Clinical pharmacology of old age syndromes

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Several syndromes occur in old age. They are often associated with increased mortality and in all there is a paucity of basic and clinical research. The recent developments in the clinical pharmacology of three common syndromes of old age (delirium, urinary incontinence, and falls) are discussed along with directions for future research.

Keywords: elderly, delirium, pathophysiology, pharmacological, nonpharmacological, treatment

Delirium (C. Broadhurst, K. C. M. Wilson)

Introduction

Between 10 and 40% of elderly medical inpatients suffer from delirium [1, 2]. This condition is associated with increased mortality and length of hospitalization [3]. Moreover, residual cognitive impairment is experienced by a significant number of people [4].

Pathophysiology of delirium

The electroencephalogram is useful in the diagnosis of delirium with early slowing of the α waves and later bilateral synchronous δ waves [5]. Anticholinergic drugs are associated with a high risk of delirium [6]. In such cases, delirium is reversed with physostigmine [7]. Elevated anticholinergic activity has been reported in delirious elderly medical inpatients [8] and other studies [9, 10]. Dopamine excess is also implicated. Dopamine agonists such as L-Dopa can cause delirium [9] and dopamine antagonists such as haloperidol and the atypical antipsychotics are effective treatments [11, 12]. However, antipsychotic drugs can also cause delirium [12]. Overactivity of noradrenaline is implicated in delirium tremens. The antiadrenergic drug clonidine is used as a treatment [13] and raised cerebrospinal fluid, serum, and

urine levels of noradrenaline have been observed [9, 14]. Overactivity of serotonin has been reported in animal models of delirium [15] and clinical studies [16, 17]. On the other hand, a reduced serotonergic activity is supported by low levels of tryptophan [18]. Drugs enhancing serotonergic function can cause delirium [19] but are also used to treat the disorder [20]. Benzodiazepines are a useful treatment of delirium tremens [21] but they also cause delirium [11]. Flumazenil, a benzodiazepine antagonist, can briefly restore mental capacity in delirium [22]. Abnormalities of γ amino butyric acid [23, 24] and glutamate [25] function have also been reported in delirium, particularly in hepatic encephalopathy [26]. Decreased cerebrospinal levels of β -endorphin [27] and somatostatin [28] have also been observed. Patients treated with interleukin-2 for cancer have a high incidence (30–50%) of delirium [29, 30]. Increased activity of the hypothalamic–pituitary–adrenal axis is observed in up to 78% of patients with delirium [31].

Nonpharmacological treatment of delirium

The management of delirium requires a dedicated multidisciplinary team. Good evidence for this is lacking, however, [32]. Diagnosis can be difficult [33] and the team needs knowledge of the syndrome of delirium, time to make repeated assessments and talk with relatives, and skills to assess an uncooperative patient. The many causes of delirium need to be adequately explored by full physical examination and investigations [11, 34]. Carers and nursing staff need to be aware of the states of perplexity, fearfulness, and paranoia that frequently accompany delirium [11]. The patients require repeated re-orientation and reassurance [34]. Measures to maximize these by modifying the environment include windows in intensive care units [11], good lighting, spectacles and hearing aids made easily available [34–37].

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Pharmacological symptom control

A recent review engendered debate in relation to the use of high-dose haloperidol [36, 38, 39]. Compared with other neuroleptics it has fewer anticholinergic side-effects and there are few metabolites. An ECG is advisable with respect to monitoring the QTc interval. Intravenous haloperidol has been associated with risk of fatal arrhythmia. The evidence base supporting its use and the use of the newer neuroleptics is very weak. All psychotropic drugs can cause delirium, mask a lowering of the conscious level, and induce important adverse drug reactions, such as falls, hypotension and parkinsonism.

Breitbart studied 244 hospitalized patients with acquired immunodeficiency syndrome and delirium [40]. There was a significant improvement with haloperidol and chlorpromazine, but not with lorazepam. Although two double-blind trials comparing the efficacy of haloperidol and droperidol reported similar efficacy [41, 42], the latter has subsequently been withdrawn from clinical use in the UK [43]. Haloperidol is effective when used to treat agitation and/or psychosis in elderly medical inpatients [44]. The dose range advised in this group is 0.5–2 mg 1–4 hourly (maximum 10 mg 24 h⁻¹) [34].

Intravenous haloperidol has become the drug of choice for sedation of the acutely agitated delirious paediatric or adult patient in the critical care setting [45]. Close ECG monitoring is advised because of a risk of ventricular arrhythmias and prolongation of the QTc interval. This appears to be an unpredictable idiosyncratic reaction [46, 47]. Midazolam can be used as an alternative in very agitated patients and is administered as an i.v. infusion [48].

A recent review has summarized evidence concerning risperidone, olanzapine, and quetiapine in treating the symptoms of delirium [49]. The new atypical antipsychotics focus on serotonergic pathways and have fewer side-effects. The effects of risperidone have been described in case reports but no large trial has been performed. Three studies looked at small groups of patients receiving 1–2 mg of risperidone daily and reported significant improvement after 5–10 days with minimal side-effects [50–52]. These and other studies have led to an increasing trend towards the use of low-dose risperidone (0.5 mg twice daily).

Likewise, olanzapine has been studied through a series of case reports. In three studies, a significant improvement was observed after 3–7 days in 1–20 patients receiving doses of olanzapine between 5 and 10 mg [53–55]. In one study there were more side-effects in the haloperidol comparison group. In a group of cancer patients, olanzapine induced a complete resolution of delirium in 76% of cases [56] although it was mostly ineffective in treating patients over 70 years of age. Therefore, olanza-

pine appears to be a clinically efficacious and safe drug for the treatment of the symptoms of delirium in the hospitalized medically ill but may be less effective in elderly patients. A reasonable starting dose in this group is 2.5–5 mg nocte. Schwartz *et al.* compared quetiapine with haloperidol in a small retrospective study of patients with delirium and reported similar efficacy [57]. For quetiapine, 25–50 mg twice daily is a reasonable starting dose in the elderly, although evidence is minimal.

Benzodiazepines may be useful in severe agitation in delirium but have also been associated with increased adverse reactions. Lorazepam is the preferred agent as it has a short half-life and few metabolites. The usual dose is 0.5–1 mg 4-hourly. When used with haloperidol, it reduces the dose requirement of the latter [58].

Mianserin (a tetracyclic antidepressant) has been shown to have similar efficacy in the treatment of delirium to haloperidol in two small prospective studies from the same centre [20]. An involvement in the acetylcholinergic pathways has been hypothesized in the pathogenesis of delirium [2, 9], therefore suggesting a possible therapeutic role for the new anticholinesterase inhibitors used in Alzheimer's disease [59]. Studies addressing this issue are currently underway. Wengel *et al.* reported a single case of a patient with dementia who had an episode of delirium, which resolved rapidly with donepezil [60]. The pro-cholinergic drug citicoline was studied in a randomized study of 46 placebo and 35 treated elderly patients before and during hip fracture surgery, but the incidence of delirium was not reduced [61]. Aizawa *et al.* treated 42 elderly patients with diazepam, flunitrazepam, and pethidine for three nights postoperatively [62]. The incidence of postoperative delirium was markedly reduced but there was morning lethargy in 40% of the treatment group.

Symptom control in acute alcohol withdrawal

The use of i.v. thiamine in all elderly delirious patients has been recommended by Sumner *et al.* [63]. Chlormethiazole and benzodiazepines are the most effective treatments. They are often combined with neuroleptics. Clonidine has been reported as being useful for controlling the adrenergic symptoms [13, 64]. The standard therapy in Europe (except the UK) is oral monotherapy with chlormethiazole with severe symptoms necessitating i.v. chlormethiazole or benzodiazepines [65]. However, chlormethiazole carries the risk of respiratory insufficiency, cardiovascular complications and uncertain blood levels [66]. In a recent prospective study, chlormethiazole, tiapride, and carbamazepine were similarly effective [67]. Less severe alcohol withdrawal syndromes can be treated with carbamazepine [68]. In the UK, benzodiazepines are the preferred agents where there is withdrawal

from alcohol or other substances [21]. A reducing course of chlorthalidone and thiamine injections is used in cases of acute alcohol withdrawal [69]. Benzodiazepine therapy seems to be more effective if specifically triggered by the patient's symptoms rather than prescribed regularly [70].

Future directions

Britton and Russell [32] performed a Cochrane review on the multidisciplinary team interventions for delirium in patients with chronic cognitive impairment. They concluded that 'there is scope for research in all areas, from basic pathophysiology and epidemiology to prevention and management'.

Prevention of delirium is difficult but a recent large multicomponent intervention study of 852 hospitalized elderly patients reduced the incidence of delirium significantly [71]. Putting the active intervention measures into use requires time and funding which are lacking in acute medical wards in the UK. In the area of pathophysiology, we are starting to understand more about the mechanisms following neuronal insults. Cytokine research has given us new lines of treatment either to augment neuroprotective cytokines such as insulin-like growth factor-1 (IGF-1) [72] or to antagonize cytotoxic cytokines such as tumour necrosis factor- α and interleukin-1 [73, 74]. The latter are now licensed to treat diseases involving cellular insults. However, there has been a lack of such research in delirium [75] when compared with other areas of psychiatry [76]. Clinical studies are needed in different populations of delirious patients both to examine the putative neurotransmitters/modulators discussed earlier and to assess whether or not agents that modify their action are effective. Controlled studies are essential since treatment with psychotropic drugs in the elderly with delirium might prove to cause more problems than they solve. Careful systematic studies assessing the appropriate starting doses are also required, as are further studies assessing the nonpharmacological treatments. Education is particularly needed. One way forward might be for a group of old-age-specialist physicians and psychiatrists to meet and draw out a number of clear steps in the management of delirium (similar to the guidelines for asthma) which could then be widely disseminated.

Summary

The evidence for efficacy of the management of delirium is not based on large randomized controlled trials [32] in either general [11, 63] or intensive care setting [77]. On the contrary, it is based on small trials, case-controlled studies and consensus. This is particularly surprising, considering the high prevalence, significant morbidity and

mortality [11, 34]. There is a need for more research into the pathophysiology of delirium, much of which involves animal studies. Large randomized controlled clinical studies are needed for both pharmacological and nonpharmacological interventions. We need to be actively working to prevent this disorder as outlined. Perhaps most importantly, we need to apply the knowledge we have on diagnosis and management of delirium at grass roots level and a possible way forward is by drawing up national guidelines.

Urinary continence problems

(A. Wagg, M. T. Kinirons)

The micturition cycle and its control

In man, bladder contraction results from release of acetylcholine and its action upon M_3 muscarinic receptors. Stimulation of β_3 -adrenergic receptors may have a role in active detrusor relaxation. The mechanisms underlying much bladder disease remain poorly understood but there is evidence for the action of other neurotransmitters, probably ATP, acting upon P_{2X} purinergic receptors [78]. Stimulation of the M_3 receptor results in the release of intracellular calcium, opening of voltage gated membrane calcium channels and subsequent activation of the contractile machinery (Figure 1).

Tissue ischaemia, occurring during filling and subsequent contraction of the bladder, may lead to depletion of acetylcholine-containing nerves, supersensitivity to neurotransmitters [79, 80], and, perhaps, reduced contractile ability. Detrusor overactivity therefore probably results from myogenic and neurogenic mechanisms [81–84]. The bladder sensory afferents respond to wall tension as filling increases and communicate the urge to void. Immunocytochemical and tracing studies have revealed that numerous peptides, including substance P, calcitonin gene-related peptide, vasoactive intestinal polypeptide, enkephalins, and cholecystokinin are localized either alone, or in combination, in afferent pathways of the bladder and urethra. The receptors on these nerves include vanilloid receptors, purinoceptors, tachykinin, and prostanoid receptors.

Overactive bladder (detrusor overactivity)

The incidence of symptomatic detrusor overactivity is estimated at between 10 and 15% in men and women between 10 and 50 years, rising to 35% in those aged over 75 years [84, 85]. It is commonly associated with pelvic surgery in women, possibly via outflow tract obstruction, spinal cord injury, multiple sclerosis, cerebrovascular disease, Parkinson's disease and Alzheimer's disease [86].

Figure 1 Pharmacology of bladder contraction. Diacylglycerol (DAG); adenosine triphosphate (ATP); inositol triphosphate (IP₃); G protein complex (G); n orepinephrine (NE); phospholipase C (PLC).

Drug therapy The development of pharmacological treatment for bladder problems has been slow and only recently have drugs designed specifically for the bladder been developed. Antimuscarinic drugs are the most widely used treatment in the UK. Data suggesting that such drugs inhibit contractions of the detrusor are conflicting, but this does not appear to affect response to treatment [87–89]. Urodynamic studies have shown that bladder capacity is significantly increased following treatment [90]. There are also data suggesting that patients' symptoms respond well to antimuscarinic agents regardless of the diagnosis being made by urodynamic or clinical characterization [91]. The chief drawback of these agents has been their side-effect profile, as the target receptor is ubiquitous in the body. Side-effects such as dry mouth, constipation, blurred vision and oesophageal reflux have limited their tolerability, particularly in elderly subjects.

Oxybutynin The most commonly prescribed treatment for the overactive bladder in the UK is oxybutynin. Oxybutynin is both antimuscarinic, a direct muscle relaxant, and a local anaesthetic agent. Its chief metabolite, N-desethyl-oxybutynin, is also pharmacologically active and is thought to be responsible for many of the adverse effects related to this drug. The efficacy of oxybutynin has been shown in both open and controlled trials [92, 93]. However, the withdrawal rate due to side-effects with high-dose oxybutynin (5 mg tds) has varied between 22 and 40% with up to 80% suffering significant adverse reactions. The use of lower doses has shown efficacy with a concomitant reduction in the adverse effects and increased tolerability [94, 95].

However, only 10–30% of patients will still be taking the drug 1 year after initiation [96]. Moreover, oxybutynin adds little to the clinical effectiveness of a prompted voiding regimen in a nursing home population [97].

The modified release preparation, oxybutynin XL, is associated with 40% fewer reported side-effects [98]. Recent studies comparing this compound with immediate release oxybutynin showed similar efficacy. The occurrence of dry mouth was similar, but with a reduced severity in one study, and reduced in a second one [99, 100]. Approximately two-thirds of patients up to the eighth decade on extended-release oxybutynin were still taking the medication 6 months later.

Tolterodine Tolterodine is a newer, nonselective antimuscarinic agent, which appears to have some functional selectivity for bladder muscarinic receptors over those in the salivary glands [101]. This might explain the lower incidence of dry mouth and the lower withdrawal rates. Like oxybutynin, it has an active metabolite, which appears to be responsible for some of the therapeutic effect [102]. Several studies in patients with detrusor instability, detrusor hyperreflexia, overactive bladder and specifically in the elderly, have been performed [103–107]. In doses of 2 mg twice daily, tolterodine has consistently resulted in a reduction in urinary frequency and the number of incontinence episodes. Where tolterodine has been compared with oxybutynin, the drug has been found equally efficacious. Although tolterodine appears to have greater tolerability and fewer adverse effects, there has been no direct comparison with the lower doses of oxybutynin used widely in UK practice. The proportion of patients continuing therapy for 6 months in one

study comparing approximately 500 patients taking either tolterodine or oxybutynin was statistically superior for tolterodine (32%) compared with IR oxybutynin (22%, $P < 0.001$). For those discontinuing either drug, oxybutynin was stopped significantly earlier [108]. In one open-label study, including patients over 65 years, 70% of 854 patients remained on treatment for 9 months. Dry mouth was the most frequently reported adverse event, occurring in 28% of patients, and 9% of patients withdrew due to adverse events [107, 108]. Tolterodine is also available in an extended-release formulation, which appears to be more effective in reducing urge incontinence episodes and is associated with a lower frequency of dry mouth [109, 110]. This compound has been shown to be effective in an older population [111].

Although tolterodine is more costly than oxybutynin, its use allows treatment of a greater number of patients with a lower withdrawal rate. What is not known, and not yet tested, is whether tolterodine has any other advantages. Its effect upon cognitive impairment in demented individuals and even in the cognitively intact elderly is not known, although tolterodine is not associated with significant electrophysiological CNS effects [112]. In addition, the effect of bladder retraining with or without the drug has not been assessed.

Imipramine The older antimuscarinic drug imipramine, although not licensed for treatment of detrusor overactivity or overactive bladder, is commonly used for this indication. It is both a centrally and peripherally acting antimuscarinic agent, it blocks reuptake of 5HT and norepinephrine and has a adrenergic agonist properties. Several small trials have shown efficacy in the treatment of detrusor instability in doses between 25 and 150 mg [113, 114]. However, the potential of this drug for treatment of bladder overactivity in the elderly has not yet been fully examined. A commonly used antidepressant, doxepin, has also been assessed in a single-blinded crossover study at a dose of either 50 mg nocte or 50 mg nocte and 25 mg mane [115]. There was a significant decrease in nocturnal frequency.

Propiverine Propiverine hydrochloride has combined antimuscarinic and calcium channel blocking activity. It has several active metabolites and is rapidly absorbed orally where it undergoes significant first-pass metabolism. There has been no cardiac toxicity documented to date. Placebo-controlled clinical trials have demonstrated superiority to placebo in the treatment of detrusor hyperreflexia in a 2-week double-blind placebo-controlled trial [116]. Comparative trials against flavoxate and placebo and oxybutynin and placebo have demonstrated that propiverine has a similar efficacy to oxybutynin [117, 118].

There are as yet no longer-term data from European trials of the drug and its use has been confined to patients with urodynamically confirmed detrusor instability, thus not including the 25% of patients with symptoms of bladder overactivity but normal urodynamics. In addition, there is no evidence regarding use of the drug in relation to behavioural intervention. The place of propiverine in the treatment of overactive bladder in the UK remains to be resolved but given its equal efficacy and apparent milder incidence of side-effects it is likely to remain as an alternative second-line treatment.

Tropium chloride Tropium chloride, an antimuscarinic agent derived from atropine, has recently been approved for use in the UK. This drug has been shown to be effective in several randomized controlled trials using urodynamic measures of diagnosis and extent of disease as well as clinical and quality of life outcomes [119, 120]. These studies have included patients up to the age of 70 years and there are no data to suggest that the elderly do less well.

The drug is superior to placebo and equivalent to oxybutynin at doses of 5 mg three times daily. The number of withdrawals in the tropium group was lower than the oxybutynin group [121]. The potential for antimuscarinic agents to cause deterioration in cognition, especially in the elderly, has been well recognized in association with oxybutynin [122, 123]. The effect of tropium chloride on EEG activity has been assessed compared with oxybutynin administration in one study of 12 healthy volunteers. Tropium did not cause a significant reduction in EEG activity. The relationship of this to functional cognitive ability, however, is unknown and needs further study [124]. A similar minimal reduction in EEG activity has also been reported for tolterodine [112]. Clinical trial results of darifenacin, a selective M_3 receptor antagonist for the treatment of bladder overactivity, are awaited.

Flavoxate Flavoxate has been widely promoted for the treatment of the overactive bladder. Its possible mechanism of action is unclear but it appears to have no anticholinergic properties [125]. Studies of its efficacy *vs.* placebo have failed to show any beneficial effect, the reported reduction in urinary frequency ranging between -21 and +5% [126, 127]. In comparative, double-blind crossover studies *vs.* emepromium or oxybutynin, flavoxate was found to be equally efficacious [128, 129]. The use of flavoxate was associated with few side-effects. Given the lack of effect in placebo-controlled studies of flavoxate, it is difficult to recommend its use.

Bladder retraining as part of treatment Most drug therapy has conventionally been used in combination with blad-

der retraining [130]. Data on this method alone are conflicting and no firm conclusions can be drawn. In a study of elderly patients, behavioural techniques alone may improve patients' experience of their disease to a similar extent to drug therapy when used alone [131]. There are data to suggest that a combination of pharmacotherapy and behavioural techniques may achieve results superior to either technique in isolation, although the number of patients studied is small [132]. Where the patient is cognitively impaired or institutionalized, a progressive regular toileting regimen may be employed. There are no data to support the additional use of oxybutynin in this population, but tolterodine does have efficacy data as a sole treatment modality [97]. Care has to be taken when introducing antimuscarinic medication to those with pre-existing cognitive impairment, and to those already taking anticholinergic medication, as this may be exacerbated.

Nocturnal frequency

Ten to 15 percent of older people suffer from nocturnal frequency. Some of this is undoubtedly due to excessive fluid intake. Causes of rising at night for reasons other than passing urine should not be neglected in the assessment. There is an association with sleep apnoea and sleep disturbance in the elderly is a common finding [133].

There is evidence for the efficacy of DDAVP [134] and early evening diuretic [135], and limited evidence for daytime recumbence [136], but these are not well tolerated by all. A recent observation on the use of aspirin, presumably acting via cyclooxygenase inhibition, to reduce the glomerular filtration rate has been made, but there has been no systematic attempt to examine this [137].

The usefulness of DDAVP appears to be limited to subjects with true nocturnal polyuria, defined as producing >50% of total daily urine output at night, rather than in nocturnal urinary frequency, and its use may be hampered by drug-drug interactions predisposing to hyponatraemia or excessive drinking habits [138].

Stress incontinence

Currently, there is no good evidence for the drug treatment of stress incontinence. α -agonists have been tried but their usefulness is limited by systemic side-effects. Phenylpropanolamine has been studied either as a single agent or in combination with oestrogen, but only in several small-scale trials, the results from which have been conflicting. α -adrenergic drugs are not recommended for use on current available evidence [139–141].

The serotonergic-noradrenergic reuptake inhibitor duloxetine is currently under investigation. Increasing the

levels of these neurotransmitters in the outflow from the pudendal nerve increases urethral sphincter tone and potentially leads to detrusor muscle relaxation.

Conclusions

Urinary incontinence brings with it a huge burden in terms of associated morbidity. Drug treatments are established but tolerability limits their effectiveness. Much work has concentrated on maximizing the acceptability of currently available medications, with some success, but nevertheless, effectiveness in terms of improvement or cure remains at approximately 50% of patients at 1 year.

Falls, fractures and vitamin D (J. K. Dhesi)

Introduction

Falls are common amongst the older population and are the leading cause of injury-related deaths and hospitalization. Morbidity associated with falls comprises physical injury, psychological trauma and loss of independence, with early institutionalization. Falls occur as a result of impairments in sensorimotor systems that maintain stability. Age-related declines in these systems contribute to the exponential rise in falls with age. Both proximal muscle strength and postural sway deteriorate with age and are associated with an increased risk of falls [142].

The incidence of fracture also increases exponentially with age, with hip fracture being the most expensive in terms of morbidity and financial cost. Nonvertebral fractures are related to bone fragility and are unlikely unless bone mineral density is below the 70th percentile [143]. However, 90% of fractures in the elderly occur following a fall and in this group falls are stronger predictors of fracture than bone mineral density [144]. Risk factors for falls such as body sway and quadriceps strength are also independent predictors of fracture [145].

Supplementation with vitamin D and calcium reduces the incidence of nonvertebral fracture [146, 147]. However, the modest improvement in bone mineral density observed with supplementation is unlikely to explain fully the early and significant reduction in fracture rate. While the effects of vitamin D on bone metabolism are well established, a developing area of research is the role of vitamin D in reducing the incidence of falls and thereby fractures.

Vitamin D receptors in muscle

Recent studies have demonstrated $1,25(\text{OH})_2\text{D}_3$ receptors on human muscle [148]. These receptors mediate genomic and nongenomic actions, including alteration of calcium regulation, metabolism of phospholipids, and

modification of the actomyosin contractile complex. Nongenomic pathways include direct effects on calcium channels in the muscle membrane [149]. Vitamin D deficiency is associated with amino acid accumulation and protein degradation directly resulting in muscle atrophy [150].

Vitamin D, parathyroid hormone and muscle

Although an inverse relationship between vitamin D and parathyroid hormone (PTH) is well established [151], few clinical studies have examined their role in muscle function. An independent role for PTH in muscle function is supported by studies demonstrating altered skeletal muscle energy metabolism [152] and improvements in muscle strength following treatment for hyperparathyroidism [153]. However, as PTH reflects end organ response, it may be acting as a surrogate marker for vitamin D deficiency.

Osteomalacia and myopathy

Myopathy is an established clinical feature of osteomalacia, resulting in a proximal selective asymmetrical weakness. Muscle biopsies demonstrate type IIa fibre atrophy and nonspecific changes of fatty infiltration and interstitial fibrosis, which may be consequent upon disuse and malnutrition. Electromyography demonstrates nonspecific polyphasic potentials with reduced motor unit potential amplitude and duration [154].

Subclinical vitamin D deficiency and muscle function

Recently, cross-sectional studies have examined the relationship between subclinical vitamin D deficiency and muscle function. Boonen *et al.* found no correlation between free $1,25(\text{OH})_2\text{D}_3$ and knee extensor strength; however, free $1,25(\text{OH})_2\text{D}_3$ is unstable and may not accurately reflect circulating vitamin D [155]. Mowe *et al.* demonstrated a significant correlation between 25OHD and lower limb muscle strength in elderly subjects, even though the majority were fully replete [156]. Bischoff *et al.* found that 25OHD and $1,25(\text{OH})_2\text{D}_3$ correlated with leg extension power, particularly in those with subclinical deficiency [157].

Effects of vitamin D supplementation on muscle function

The beneficial effects of vitamin D supplementation on muscle function in osteomalacia are well known, but more recent studies have examined supplementation in subclinical vitamin D deficiency. In a 6-week study treatment did not improve strength [158]. However, this is too short a study period, since type II atrophy typical of

osteomalacia takes 3–6 months to recover. Geusens *et al.* demonstrated a nonsignificant improvement in quadriceps strength, which may have been due to too low a dose of vitamin D [159]. Verhaar *et al.* studied elderly 25OHD subdeficient women and did observe improvements in knee extensor strength and walking distance [160]. Interestingly, in elderly men with prostatic cancer, supplementation improved muscle strength and reduced muscle discomfort [161].

VDR genotype and muscle strength

With the advent of genetic studies, it is suggested that VDR genotype may determine muscle strength, since VDR polymorphism has been shown to be associated with muscle strength in elderly nonobese women [159].

Effects on nerve function

$1,25(\text{OH})_2\text{D}_3$ induces VDR expression in brain glia as well as nerve growth factor synthesis, and monoamine-oxidase activity involved in nerve cell growth [162]. $1,25(\text{OH})_2\text{D}_3$ administration impairs progression of encephalomyelitis and exhibits antiproliferative and prodifferentiating effects in a neuroblastoma cell line [163]. In addition, cultures of new-born brain microglia synthesize $1,25(\text{OH})_2\text{D}_3$.

Effects on postural sway

Vitamin D deficiency is associated with myopathy and neuropathy, with possible disturbances in balance and neuromuscular coordination. Vitamin D and postural sway were related in a cross-sectional study [164], and more recently short-term vitamin D and calcium supplementation have been shown to reduce body sway [165].

Effects on functional performance

Functional performance can be used as a measure of coordinative muscle function. In a cross-sectional study of independent elderly women, exercise capacity was related to 25OHD levels [166]. An uncontrolled study demonstrated time to dress was reduced after vitamin D and calcium supplementation [167]. However, these subjects had vertebral fractures; functional improvement may have been due to reduction in pain and disability as the fracture healed. In a small case study, an improvement in functional status was related to increases in vitamin D levels [168].

Impairment in functional performance may be related to deep musculoskeletal limb pain, hyperaesthesia and neuropathy frequently described in vitamin D deficiency as well as the effects on muscle strength. There are a

number of case reports of reduced pain after correction of vitamin D status [169], but there are no systematic studies of supplementation and pain.

Conclusions

Mounting evidence suggests that vitamin D supplementation, by improving postural stability, muscle strength and function, may reduce the incidence of falls and thereby fractures over and above the effects on bone. The clinical and cost implications of reducing falls and fractures by the cheap and simple administration of vitamin D are potentially very significant.

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