et al., 2000), patients with RLS had less severe changes in SAPs. This pathogenetical mechanism could explain, at least partially, the association between RLS and ESRD.

There is a lack of studies about prevalence of RLS in patients undergoing PD. Personal preliminary observations suggest that PD patients might have a lower prevalence of RLS than HD patients but higher than "pre-dialysed" patients, with characteristics which resemble more to those of idiopathic forms than of secondary forms. These aspects confirm

the possible role of hemodialysis in causing RLS. RLS symptoms in dialysis are severe and have a negative impact on quality of life and increase the risk of mortality in this specific population. In particular, different studies have showed a correlation between RLS and an increased cardiovascular risk. In particular, periodic limb movements during sleep induce rises in blood pressure, which may play a role in the pathogenesis of cardiovascular diseases (Winkelman et al., 2008). Another possible mechanism is that sleep deprivation, tipically found in patients with severe forms of RLS, can increase inflammatory markers. A persistent and chronic increase of inflammatory markers can be associated with and increased cardio and cerebrovascular risk.

2.4 Sleep apnea syndrome

Sleep apnea syndrome (SAS) is characterized by disordered breathing during sleep, resulting in heavy snoring, repetitive apnea, restless sleep, fragmented sleep structure, morning headache, and daytime sleepiness. Often SAS is associated with personality and mood change such as depression. The following types of apnea can be distinguished: i- obstructive apnea ii- central apnea iii-mixed apnea. Obstructive sleep apnea syndrome is characterized by repetitive closures of the upper airways during sleep, usually at the pharyngeal level, which produce apneas, increasing respiratory effort against the collapsed airways inducing repetitive arousals. Central sleep apnea is characterized by unstable decrease or even absent regulatory motor activity of the respiratory centers in the central nervous system during sleep, leading to apneic episodes. Most central apneas occur at sleep onset. They are characterized by a cycle of decreased or absent respiratory effort or absent respiratory effort and are terminated by ongoing arousals. Apneic episodes lead to microarousals determining a fragmentation of sleep and the activation of sympathetic nervous system.

Studies have reported a high prevalence of SAS in patients with chronic kidney disease. Compared with the general population where the prevalence of SAS is estimated to be 2-4%, prevalence in the ESRD population appears to be 30% or more (Kuhlmann et al. 2000; Young et al. 1993; Kimmel et al. 1989). This is partly explained by the fact that the most common comorbid conditions of ESRD, such as atherosclerosis and diabetes, are also independently associated with ESRD. Among dialysis patients, central and obstructive sleep apnea are almost equally observed, whereas, in the general population the prevalence of obstructive sleep apnea is higher. A mechanism able to cause both destabilization of central ventilator and upper airway obstruction has been suggested. Indeed, central events could be due to metabolic acidosis that may change the apnea PCO2 threshold and consequently destabilize respiratory control. In addition, dialyzed patients show an accumulation of uremic toxins and endogenous opioids that may result in an unstable breathing pattern. Other factors that can worsen SAS in dialysis are: i- the central uremic neuropathy that might reduce airway muscle tone during sleep or destabilize respiratory control; ii- edema from fluid overload that tend to favor upper airway collapse; iii- elevated values of several cytokines (observed during dialysis) that can influence sleep (Vgontzas et al. 2000). Sleep apnea syndrome is frequent both in HD and in PD. In past studies, it was not found a significant difference between these two types of dialysis for sleep apnea. Studies have found that nocturnal peritoneal dialysis (NPD) seems to improve SAS. In a study, Tang et al. recruited 23 NPD patients and 23 Continuous ambulatory peritoneal dialysis (CAPD) patients. The prevalence of sleep apnea with AHI > 15 was 52 % for NPD and 91% for CAPD. Bioelectrical impedance analysis revealed that total body water (TBW) content was significantly lower during NPD

than CAPD (32,8 L vs 35,1 L; p< 0,004). Probably, the improvement of sleep apnea by NPD is due to the improved extracellular fluid control during sleep (Tang et al. 2006).
Similar to nocturnal haemodialysis, improved clearance of uremic toxins after successful kidney transplant would be expected to alleviate SAS, but the relationship between SAS and renal transplant can be viewed as a paradox. In fact, although renal transplant can potentially improve SAS in the dialysis population, the post-transplant state may add another risk for SAS, specifically by predisposing patients to the metabolic syndrome. The prevalence of SAS among renal transplant patients is comparable with the dialysis population: in a study with a population of 1037 kidney transplant patients and 175 patients wait-listed for transplant, 27% of transplant patients had a high risk of SAS that was comparable with 33% in the wait-listed group (Molnar et al. 2007). The possible mechanism that can cause SAS in renal transplant patients is that immunosuppressive therapy, particularly corticosteroids, has been associated with the cushingoid features such as weight gain, obesity, abnormal fat distribution and development of the metabolic syndrome. Brilakis et al. in a study in a population of 17 heart transplant recipients, found an average weight gain of 10,7 kg in 16 patients (Brilakis et al 2000) who were diagnosed with SAS. In another study on cardiac transplant patients, SAS was diagnosed in 36 of 45 patients (80%) studied with polisomnography. In patients with SAS, weight gain was greater that in patients without SAS (Javaheri et al. 2004).

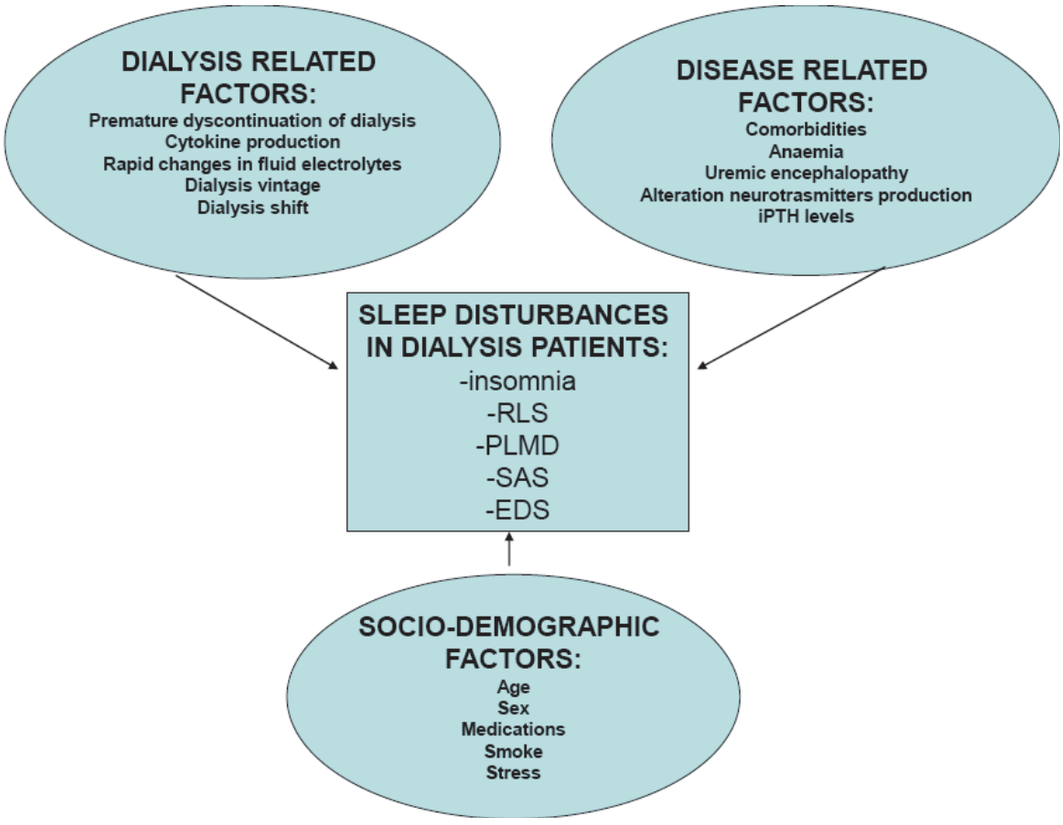


Figure. The possible causal relationships between the different sleep disturbances and the phatogenethical mechanisms is outlined. RLS: Restless Legs Syndrome; PLMD: Periodic Limbs Movement Disorder; SAS: Sleep apnea Syndrome; EDS: Excessive Daytime Sleepiness. Modified from Parker et al., 2003.

The clinical presentation of sleep apnea in ESRD patients is similar to that observed in patients without chronic renal failure, namely the presence of loud snoring and witnessed apneas during sleep, nocturnal awakenings, and excessive daytime sleepiness. However, some of these symptoms may be mistakenly attributed to Chronic renal failure (CRF) itself, or to comorbid condition. This has led to the under-diagnosis and under-treatment of sleep apnea in this specific population. The presence of untreated SAS in this population, can exacerbate the symptoms of CRF, contributing to daytime fatigue and sleepiness and, may exacerbate the cardiovascular complications of ESRD, which are the most important cause of death in this population of patients.

3. Conclusions

In conclusion, sleep disorders are very common among dialysis patients and the pathogenethical mechanism that have been hypothesized are various (see Figure). These disorders play an important role among dialysis patients affecting both the quality of life (sleep disturbances are referred as to one of the most important distressing symptoms) and the mortality risk. The increased mortality risk among dialysis patients affected by sleep disturbances has been demonstrated by many epidemiological studies. In addition, recent studies have also confirmed the association between sleep disturbances, such as RLS, and vascular diseases . These data confirm once more the role of sleep in contributing to the increased vascular risk in dialysis patients. However, more studies are needed in order to better define the pathogenetical mechanism of sleep disorders.

Nephrologists should became familiar with these disorders, promptly identify them in this group of patients and start a proper management in order to improve the quality of life and reduce the vascular risk.

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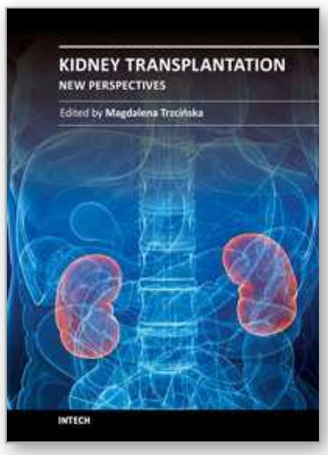
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Although many years have passed since the first successful kidney transplantation, the method, although no longer considered a medical experiment, is still perceived as controversial and, as such, it triggers many emotions and thatâ€™s why conscious educational efforts are still needed for kidney transplantation, for many people being the only chance for an active lifestyle and improved quality of life, to win common social acceptance and stop triggering negative connotations. Apart from transplantation controversies piling up over years transplantologists also have to face many other medical difficulties. The chapters selected for this book are of high level of content, and the fact that their authors come from many different countries, and sometimes even cultures, has facilitated a comprehensive and interesting approach to the problem of kidney transplantation. The authors cover a wide spectrum of transplant-related topics.

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