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The Cycle of Comorbidities

Potential Risks With Delayed Joint Replacement

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Joint replacement is an option that has demonstrated significant improvement in the quality of life for individuals with severe arthritis. However, it is often delayed either in an attempt to avoid future revision surgeries or for other personal reasons. Increasing disability leads to inactivity, chronic pain, and sleep disruption, each of which cycles into significant comorbid risks, many of which are life-threatening. A beginning conceptual framework identified as the cycle of comorbidities is presented to identify these risks and help guide both the patient and the provider in the decision-making process associated with joint replacement surgery.

Approximately 327,000 total hip and 676,000 knee replacements are performed in the United States every year (Centers for Disease Control and Prevention, 2009b). These are large numbers, but they pale in comparison with the number of men and women whose activities are limited because of arthritis, a staggering 50 million adults (Cheng, Hootman, Murphy, Langmaid, & Helmick, 2010). Although quality of life has been shown to be significantly improved with joint replacement, there are many primary care providers who counsel their patients to "wait as long as possible" before considering this option. Their concerns are generally related to the need for future revision surgery.

There is a point in time when the risks of delaying this surgery outweigh the benefits (Camillo, Goodman, Thompson, & Imrie, 2012). A significant number of comorbid conditions can result as functional abilities decline. A comprehensive look at these potential comorbidities is needed to more adequately counsel potential candidates in the decision-making process regarding this surgery. This article offers a beginning conceptual framework for identifying comorbidity risks for individuals with severe hip or knee arthritis who choose or are unable to obtain a joint replacement.

The Cycle of Comorbidities

To fully understand the magnitude of potential risks associated with delayed joint replacement, it is important not only to identify these risks but also to appreciate how they interplay with each other in what we have described as a cycle of comorbidities. We suggest that once an individual becomes affected by one of three conditions that commonly occur with severe arthritis, the risk for significant additional comorbidities is magnified. These conditions are identified as inactivity, chronic pain, and sleep deprivation. A review of the potential impact of each of these states will demonstrate that a vicious cycle of comorbid conditions can potentially result in far more serious outcomes than the risk for future revision surgery.

Inactivity and Arthritis

Analyzing data from the 2001 Behavioral Risk Factor Surveillance Survey, Fontaine, Heo, and Bathon (2004) determined that nearly one-quarter of U.S. adults (23%) reported having doctor-diagnosed arthritis. Of these, 23.8% were physically inactive and 38% reported insufficient levels of physical activity. A similar analysis of data from the 2002 National Health Interview Survey (NHIS) found that almost 44% of adults with doctor-diagnosed arthritis reported no leisure time physical activity compared with 36% of adults without arthritis (Shih, Hootman, Kruger, & Helmick, 2006). Certainly, pain and stiffness account for a large part of these limitations, but this is compounded by the increase in industrialization and computerization over the past few decades, leading to an increase in sedentary lifestyles (Chaput & Tremblay, 2009). The World Health Organization identifies inactivity as an international health concern (Bauman, Finegood, & Matsudo, 2009).

Comorbidities associated with inactivity constitute the first cycle depicted in Figure 1. It includes many

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potentially life-threatening conditions that, when considered individually, are well-known consequences of prolonged inactivity. However, to fully understand the benefit–risk to delaying joint replacement, there needs to be a better macroperspective, one that illuminates all of the possibilities that exist for those individuals with arthritis who delay surgery and become increasingly inactive.

The Diseasome of Inactivity

Simply stated, a diseasome is a method of analyzing and understanding disease using a framework-based approach. Pedersen (2009) modifies and applies this approach in describing the "diseasome of inactivity." In recognizing the relationship of inactivity with several very different diseases, this framework provides an understanding of the underlying pathologies that connect these diseases. The first cycle in Figure 1 is an adaptation of this framework.

At the core of this diseasome is inflammation. Inactivity leads to the accumulation of visceral fat, which then becomes the cause of low-grade chronic systemic inflammation, resulting in a state that fosters insulin resistance and an increased risk for type 2 diabetes. Once this occurs, the individual's risks increase substantially for cardiovascular disease, impaired cognitive function, depression, and several cancers, including colon, breast, pancreatic, liver, and endometrial cancer. If nothing changes, this cascade of comorbidities that was initiated by inactivity will likely continue to perpetrate additional proinflammatory consequences. Recent data from the Centers for Disease Control and Prevention (2008) revealed that inactivity among adults was higher for those who had both diabetes and arthritis than for those who had diabetes alone. This was independent of age, sex, or body mass. Interestingly, the risks for systemic inflammation increased, independent of obesity, in the absence of regular exercise (Fischer, Berntsen, Perstrup, Eskildsen, & Petersen, 2007). There is growing evidence supporting the notion that exercise is anti-inflammatory (Golbidi, Badran, & Laher, 2012; Nader & Lundberg, 2009; Pedersen, 2011; Pedersen & Pedersen, 2005).

Exercise increases circulating levels of well-known anti-inflammatory cytokines and cytokine inhibitors. Classical proinflammatory cytokines such as tumor necrosis factor and interleukin 1 do not increase with exercise (Starkie, Ostrowski, Jauffred, Febbraio, & Pedersen, 2003). This important systemic benefit derived from exercise is lost to those whose arthritic joints might force them to remain inactive while they are delaying surgery.

Inactivity and Heart Disease

Heart disease is the leading cause of death in the United States for both men and women. A 2002 World Health Report estimated that more than 20% cases of coronary heart disease cases in developed countries were due to inactivity (Wise, 2010). For the individual experiencing both arthritis and heart disease, the likelihood of inactivity is 30% greater compared with that for those who have heart disease without arthritis (Centers for Disease Control and Prevention, 2009a). This can lead to even more barriers to physical activity, continuing to stoke the fires of inflammation.

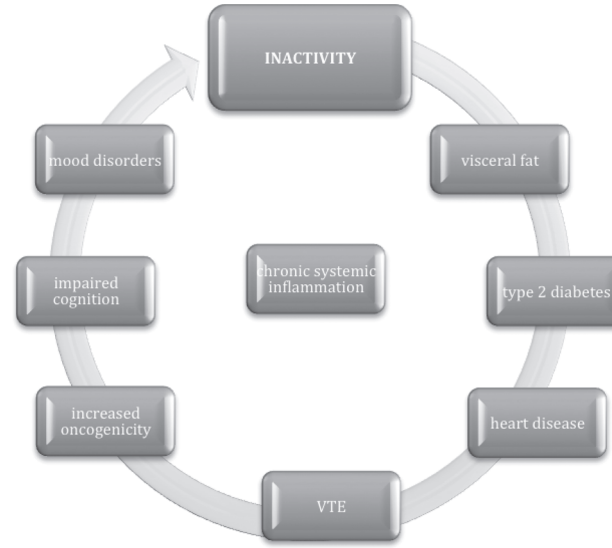

Figure 1. The cycle of inactivity potential comorbidities. VTE = ….

Inactivity and VTE

Although the risk for venous thromboembolism (VTE) on prolonged air flights is widely recognized, recent studies have identified that prolonged seated immobility, outside of air travel, may pose an even greater risk (Aldington et al., 2008). This risk appears to be related to a marked reduction in lower limb venous blood flow. Many inactive individuals with lower extremity arthritis fit this risk profile.

The Impact of Inactivity on Cognition and Mental Health

Several studies have shown that physical activity acts to protect against dementia or cognitive decline (Ahlskog, Geda, Graff-Radford, & Petersen, 2011; Lautenschlager, Cox, & Cyarto, 2012; Rovio et al., 2005). During prolonged inactivity, the release of proinflammatory cytokines can promote neurodegeneration and lead to significant cognitive impairment. Scherder, Bogen, Eggermont, Hamers, and Swaab (2010) argue that as residents of a nursing home become increasingly inactive, they display more behavior associated with agitated dementia.

Chronic elevations in proinflammatory cytokines can also culminate in major depressive disorders (O'Connor, Irwin, Seldon, Kwan, & Ganz, 2007). An analysis of data from the 2002 National Health Interview Survey (NHIS) found the national prevalence of depression in noninstitutionalized persons to be three times higher in adults with arthritis than in those without arthritis (Shih, Hootman, Strine, Chapman, & Brady, 2006). For anxiety, it was 2.5 times higher. The burden of chronic illness often carries a higher risk for depression as evidenced in

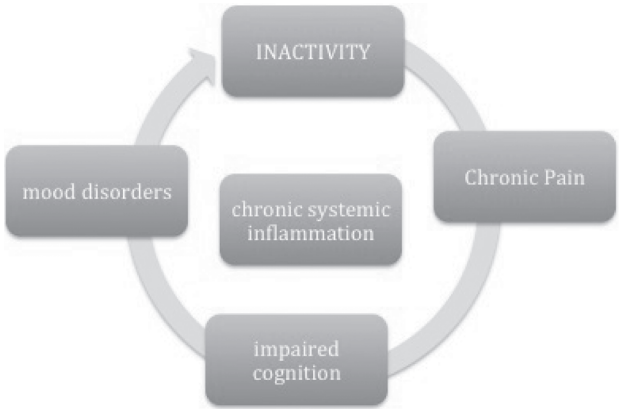

FIGURE 2. Cycling from inactivity to chronic pain potential comorbidities.

other chronic diseases within the cycle of comorbidity, including cardiovascular disease, diabetes, and cancer.

Additional Risks Associated With Inactivity

Although not confirmed, there are observational data suggesting that individuals who are inactive have an increased incidence and severity of nonalcoholic fatty liver disease (Rector & Thyfault, 2011). Characterized by high triglycerides not associated with alcohol intake, this disease can cycle into significant cardiovascular concerns, especially for women.

Inactivity also increases the risks of activity-related injuries. In one study, inactive men were 70% more likely to report walking-related falls (Buchner & Campbell, 2010). This increased risk is attributed to poor balance, less muscle strength, and slower corrective reflexes. Because bone loss is another consequence of inactivity, the risk for fractures occurring as a result of these falls is significant.

There is no doubt that once an individual becomes inactive as a consequence of arthritis, the risk increases for a wide range of potentially life-threatening diseases. These potential comorbidities cannot be ignored when considering joint replacement surgery.

Cycling From Inactivity Into Chronic Pain

There are several points on the inactivity cycle that can lead to chronic pain and vice versa. This cycle moves both within itself and also in relation to chronic pain (see Figure 2). It is especially evident in individuals suffering with arthritis. A population survey conducted in Canada found that 49% of those with arthritis complained of chronic pain (Tunks, Crook, & Weir, 2008). An analysis of the NHIS in the United States found that among adults with arthritis, 25.6% reported severe pain (7 or higher on a 0–10 point scale; Bolen et al., 2010). Of these same adults, 37.7% reported activity limitation and 31.2% work limitation.

Until recently, there have been few population-based studies that focused on the impact of inactivity as a causative factor for pain. A 3-year prospective study following middle years and older women in Australia found the link between physical activity and pain to be related to the amount of activity these women engaged in (Heesch, Miller, & Brown, 2007). With increasing levels of physical activity, older women who did not have or "rarely" had stiff or painful joints were less likely to initiate complaints of arthritis-related pain during the course of the study. Over time, individuals who delay joint replacement surgery and who are unable to remain active because of arthritic joints are at increasing risk of chronic pain and the inflammatory processes created by that physiologic state.

The pathophysiology of acute pain has been well documented (Middleton, 2003); however, chronic pain is very different. It likely involves proinflammatory cytokines as well as a number of neurotransmitters including γ-aminobutyric acid and serotonin. It is the latter that often cycles many chronic pain sufferers into depression.

Chronic Pain and Mood Disorders

Depression is much more common in people suffering with chronic pain than in those in the general population (Bras, Dordevic, Gregurek, & Bulajic, 2010). One study conducted in Canada found a 55.9% depression rate among those with the most disabling pain (Carroll, Cassidy, & Cote, 2000).

Similar to the forward and reverse cycling that takes place with inactivity and pain, chronic pain predicts new depressions and depression predicts the onset of new chronic pain (Tunks et al., 2008). This interconnectedness of chronic pain and depression has been linked once again to inflammation. A prospective study of individuals with no prior history of depression revealed an increase in biomarkers of inflammation prior to the onset of depressed mood (van den Biggelaar et al., 2007). Proinflammatory cytokines appear to increase tryptophan uptake in the brain and enhance serotonin turnover (Dunn, Swiergiel, & Beaurepaire, 2005). Indoleamine 2,3-dioxygenase, an enzyme that is activated by a number of these cytokines, metabolizes tryptophan, an amino acid needed for the synthesis of serotonin (Tektonidou, Caban-Martinez, & Ward, 2011).

Patients with chronic pain also experience a wide range of anxiety disorders. The cycling continues here with pain often signaling anxiety, although anxiety has the propensity to increase the experience of pain. Similar to depression, proinflammatory cytokines as well as certain neurotransmitters are likely involved (Bras et al., 2010). Brain imaging shows a large overlap in those parts of the brain that focus on pain and anxiety (Symreng & Fishman, 2004).

This cycle is further complicated by psychosocial stressors that have also been shown to activate proinflammatory cytokines (Bierhaus et al., 2003). Several of these issues have been documented in a case study focusing on contextual issues related to delaying joint replacement surgery (Camillo et al., 2012). Combined with the need for pain medication, this might help explain the increased prevalence of substance misuse and abuse in this population (Bras et al., 2010).

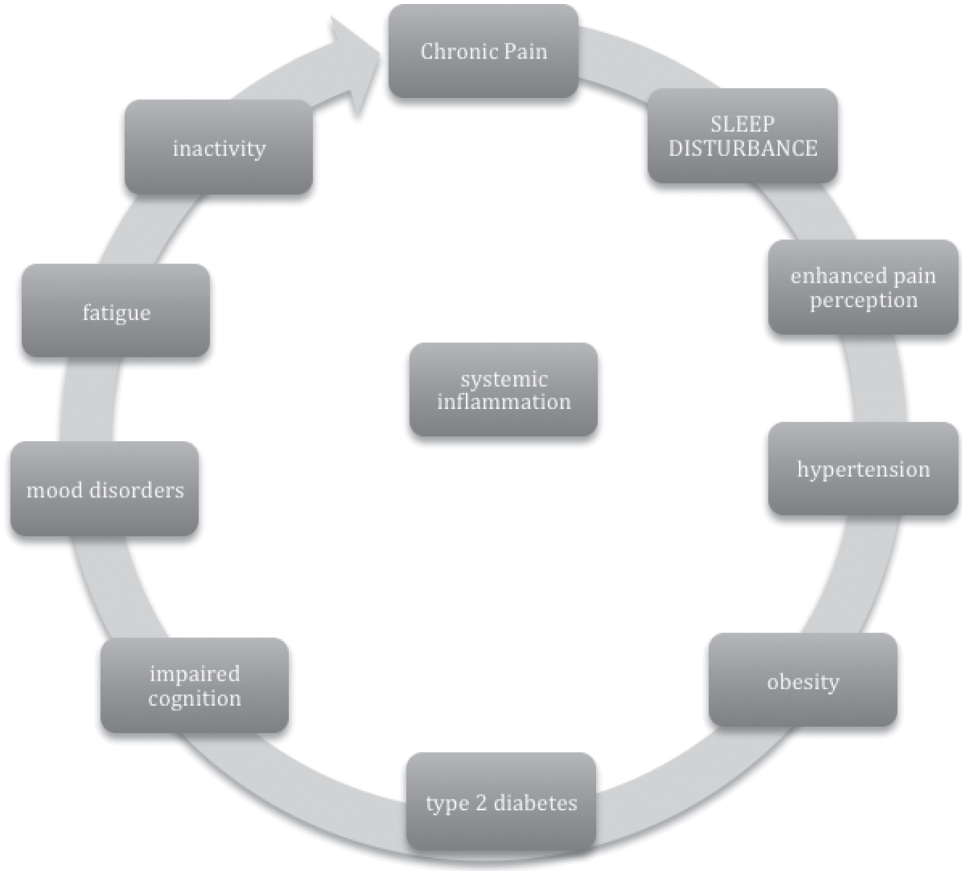

FIGURE 3. Cycling from chronic pain to sleep disturbance potential comorbidities.

Chronic Pain and the Brains Gray Matter

Several imaging studies have demonstrated changes in the brains gray matter in individuals dealing with chronic pain (Kuchinad et al., 2007; Rocca et al., 2006). These changes have been documented as atrophy, damage, or loss leading to the conclusion that this change is permanent. To challenge this assumption, researchers studied the brain imagery of patients before and at various intervals following total hip replacement (Gwilym, Filippini, Douaud, Carr, & Tracey, 2010; Rodriguez-Raecke, Niemeier, Ihle, Ruether, & May, 2009). Presurgery scans showed the typical loss of gray matter found in prior studies of chronic pain. However, there was a significant increase in gray matter detected postoperatively at 9 months, once the patients were completely pain-free. This reversal indicates that at least some of these changes, if not all, are not permanent although there is still a great deal of research needed in this area.

Individuals engaged in the decision-making process related to joint replacement are probably not considering the potential loss of gray matter or their increased risk for mood disorders as a consequence of chronic pain. And yet these comorbidities exact a high price on quality of life that very possibly exceeds the benefit of delaying surgery.

Cycling From Chronic Pain to Sleep Disturbance

Not surprisingly, there is a strong association between chronic musculoskeletal pain and sleep disturbances (Blay, Andreoli, & Gastel, 2007). In evaluating the sleep quality of women with hip arthritis, Parimi et al. (2012) found that for every 5-point increase in their hip pain scores, there was an increase in the odds of spending 90 minutes or more awake after sleep onset. Data from several large studies confirm this relationship. Analysis of the 2007 NHIS found that up to 10.2 million Americans experienced sleep disturbance due to arthritis pain (Louie, Tektonidou, Caban-Martinez, & Ward, 2011). The Canadian Community Health Survey found that sleep disturbances were twice as high for individuals suffering with arthritis (Power, Perruccio, & Badley, 2005).

Similar to inactivity and chronic pain, the cycle of sleep disruption also has components that are bidirectional (see Figure 3). Chronic pain leads to sleep disturbances and a person's perception of pain is often enhanced in the absence of sufficient sleep (Lautenbacher, Kundermann, & Krieg, 2006). The latter once again is probably mediated through proinflammatory cytokines, specifically interleukin 6, which increases with sleep disruption and plays a role in pain perception (Heffner, France, Trost, Ng, & Pigeon, 2011). Evidence suggests that this proinflammatory activity takes place early in the

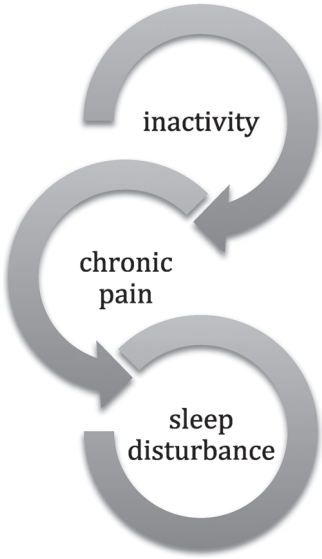

FIGURE 4. Cycles of comorbidity—a macro perspective.

cycle during slow wave sleep (Hong, Mills, Loredo, Adler, & Dimsdale, 2005).

Sleep Disturbances, Obesity, and Insulin Resistance

Although obesity is the result of many complex biopsychosocial interactions, it appears that sleep disturbance can play a significant role. Among sleep-deprived individuals, the risk for obesity was found to increase by 27% compared with those who had adequate sleep (Chaput, Despres, Bouchard, & Tremblay, 2008). Epidemiologic studies confirm that less than 6 hours of sleep per night is associated with increased adiposity (Patel & Hu, 2008).

Metabolic changes related to sleep disturbance contribute to the development of obesity. There is evidence that even short-term, partial sleep restriction decreased carbohydrate tolerance and insulin sensitivity (Donga et al., 2010). Glucose utilization is highest during the waking hours and lowest during REM sleep. After a single night of shortened sleep for healthy individuals, insulin sensitivity dropped 19%–25% (Van Cauter et al., 1991).

Hormones that regulate appetite have also been implicated in sleep-related obesity. Ghrelin stimulates hunger and plasma concentrations have been found to increase with prolonged sleep disruption (Schmid, Hallschmid, Jauch-Chara, Born, & Schultes, 2008). On the contrary, leptin, the hormone that signals a sense of "being full," decreases under these same conditions. Recently, the association between reduced sleep and overeating has also been linked to neuronal patterns specific to restricted sleep that included brain activity in areas linked with reward (St-Onge et al., 2012).

Sleep Disturbances and Cardiac Risk

The cycle from sleep disturbance to obesity can potentially lead to diabetes (Gottlieb et al., 2005) and increased cardiac risk. Individuals who slept less than 6 hours per night were found to be 66% more likely to have hypertension than those getting 7 or 8 hours of sleep (Mullington, Haack, Toth, Serrador, & Meier-Ewert, 2009). As little as half a night of sleep loss could increase blood pressure in individuals with hypertension or prehypertension (Wang, Xi, Liu, Zhang, & Fu, 2012). Although the findings are still inconsistent, C- reactive protein (CRP) has been elevated in several studies addressing the consequences of restricted sleep. As a marker of future adverse cardiac events, elevation of CRP in combination with obesity and insulin resistance makes a compelling argument for the potential risks associated with sleep disruption.

Impact of Sleep Disturbance on Cognition and Mental Health

Cognition can be impacted negatively especially when sleep disruption is chronic. Functions related to operant memory and attention are especially affected and can mimic the disruptions resulting from acute total sleep deprivation of several hours (Orzel-Gryglewska, 2010).

An association between disrupted sleep and mood disorders has been found in individuals with various forms of arthritis, both inflammatory and osteoarthritis (Allen, Renner, Devellis, Helmick, & Jordan, 2008; Leigh, Hindmarch, Bird, & Wright, 1988; Nicassio & Wallston, 1992). Similar to each of the cycles described, sleep disruption can be both a cause and a consequence of various mood disorders. Analysis of the 2007 NHIS found that among adults with arthritis who had sleep disturbances, depression and anxiety were the most common comorbid conditions (Louie et al., 2011).

Sleep Disturbance and Daytime Fatigue

It seems fairly obvious that if a person is not getting sufficient sleep, they might have less energy the following day to be active. For individuals experiencing significant sleep disturbance related to arthritic pain, the odds are much higher. Several of the symptoms presented in these three cycles, including depression, anxiety, joint pain, and limitation due to joint pain, have all been associated with excessive daytime sleepiness (Louie et al., 2011). The higher the level of functional disability among those with osteoarthritis, the greater the fatigue (Stebbings, Herbison, Doyle, Treharne, & Highton, 2010). Many of the same markers of inflammation identified with inactivity and chronic pain are also associated with fatigue and poor health-related quality of life (Thomas, Motivala, Olmstead, & Irwin, 2011).

Cycling Back to Inactivity

With increasing sleep loss comes reduced physical activity. The result is a shift in energy homeostasis toward weight gain. This increases the odds for developing visceral adiposity and the associated inflammatory processes that accompany it. And, once again the individual is back into the cycle of inactivity (see Figure 1). Each of the three cycles described in this study can lead

Table 1. Impact of Joint Replacement on Comorbid Risks

Joint Replacement Benefits	Risk Reduction
Improved mobility	Type 2 diabetes
	Heart disease
	VTE
	Obesity
	Mood and cognition disorders
	Cancer
	Chronic pain
Decreased pain	Depression
	Anxiety
	Lose of gray matter
	Sleep disturbance
	Hypertension
	Obesity
	Type 2 diabetes
	Impaired cognition
	Fatigue
	Inactivity
Better quality sleep	Pain
	Fatigue
	Obesity
	Diabetes
	Hypertension
	Impaired cognition and mental health
	Inactivity

Note. VTE = ….

into each other and create a very disabling maze of comorbid conditions (see Figure 4).

Summary

The purpose of this article is to begin development of a conceptual framework for understanding the complexity of comorbidities that can occur once an individual becomes inactive with severe arthritis and delays joint replacement surgery. Three major areas of concern typically found in individuals experiencing significant joint disease were isolated, each creating a predictable cycle of comorbid conditions. Central to each of these cycles is chronic systemic inflammation.

An understanding of these comorbidities is critical when considering the benefit–risk for joint replacement surgery. Currently, there are no objective criteria to help guide the patient or the practitioner in this decision. The advice among many primary care providers is to "wait as long as possible." The risk that is often identified is the need for future revision surgery, but the magnitude of this risk pales in comparison to some of the potentially life-threatening conditions outlined in this article. Table 1 presents a summary of benefits associated with joint replacement and the associated reduction in risk for several of these comorbid conditions.

Quality-of-life conversations are important and certainly address several elements within each of these cycles, but when it is the only consideration in the decision for or against surgery, the extent and severity of potential comorbidities might not be fully appreciated. The development of a conceptual framework to highlight these comorbidities can be a useful tool for both the practitioner and the patient who are engaged in these conversations.

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