Keywords Urinary retention/Renal calculi/Libido/Immune response

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In this article...

- Harmful effects of prolonged bedrest on renal excretion, libido and immune response
- How urinary retention can lead to urinary tract infection and renal calculi formation
- Prolonged immobility and risk of reactivation of latent viruses

Effects of bedrest 4: renal, reproductive and immune systems

Key points

Prolonged bedrest can cause electrolyte imbalances, urinary retention, urinary tract infection and renal calculi

It has also been linked with falling levels of sex hormones in men and women

The idea that bedrest may increase the chance of pregnancy after intrauterine insemination is disputed

Immobility has a pro-inflammatory effect and bedrest weakens the immune system

Encouraging mobilisation in bed or from the bed to a chair appears to reduce the risk of urinary tract infection

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Abstract This article – the fourth in a series exploring the physical and psychological consequences of bedrest – describes changes to the renal, reproductive and immune systems induced by prolonged bedrest and immobility.

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Periods of prolonged bedrest are often unavoidable, for example when recuperating from a traumatic injury in which multiple bones have been fractured or when recovering from a severe infection or sepsis. Indeed, in some cases, bedrest is still prescribed, most frequently in pregnant women who are at risk of entering preterm labour or in those who have had prematurely ruptured membranes or required a cervical stitch.

However, bedrest has many adverse effects on body function and the body's systems, including the renal, reproductive and immune systems. For example, patients confined to bed for longer periods are at increased risk of urinary retention, urinary tract infections (UTIs) and kidney stones (renal calculi). Prolonged bedrest may reduce libido and, in women, disrupt the menstrual cycle. It is also likely to weaken the immune response, increasing the risk of infection as well as the risk of reactivation of latent viruses.

Effects on the renal system

Renal function and excretion

The rare studies that exist on the subject have shown that prolonged bedrest (≥60 days) was associated with a reduction in glomerular filtration rate (the rate at which fluid is filtered through the kidney and an indicator of renal health) (Arinell et al, 2011). Urea is the main nitrogenous waste product resulting from protein breakdown (catabolism) and is rapidly eliminated in the urine by the kidneys. During bedrest, the concentration of urea in the blood increases and the kidneys eliminate larger amounts of urea.

As food intake usually decreases during bedrest (see part 3), it is speculated that these higher concentrations of urea in blood and urine can only come from the catabolic breakdown of endogenous protein sources, such as muscle and other lean tissues (Bilancio et al, 2014). This correlates with the reduction in lean tissue mass and sarcopenia that are characteristic of prolonged immobility.

Electrolyte concentrations

With prolonged bedrest, diuresis (see part 1) brings about a loss of electrolytes such as sodium, potassium, calcium, zinc, phosphorus, sulphur and magnesium over time (Rousseau, 1993). This loss of electrolytes is exacerbated in patients on long-term diuretic medications, as well as in

older people, in whom normal ageing leads to a loss of nephrons and a reduced tubular area for electrolyte reabsorption into the blood (Andrade and Knight, 2017).

Sodium loss occurs rapidly in the early stages of bedrest, primarily because reduced levels of antidiuretic hormone (see part 1) cause diuresis and lead to a drop in total body sodium (Rousseau, 1993). As hyponatraemia (low blood sodium) and reduced blood volume trigger the release of aldosterone (see part 3), sodium levels tend to stabilise. Increased aldosterone secretion limits the further loss of sodium, but it also causes a progressive loss of potassium in the urine.

Fluid and salt supplements have been shown to help normalise both hydration status and electrolyte levels in people who are confined to bed (Zorbas et al, 2002). However, patients will require careful assessment of their health status, electrolyte levels and renal function before such supplements can be safely given, and will also need continuous monitoring of their electrolyte levels.

In people who are confined to bed, plasma calcium levels gradually increase, largely due to bone demineralisation (see part 6). Mild hypercalcaemia is commonly seen within the first days or weeks of immobility. It usually causes no physical symptoms or clinical signs and can be reversed on resumption of normal weight-bearing exercise (Lewis, 2018). Patients who do display clinical signs of hypercalcaemia need careful assessment and immediate treatment, because this can quickly become a medical emergency due to the risk of dysrhythmia and coma (National Institute for Health and Care Excellence, 2014).

Fig 1. **Formation of renal calculi**

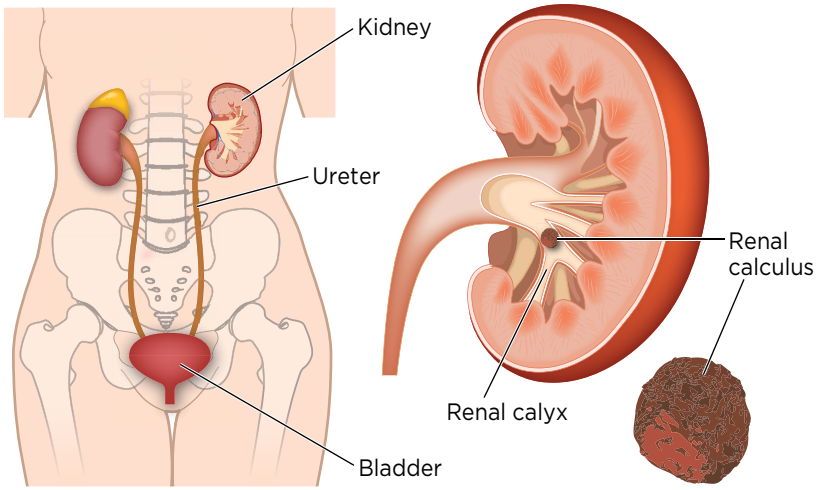
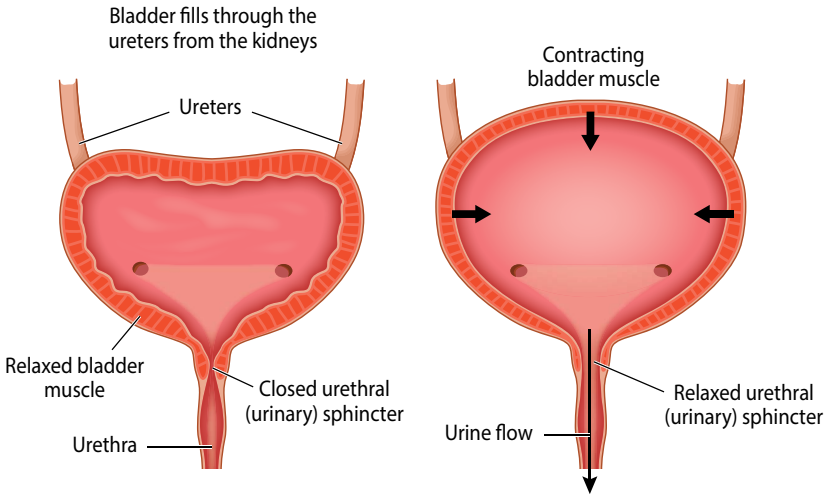


Fig 2. **Filling and emptying of the bladder**



Urine distribution

When the body is in the upright position, gravity encourages urine to drain from the kidneys through the ureters into the bladder. In the supine position, urine is transported from the kidneys to the bladder by peristaltic waves generated in the walls of the ureters. However, the renal calyces rely entirely on gravity to drain fully so, when the body is in the supine position, urine collects in the lower portions of the renal calyces, where it forms small static pools. This increases the risk of renal calculi formation (Fig 1).

Urinary retention

In the upright position, gravity makes urine collect in the lower portion of the bladder. It also causes the abdominal organs to move downwards and press on the bladder. As the bladder fills, pressure is exerted on its walls, neck and urinary sphincter, stimulating stretch receptors (which monitor bladder filling) and the urge to urinate (VanPutte et al, 2017) (Fig 2). In the supine position, the abdominal organs shift towards the thorax (see part 1) and pressure on the bladder is reduced. This can significantly decrease the urge to urinate, even when the bladder is full.

Urinary retention is the inability to completely or partially empty the bladder. When confined to bed, patients often find it difficult to completely empty the bladder into a bedpan or urine bottle. They may feel uncomfortable and embarrassed. The risk of urinary retention is increased by factors, such as constipation or pain, which may restrict movement. An over-distended bladder stretches the smooth muscle layer in the bladder wall and, over time, the stretch receptors may lose sensitivity – this will further reduce the urge to urinate.

Urinary retention is more likely in patients who have neurological deficits or mobility problems. Additionally, an enlarged prostate, bladder tumours or kidney stones may obstruct urine flow and lead to accumulation of urine in the bladder. This may

PETER LAMB

require urgent attention and a catheter may be required to empty the bladder. However, catheters should not be used unless clinically necessary, as they increase the risk of UTIs. If their use cannot be avoided, they must be removed as soon as clinically indicated.

Urinary retention is more common in patients who are taking non-steroidal anti-inflammatory drugs (NSAIDs), because these drugs can interfere with the production of prostaglandins (which play a role in regulating the contraction of the smooth muscle in the bladder wall). Verhamme et al (2005) showed that men taking NSAIDs were twice as likely to have acute urinary retention as those not taking NSAIDs.

Nurses need to encourage patients to drink water on a regular basis. This will not only promote hydration but will also lead to more rapid filling of the bladder, which will, in turn, increase the urge to urinate. When possible, patients should also be encouraged to go to the toilet, rather than using a bedpan or a urine bottle in bed, as gravity in the upright position will increase the urge to urinate. In the absence of pathology, patients who can resume normal activities upon remobilisation usually regain normal bladder function relatively quickly.

Renal calculi and UTIs

Prolonged bedrest increases the risk of precipitation and crystallisation of urinary solutes, which can lead to the formation of renal calculi.

A major detrimental effect of prolonged bedrest is the gradual demineralisation of bone tissue (see part 6). The main minerals that are lost from bone are ionic calcium and phosphate, which accumulate in the blood and are excreted in the urine and faeces. After five weeks of bedrest, calcium excretion by the kidneys typically increases by around 50mg per day (Zerwekh et al, 2007). As urine pooling in the renal calyces is common in patients who are confined to bed, an excess of calcium in the glomerular filtrate – and subsequently in the urine – will increase the risk of renal calculi formation (Fig 1).

Urine retention and pooling encourage the growth of urea-splitting bacteria such as *Proteus* species, which are a common cause of UTIs. These motile bacteria can work their way up the urinary tract in large numbers, which gradually:

- Increases the pH of the urine (making it more alkaline);
- Encourages the precipitation of calcium;
- Contributes to the formation of the most common type of renal calculi, composed of calcium oxalate.

The risk of renal calculi may be reduced by light bed exercises (if patients are able to do them) and by intake of bisphosphonates (Okada et al, 2008) and potassium-magnesium citrate (Zerwekh et al, 2007). However, bisphosphonates and potassium-magnesium are not routinely prescribed to patients during bedrest because their beneficial effects have only been demonstrated in small groups of patients. Increasing the consumption of fresh fruit and vegetables will help alkalise the urine, thereby impeding the formation of calculi (Frassetto and Kohlstadt, 2011) as well as boosting vitamin and mineral intake.

> *"There is a higher risk of UTI in patients with urinary or faecal incontinence as many bacteria can migrate into the urinary tract"*

Immobility is known to increase the risk of UTI, with older people being particularly at risk (Ariathianto, 2011; Rogers et al, 2008). Urinary retention fosters infection so normal urinary flow is essential to flush bacteria such as *Staphylococcus aureus* and *E. coli* from the bladder. In addition, overdistension of the bladder can cause small cuts or tears in its epithelial lining, providing sites for opportunistic infection.

Immobile patients with a catheter are at additional risk of UTI, as catheters offer a route from the exterior environment directly into the bladder. In post-menopausal women, decreasing oestrogen levels increase vaginal dryness, which is associated with a depletion of the 'friendly' lactobacilli that usually outcompete pathogenic species (Raz, 2001).

There is also a higher risk of UTI in patients with urinary or faecal incontinence, because many bacteria are motile and can migrate into the urinary tract. In older men, benign enlargement or inflammation of the prostate makes micturition difficult, which increases the risk of urinary retention and UTI.

Encouraging mobilisation, even in bed or from the bed to a chair, appears to reduce the risk of UTI (Rogers et al, 2008).

Effects on the reproductive system

The effects of immobility on the male and female reproductive systems have not been extensively studied and are poorly understood. In men and women, prolonged bedrest has been linked with decreasing levels of circulating sex hormones (Brown, 2008). Studies examining the levels of testosterone in men who are immobile are contradictory: some report reductions in testosterone, which may be linked to reductions in muscle and bone mass (see parts 5 and 6), while others report little change, even with prolonged bedrest (Smith et al, 2012).

Immobility is certainly associated with reduced sexual desire (Brotto and Smith, 2014). Conversely, regular physical activity is associated with a healthy libido. Many immobility-induced factors may affect libido, such as increased frailty and reduced ability to maintain routines of personal hygiene and grooming, which can also have a negative affect on an individual's self-image and confidence.

In women, an active sex life and regular exercise are associated with a stable menstrual cycle. Prolonged bedrest or a very sedentary lifestyle can lead to menstrual cycle irregularities. In a study of prolonged bed rest of 60 days, a general lengthening of the menstrual cycle is often observed (Wade and Baer, 2007).

Low levels of physical activity in women are also associated with a reduction in circulating oestrogen and androgens (Bertone-Johnson et al, 2009). As oestrogens are important for maintaining bone health, this may contribute to the reduction in bone density that has been seen in women who are confined to bed (see part 6), while the reduction in circulating androgens may aggravate the possible loss of libido.

Other research has noted not only a longer menstrual cycle in those women who are inactive, but also longer menstruating times (Gudmundsdottir et al, 2014). Bedrest used to be – and in some cases still is – prescribed in the hope that it will increase the chance of fertilisation and implantation when assisted reproduction methods have failed. However, a recent systematic review shows that bedrest is actually detrimental to the chances of a successful pregnancy after embryo transfer (Craciunas and Tsampras, 2016).

Similarly, in the past there has been a belief that prescribed bedrest would help to increase the chance of pregnancy after intrauterine insemination; this is now also disputed, with current research indicating no increase in pregnancy rates (European Society of Human Reproduction and Embryology, 2016).

Effects on the immune system

Changes in immune responses after bedrest have been reported. Most studies explore the immunity of volunteers undergoing head-down bedrest to simulate spaceflight, but similar effects would be expected from prolonged bedrest in patients in hospital.

The haematopoietic activity of red bone marrow is increased in bedrest, with increased numbers of lymphocytes and pro-inflammatory phagocytic neutrophils; adhesion molecules (which allow neutrophils to attach to the walls of blood vessels before leaving the vascular system to enter tissues) are up-regulated during periods of immobility (Choukèr et al, 2001). This reinforces the belief that immobility is pro-inflammatory.

One of the most significant findings regarding the effects of prolonged immobility on the immune system is that it tends to reactivate latent viruses. Immobility for 21 days is associated with decreased levels of interferon gamma and tumour necrosis factor alpha, key chemicals involved in the cell-mediated immune responses that fight off viral infections (Kelsen et al, 2012). Sonnenfeld et al (2007) found that the Epstein-Barr virus was reactivated in subjects exposed to a 60-day bedrest, with a dramatically increased viral load.

Maintenance of viral latency is largely determined by immune status: many studies relate viral reactivation to an immunocompromised or an immuno-suppressed state. Sonnenfeld et al (2007) suggested that patients with known immunosuppression – such as patients who are HIV positive or those on immunosuppressive medication – may be at particular risk of viral reactivation during prolonged immobility. Patients in intensive care units can often be immunocompromised, and there is a risk of reactivation of viruses such as cytomegalovirus and other herpes viruses, which can cause potentially fatal complications such as viral pneumonia (Textoris and Mallet, 2017).

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The production of interleukins (ILs) seems to be adversely affected by bedrest. A decrease in the production of IL-2 (responsible for growth, proliferation and activation of T and B lymphocytes and natural killer cells) has been found in patients confined to bed. This may compound an already weakened immune system. Increased levels of IL-1 beta have also been reported: this IL is a pro-inflammatory messenger associated with fever that may also be involved in bone mineral loss.

> *"Patients who are on immunosuppressive medication may be at particular risk of viral reactivation during prolonged immobility"*

Antibodies work by binding to foreign pathogens, marking them out for destruction by leukocytes; as such, they have a key role in the immune response. Immobility has been associated with a significant decrease in the level of circulating plasma antibodies. However, people who undertake exercise during periods of bedrest appear to maintain higher levels of circulating antibodies (Craven and Hirnle, 2016; Shearer et al, 2009).

Conclusion

To counter some of the negative effects of prolonged bedrest on the renal, reproductive and immune system, patients confined to bed need to be encouraged to stay well hydrated and mobilise as much as possible, undertaking exercise in bed and, when possible, out of bed. **NT**

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