

ENDOCRINE DISORDERS IN THE ELDERLY

Space does not allow a comprehensive review of endocrinology in the elderly, so this article covers three common problems: type 2 diabetes mellitus, thyroid disorders and metabolic bone disease.



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DIABETES

Ageing *per se* is the single biggest risk factor for developing diabetes and impaired glucose tolerance (IGT). Studies in the USA show that at least 10% of people over 65 years of age are diabetic, compared with 5% in the 45 - 64-year age group and 1% in younger age groups. Over the age of 80, approximately 40% of Americans are diabetic! In a 1997 survey of elderly coloured Capetonians 28.7% were found to have type 2 diabetes and a further 15% to have IGT. The management of elderly diabetics is complicated by the presence of co-morbid disease, multiple drug use and, often, reduced functional status. The diagnostic laboratory criteria for diabetes are independent of age. Treatment principles for elderly diabetics are the same as those for younger diabetics, and the aim is to prevent the symptoms and acute complications of uncontrolled hyperglycaemia, to avoid hypoglycaemia and to delay the onset, or prevent the progression, of chronic diabetic complications.

There are no randomised controlled clinical trials (RCTs) looking specifically at the outcome of good or improved levels of glucose, blood pressure and lipids in diabetic patients over 65 years of age. Most recommendations are extrapolated from studies in younger patients. There are, however, specific areas where the management of elderly diabetics differ:

- unusual presentations
- diet
- exercise
- drugs (including newer agents)
- hypoglycaemia.

Unusual presentations

The classic triad of polyuria, polydipsia and polyphagia is less common in elderly patients with diabetes or IGT. Presenting manifestations are often nonspecific: weight loss, anorexia, fatigue, incontinence, altered sleep patterns and cognitive impairment. Diabetic complications occur more often in the elderly and may be the presenting problem. Moreover, certain geriatric problems are more common in elderly diabetics: urinary incontinence, falls, cognitive dysfunction, depression, pain, erectile dysfunction and polypharmacy. Elderly people may have a normal fasting glucose, but an impaired postprandial glycaemia.

Diet

Dietary discretion remains important in the elderly diabetic.

Caloric restrictions applied to younger patients remain unchanged in the older obese patient. However, many of the frail elderly have a limited intake and are already underweight, increasing their risk for hypoglycaemia. Here the emphasis should be on maintaining adequate nutrition and avoiding highly refined carbohydrates. A careful assessment of individual cases by a dietician is beneficial.

Exercise

In elderly people, the potential benefits of exercise include increasing insulin sensitivity, decreasing blood pressure and lipids, and maintaining bone mineral density. Healthy elderly patients should be encouraged to continue with their existing exercise programmes. However, sedentary elderly diabetics need cardiovascular assessment, including exercise stress testing, before starting exercise. Emphasise improving flexibility, strength, co-ordination and balance in those unable to walk. As exercise may reduce blood glucose levels patients on sulphonylureas or insulin should monitor these levels before exercise – and if low, take an additional snack.

Drugs

As up to 80% of premature mortality in diabetics is caused by macrovascular complications, the American Diabetes Association recommends that all elderly diabetic patients, unless contraindicated, should be on aspirin.

Oral agents

Sulphonylureas (SUs) are insulin secretagogues and can be used cautiously in the elderly. Renal function should be assessed (creatinine is a poor indicator of renal function, particularly in the elderly with low muscle mass). Shorter-acting agents such as gliclazide and glipizide are preferable as they are metabolised by the liver and inactive metabolites are excreted in the urine. SUs are associated with an increased risk of hypoglycaemia. Therapy should be initiated with the lowest available dose and given only

once daily. Chlorpropamide should never be used in elderly patients.

Meglitinides (repaglinide and nateglinide) are newer insulin secretagogues with a short half-life. They have a favourable pharmacokinetic profile as they target postprandial hyperglycaemia, their potential advantage being fewer hypoglycaemic episodes. Although metabolised by the liver and excreted in the bile, drug elimination is variable and elderly patients have been found to have significantly higher plasma concentrations than healthy controls.

All insulin secretagogues should be avoided in patients with liver disease.

Metformin acts mainly as an insulin sensitiser, with possible modest beneficial effects on the blood pressure and lipid profile. When used independently it does not cause hypoglycaemia. Its major disadvantage is lactic acidosis, the risk increasing with age and decreasing creatinine clearance, but also with other organ dysfunction, hypotension and sepsis. In the absence of these exclusion criteria metformin does have a role in the obese patient, provided that there is regular monitoring of the creatinine clearance and that it is discontinued with acute illness or hospitalisation. It is contraindicated in patients over 80 years old.

Thiazolidinediones (rosiglitazone and pioglitazone) are specific insulin sensitisers, and rosiglitazone has been shown to be safe and effective in elderly patients. Their use is indicated fairly early in the therapeutic cascade, and more particularly as initial therapy. These drugs must be avoided in cardiac failure, and potentially may precipitate it.

Insulin

Individualise insulin therapy and keep the regimen as simple as possible. Encourage home glucose monitoring – once a day at different times or 4 times a day, twice a week, is acceptable. The readings should be record-

ed. A single daily dose of intermediate-acting insulin (NPH/glargine) before bedtime may be sufficient to control fasting hyperglycaemia. Administering NPH insulin before supper may cause nocturnal hypoglycaemia because the peak of action occurs in the middle of the night, rather than coinciding with breakfast (when given at bedtime). Frail elderly patients are better controlled on a daytime dose so that possible hypoglycaemia may be recognised. Intermediate-acting insulin should be initiated at 0.2 IU/kg/day. Dose adjustments of 2 - 4 IU/day can be made at 1 - 2-week intervals, provided that the blood glucose is monitored frequently. Patients who are inadequately controlled on NPH insulin and oral hypoglycaemic agents may be changed to biphasic insulin (or short-acting insulin added), used in the same fashion as in younger patients. When short-acting insulin therapy has been added, secretagogues should be stopped.

Hypoglycaemia

This is a complication of either insulin secretagogues or insulin therapy. Hypoglycaemic symptoms include adrenergic-mediated symptoms (sweating, tremor, anxiety, palpitations, hunger) and neuroglycopenic symptoms (impaired concentration, personality changes, seizures, coma). In elderly patients, neuroglycopenic symptoms predominate, probably owing to impaired adrenergic response to hypoglycaemia. The perception of warning symptoms is attenuated, with patients possibly presenting in a coma with no forewarning! Physical injury and bone fractures may result from hypoglycaemic episodes. Hypoglycaemia in elderly patients increases the risk of myocardial infarction and cerebrovascular accident. Hypoglycaemia should be avoided at all costs in the elderly!

THYROID DISORDERS

A higher index of suspicion and a lower threshold for screening are needed to detect thyroid dysfunction in the elderly. (Some experts suggest that a routine TSH screen should be

done in the work-up of any elderly patient who is unwell.) Although the same diseases of the thyroid occur in the elderly, there is a significant increase in prevalence. Furthermore, the clinical manifestations are usually more subtle (either virtually absent or atypical), and thyroid dysfunction may escape detection because of coexistent disease. Finally, ageing results in changes in thyroid physiology: the peripheral metabolism of thyroid hormones is reduced, with a compensatory decrease in production of thyroid hormone (up to one-third less). Consequently, the dosage of thyroxine replacement may need to be reduced in the elderly.

Auto-immunity

Thyroid autoantibodies are more prevalent with increasing age in both sexes; there is, however, a wide variability in different populations, which may either be genetic or dietary. Both the prevalence and the titre of these antibodies are higher in elderly women. However, the correlation between antibodies and thyroid failure is not that tight; in the Framingham study one-third of elderly patients with a raised TSH had normal antibody levels. Furthermore, most community-dwelling elderly who have positive antimicrosomal antibodies on screening do not have a raised TSH. Moreover, antibody levels may fluctuate over time.

Nodules

With ageing the prevalence of thyroid nodules increases markedly; above the age of 80 more than 90% of women and 60% of men have nodules. The marked increase in multinodular goitre, especially in the elderly female, remains unchanged in spite of iodised salt (i.e. it is not due to iodine deficiency).

Hypothyroidism

The high rate of hypothyroidism, especially in elderly women (up to 5%), is not always obvious, as the classic symptom complex is often absent.

Features are commonly insidious and may be attributed to the 'ageing process'. Indeed, even when the diagnosis is known, up to one-third of patients have no obvious clinical features. Irrespective of the cause of the hypothyroidism, replacement thyroxine must be instituted with care, as it may precipitate serious ischaemic cardiac pathology. There is also a wide variability in the time to response. 'Start low, go slow!' The starting dose is 25 µg of thyroxine, and should only be increased every 6 - 8 weeks until the TSH is within the normal range.

Subclinical hypothyroidism

Elevated TSH with normal T_4 and no diagnostic clinical features occurs in 5 - 15% of elderly people (especially women) in varying series. There is no consensus as to the overall benefit (versus risk) in normalising TSH with thyroxine, but recent studies suggest that these women may be at increased risk for atherosclerosis, cardiovascular events and premature mortality. In this group, the overall incidence of frank hypothyroidism is 8% per year, but the rate more than doubles in those with the highest TSH (> 10) or antibody titre.

Thyrotoxicosis

Up to 15% of all thyrotoxic patients are over 65. However, the diagnosis is often missed, as the clinical manifestations may be extremely subtle. Commonly there is no obvious goitre or heat intolerance. Paradoxically, anorexia is common. The course is insidiously progressive, and rather than appearing typically toxic, patients often appear apathetic. In any older patient with unexplained heart failure, atrial fibrillation, or psychiatric symptoms (e.g. depression) a TSH screening test is mandatory. Toxic nodular goitre becomes more frequent with age; Graves' disease is still common, but usually without the classic eye signs or enlarged smooth goitre.

Not only are features of toxicosis often not clear-cut, but frequently the levels of T_4 and T_3 seem to hover around the

upper limits of normal. Radioactive iodine uptake can be normal in up to two-thirds of toxic multinodular goitre, as well as a sizeable proportion of toxic Graves' patients. In the setting of a suppressed TSH and a relatively normal T_4 , an elevated T_3 commonly suggests underlying toxic nodular thyroid disease. However, a suppressed TSH with normal T_4 and T_3 is a common finding in euthyroid multinodular goitre. Although radioactive iodine is an effective treatment for toxic multinodular goitre, there can be recurrence of toxicosis in nodules that were not previously overactive.

In patients with multinodular goitre, thyrotoxicosis can be precipitated by excess iodine, e.g. contrast media used in radiology and amiodarone treatment, both of which are common in the elderly. (Five per cent of patients on amiodarone develop thyrotoxicosis but, paradoxically, amiodarone-induced hypothyroidism is even more common.)

Subclinical thyrotoxicosis

This is present in approximately 6% of community-dwelling people over the age of 60 years. Here the only abnormality is a suppressed TSH, which is often iatrogenic, e.g. patients on excess thyroxine replacement. In idiopathic cases, studies show that less than 2% develop overt thyrotoxicosis within the first year, all of whom had initial TSH levels below the recordable range. The two major potential complications of this condition are cardiac (there is an increased incidence of atrial fibrillation on longer-term follow-up) and decreased bone density (excess use of thyroxine in women undoubtedly contributes to osteoporosis). However, in the uncomplicated case, there is no universal consensus on the need for treatment.

METABOLIC BONE DISEASE

Osteoporosis

Osteoporosis (OP) is a skeletal disease of compromised bone strength, predis-

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posing to an increased risk of fragility fractures. OP is silent until manifesting as fractures. Over the past 15 years the increased availability of screening to detect low bone mineral density (BMD) and the rapid advances in management have all been geared to reduce fractures in at-risk patients. Osteoporotic fractures characteristically: (i) show a marked increase with age; (ii) occur more commonly in women, especially Caucasians; (iii) occur at sites rich in trabecular bone; and (iv) require minimal trauma. A 65-year-old woman has a lifetime risk above 50% of at least 1 osteoporotic fracture; over the age of 70 hip fracture incidence increases markedly in both sexes, with 30% of all these fractures occurring in men.

With age there is a natural and progressive decrease in BMD; by age 80 up to 50% of women may be at or below the 'magical' OP cut-off level of -2.5 SD. Therefore, in the elderly, other factors (especially a tendency to falls) are at least as important as the absolute BMD level; a degree of osteomalacia often occurs with OP.

Secondary causes of OP (glucocorticoid therapy, malignancy, alcohol, etc.) should be excluded as part of the work-up. This applies particularly to men — more than 50% may have an underlying cause for OP.

Impact of fractures

Vertebral

A lateral radiograph of the lumbar and thoracic spine is an essential part of the initial work-up of any patient with low BMD. Loss of height of $> 20\%$ in any part of a vertebra is regarded as a radiological fracture; only one-third of these present clinically. These prevalent fragility fractures have significant prognostic value; the risk of future (incident) vertebral fractures is increased at least three-fold (up to 20%) in the first year. If multiple prevalent fractures are present, the risk increases at least seven-fold. Furthermore, prevalent vertebral fractures increase the risk of all osteoporotic fractures, especially in the first year thereafter, e.g. hip fracture risk is increased four times.

There is marked morbidity, especially with symptomatic/multiple vertebral fractures; in the UK patients consult their GP 14 times more often than controls during the 12 months after the fracture. Surprisingly, the mortality rate after vertebral fractures is also markedly increased by 20% after 5 years.

Hip

After a hip fracture 50% of those who were previously independent will require some form of assistance. Mortality is increased six-fold; this 20% increase is directly attributable to the hip fracture and occurs in the first year. With a rapidly ageing popula-

tion worldwide, it is estimated that hip fractures will be 4 times more common by the year 2050. Any elderly patient who suffers a hip fracture must be aggressively managed to prevent a fracture in the other hip.

Treatment

BMD is only a surrogate marker for assessing therapeutic efficacy of various agents; a more important indicator is the change in fracture incidence. Until 2004, all registered OP therapies decreased bone resorption. The increases in BMD with anti-resorptives range from $< 2\%$ to almost 10% (over periods of 3 - 4 years). However, they all show similar vertebral fracture reduction (35 - 55%). Therefore, when following up patients on any of these agents, no significant loss of BMD (within 18 months - 2 years of starting therapy) may still be regarded as an acceptable response.

Obviously, these agents also have positive effects on bone architecture, etc., which help to reduce the fracture rate.

Hormone therapy

Oestrogen earned its reputation long before the era of RCTs. In the past it was the main therapy for OP, and was also thought to have positive cardiovascular benefits. The Women's Health Initiative (WHI) study for the first time provided conclusive prospective evidence that oestrogen significantly reduced the risk of both vertebral and hip fractures by about 30%. However, the overall health risks were felt to outweigh benefits except if significant vasomotor symptoms were present in the early postmenopausal period. The almost universal recommendation now is that, even in this group, hormone replacement therapy (HRT) be continued for no longer than 5 years. Consequently, many women are now discontinuing HRT, with a significant loss of BMD during the first year. In order to fill this void, our group, in a large international study, was the first to show that commencing bisphosphonate (BP) use shortly after stopping HRT reversed bone loss in these women and that it was well tolerated.

The BPs are also the first choice for idiopathic male OP and glucocorticoid-induced OP.

This intermittent form of PTH given once daily by injection is now available in South Africa.

When Paget's disease does present clinically it is usually due to bone pain or deformities, especially of the skull or tibia.

Bisphosphonates

This group of agents is the most extensively studied and has the most reproducible results for the treatment of OP. In South Africa there are 2 oral agents (alendronate, risedronate) registered for the treatment of OP. BPs are the only anti-resorptives that have been shown to reduce the risk of vertebral fracture as well as hip fracture significantly; these benefits begin within 6 months of starting therapy. The BPs are also the first choice for idiopathic male OP and glucocorticoid-induced OP. In practice a percentage of patients are unable to continue with these agents because of GIT side-effects; newer intravenous and other forms (without GIT side-effects) are becoming available.

Selective oestrogen-receptor modulators (SERMs)

The only agent presently registered is raloxifene. It has positive effects on vertebral fracture rate and cardiovascular markers, with no oestrogenic effects on the uterus or breast. As yet, there are no data to show that it is effective in reducing hip fractures. There are no GIT side-effects, and the increase in hot flushes usually only affects those in the early post-menopausal period. The ideal at-risk candidate is a woman who is more than 5 years post-menopausal, who

has not had deep-vein thrombosis and who has a high risk of breast cancer.

Teriparatide (1-34 PTH)

This intermittent form of PTH given once daily by injection is now available in South Africa. It is the only anabolic agent for bone and in theory it should be particularly useful in the elderly (with poor bone formation and very low BMD) who, in spite of other therapies, are still at high risk for future fracture. Studies show a marked increase in BMD, especially in the spine, with a significant decrease in vertebral (and non-vertebral) fractures, at least as good as with any of the other agents. Although it is very expensive, therapy is continued for only 18 months in total and it is especially indicated in those who are still prone to fractures despite adequate therapy.

Osteomalacia

In osteomalacia (OM) the collagen matrix of bone is normal in amount and character, but there is significantly decreased mineral (calcium and/or phosphate) to calcify bone, with resulting low BMD and weak bones. Varying degrees of OM frequently accompany OP in the elderly and OM on its own may present with fractures, especially of the pelvis and the upper femora. It is a significantly under-diagnosed condition as the typical features of aches and pains as well as muscle weakness are often attributed to ageing or osteoarthritis. The cause of this condition is either vitamin D deficiency, which occurs in institutionalised patients especially in winter (even in South Africa), or due to excess phosphate loss in the urine (for which there are many causes). Low levels of vitamin D (and calcium) lead to secondary hyperparathyroidism and excess bone resorption in order to maintain adequate calcium levels in the blood.

Biochemically, in vitamin D deficiency the calcium and phosphate may be borderline low or normal, but the alkaline phosphatase and PTH will be ele-

vated. Urine calcium and phosphate levels will be low, with a low serum level of 25-OH vitamin D₃. In the vitamin D-resistant type there is a very low serum phosphate with a high urinary phosphate. Sometimes the diagnosis of OM is difficult to confirm clinically and biochemically it is then necessary to do a bone biopsy.

Treatment is vitamin D (at least 800 IU daily) and calcium for the common vitamin D-deficient type and phosphate replacement for the vitamin D-resistant type. Patients with the latter need to be referred to a metabolic bone disease centre.

Paget's disease of bone

This is a focal disorder of bone characterised by a localised increase in bone turnover rate with abnormal bone remodelling. It can affect one or many bones and is typically asymmetrical. Lesions pass through phases of activity and quiescence and vary greatly in their rate of progression.

Although it is estimated that up to 10% of the population of northeastern European origin over the age of 80 have this condition, it remains asymptomatic in more than 80%. Usually it is detected incidentally on a radiograph or because of an unexplained raised alkaline phosphatase. When Paget's disease does present clinically it is usually due to bone pain or deformities, especially of the skull or tibia. The major acute complication of Paget's disease is fracture that usually occurs in the osteolytic phase (especially in the femur). Pagetic fractures heal with great difficulty. The other major complication, which is more insidious, is spinal cord or nerve compression due to bone overgrowth. Commonly, secondary osteoarthritis occurs in joints juxtaposed to active pagetic lesions. This affects especially the hip and knee joints and often requires a prosthetic joint replacement. In order to obtain the best result from this procedure, the very active pagetic bone should be treated pre-operatively. The BPs are uniformly the treatment

of choice in Paget's disease; in South Africa alendronate and risedronate are registered for this. In patients who cannot tolerate these oral preparations, intravenous BPs are highly effective (e.g. pamidronate).

Further reading

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IN A NUTSHELL

In the elderly:

Common endocrine conditions (presenting to the GP) are more prevalent.

Thyroid dysfunction and type 2 diabetes mellitus often have subtle or unusual presentations and demand a low threshold for screening.

Goals of diabetic therapy need to be individualised; insulin is *not* contraindicated.

Hypoglycaemia in patients on diabetic therapy *must* be avoided.

Initiating thyroxine replacement: start low, go slow.

Prevalent fragility fracture is a better predictor than BMD for future osteoporotic fracture.

Hip and vertebral fractures are associated with a high morbidity and mortality.

HRT prevents osteoporotic fractures, but should only be used if there are significant menopausal symptoms, and then only in the short term.

BPs are the first-choice agents for reducing both spine and hip fracture rates.

A degree of OM commonly accompanies OP.

Most cases of Paget's disease are discovered incidentally and usually do not require specific therapy.

SINGLE SUTURE

BLOW TO HYGIENE THEORY

The most popular explanation for why children born later have fewer allergies is that children born last have their immune systems primed by exposure to their older siblings, leading to fewer allergies. However, Wilfried Karmaus at Michigan State University has found that women have a weaker immune response to allergens with each successive pregnancy, which could also explain why children born later are less likely to suffer allergies than their older siblings. His team found that at birth, first-born children have the highest levels of IgE and that these levels drop with each subsequent pregnancy. This suggests that the mother's immune response is somehow influencing the baby's immune system and possibly affecting the child's sensitivity to allergens later.

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