Letter to the Editor

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Incontinence in Patients With Underactive Bladder

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In their article, "Management of Urinary Incontinence With Underactive Bladder: A Review" Cho and Kim [1] discuss different approaches to the management of urinary incontinence in patients with underactive bladder (UAB). As the authors point out, incontinence treatment requires that either the detrusor activity is decreased, which is the treatment principle in overactive bladder/detrusor overactivity, or that the bladder outlet resistance is increased, as is the basis for management of stress urinary incontinence (SUI) caused by e.g., intrinsic sphincter insufficiency or urethral hypermobility. To be able to void if the detrusor contractility is compromised, as in UAB/detrusor underactivity (DU), the outlet resistance has to be decreased or the detrusor contractility increased. Therapeutically, control of bladder outlet resistance can be achieved by surgery or by drugs, but so far there is no effective way to improve decreased detrusor contractility. Continence is dependent on the interaction between the urethral sphincter and the detrusor, and since the functional importance of each of these components may vary, the therapeutic problem in the individual patient is to find a suitable balance between them. In patients with both SUI and DU, Cho and Kim [1] point out the advantages and high success rate of conventional midurethral and adjustable slings. In most studies cited, there were no differences between SUI patients with or without DU. This calls into question whether the preoperative voiding pattern in these patients has any influence on the outcome.

In 16 normal women, investigated by simultaneous urethrocystometry, Rud et al. [2] demonstrated that at the initiation of voiding, there was a decrease in the maximum intraurethral pressure immediately before micturition. However, in 13 patients with SUI, 3 different ways of initiating micturition were observed. Five patients were able to initiate voiding by the Valsalva manoeuvre, 3 mainly by decreasing the maximum urethral pressure, and 5 emptied mainly in the same way as the normal women. Miller [3] reported that up to 20% of neurologically normal women can empty their bladder by an efficient Valsalva manoeuvre without a detrusor contraction. Several studies have suggested an association between inadequate detrusor contraction and postoperative urinary retention after anti-incontinence surgery [4,5]. Pham et al. [6] reported that the risk of urinary retention after this procedure was higher in women who voided by the Valsalva manoeuvre (22%) compared to those who voided by detrusor contraction (5%). It thus seems that in the Valsalva voiders (not using or not having a detrusor contraction) the increase in intra-abdominal pressure generated is insufficient to overcome the increased outlet resistance caused by the sling operation. These findings emphasize the importance of intra-abdominal pressure in sphincter control. However, whether its generation can be improved by pelvic floor physical therapy/biofeedback prior to sling placement can minimize the risk of postoperative urinary retention remains to be studied.

Underactive bladder (UAB)—the term covering both DU as the urodynamic diagnosis, and UAB syndrome for its symptomatic manifestations—can be caused by many diseases and disorders, several of which will simultaneously engage not only sensory and central nervous factors, but also bladder neurotransmission and the detrusor muscle [7,8]. There are no standard treatments for UAB/DU, which is not surprising considering the wide variety of aetiologies. Several reviews have dis-

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cussed current treatment alternatives and their limitations in detail, including pharmacotherapy e.g., alpha-blockers, cholinesterase inhibitors, muscarinic agonists, prostaglandin E2, and acotiamide, surgical treatments such as sacral nerve electrical stimulation, injections into the external sphincter, surgeries to be performed for bladder outlet obstruction [9,10]. Behavioural and clean intermittent catheterization treatments and pharmacotherapy are often palliative, and new treatment alternatives are urgently needed. Whether drug treatment of associated morbidities (e.g., diabetes mellitus, Parkinson disease, and multiple sclerosis) can improve impaired bladder emptying is unclear.

Among potential future alternatives, tissue regeneration by cell therapy seems attractive to provide a permanent cure. There have been promising results of different types of cell therapy in promoting detrusor activity in preclinical models of obstruction-induced and other models of DU [11], but evidence for efficacy in humans is scarce or lacking. However, the principle seems to work for improvement of sphincter function, also in humans. Despite this, stem cell therapy for SUI is not yet available for general clinical use. So far only modest efficacy has been documented [12,13]. Contributing to this may be a loss of stem cell function following *ex vivo* expansion, poor *in vivo* engraftment or survival of cells after transplantation, a general lack of understanding of the precise mechanisms of *in vivo* behaviour of stem cells administered to target organs, and/or other factors underlying therapeutic outcomes. A more current thought is that bioactive factors produced by stem cells, which have cell mobilization, vasculogenic, neurogenic and antifibrotic properties, are the major players in tissue regeneration [14]. One of these bioactive factors, the chemokine CXCL12, seemed superior to stem cells in restoring urinary sphincter function through its beneficial effects on cell mobilization, fibrosis, vascularization, and innervation in rodent and nonhuman primate models of chronic fibrotic urinary incontinence. However, CXCL12 has not yet been tested in bladder dysfunction. If CXCL12 can be shown to restore both compromised bladder contractility and improve sphincter function, it would be an attractive treatment alternative in patients with incontinence and UAB/DU, but this needs to be shown in future studies.

Among the many reviews on treatment of UAB/DU, some of which were cited previously, few have focused specifically on the treatment of incontinence in the presence of UAB/DU. Due to the many factors involved, it has to be dealt with on an individual basis. The review by Cho and Kim [1] highlights how the disorder is currently managed, but also underlines the problems. Their plea for further research is strongly supported.

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