**Olfactory loss and higher risk of mortality**

Older people often say that things don’t smell (or taste) like they used to. Poor olfaction has been linked to higher mortality. You would think that is because people who have lost their sense of smell are already in poor health, with neurodegenerative conditions such as Parkinson’s disease or dementia. But this cohort study finds that the opposite is true—poor olfaction is only an independent predictor of higher mortality among healthy people. Those in poor health are more likely to die overall, but their sense of smell doesn’t help to predict their risk. Liu et al enrolled 2289 older people and used the objective Brief Smell Identification Test. Over half of the participants had died within the 13 years of follow-up; those who had poor olfaction had a 46% higher cumulative risk of dying at year 10, and a 30% higher risk at year 13. But the increased risk was only seen among those who were in good health at enrolment, not among those who were already unwell. The mechanism is still unclear. Olfactory loss in healthy people may prove to be an important predictor of mortality, but I’m not sure what practical benefit there is for patients in knowing that.


**Aortic valve replacement: the best approach**

Aortic valve replacement is the only effective treatment for severe, symptomatic aortic stenosis, and there are two ways of doing it: transcatheter aortic valve replacement involving transfemoral placement of a balloon-expandable or self-expanding valve, or surgical aortic valve replacement. For intermediate to high risk patients, there is not much difference in outcome. But if you are at low surgical risk, which would you opt for? Mack et al found that the patients randomised to balloon-expandable transcatheter aortic valve replacement fared better at one year in terms of the primary composite endpoint (death, stroke, or re-hospitalisation) than those who had surgery (8.5% v 15.1%). Incidentally, how useful is a composite that mashes up death rate and readmission rates?


**Undetectable means untransmittable**

Among gay couples, if one is HIV positive and taking suppressive antiretroviral therapy and the other is HIV negative, what is the risk of transmission to the seronegative partner if they have condom-less sex? This study finds that, if HIV viral load is fully suppressed, the risk of transmission to a seronegative partner is effectively zero. Any new cases of HIV infection (15 in this study) were not phylogenetically linked to the couple. This is the same result as previously found among female partners of HIV positive men. The message is neatly summed up as U=U (undetectable means untransmittable) and reinforces the need for HIV infection to be diagnosed and treated as early as possible to avoid transmission to seronegative partners.

*Lancet* doi:10.1016/S0140-6736(19)30418-0

**Glomerular filtration rate estimates—all methods are equal**

Methods of estimating glomerular filtration rate may not be the sexiest subject, but the procedure is essential in the diagnosis and management of chronic kidney disease. It’s not practical to measure glomerular filtration rates directly using methods such as inulin clearance, so the various ways of calculating an estimated glomerular filtration rate need to be as close as possible to the true value. There are several different equations in use, and the question is whether the newer methods trump older ones. This single centre, cross-sectional study found no significant differences between four methods used in patients over 65 years old, and all were of reasonable accuracy compared with the reference methods.


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**FROM THE JOURNALS** Edited highlights of weekly research reviews on https://bit.ly/2PLtil8

Ann Robinson is an NHS GP and health writer and broadcaster
Hyponatraemia in primary care

Peter Jacob,1 Claire Dow,1 Shawarna S. Lasker,2 William M. Drake,1 Tahseen A. Chowdhury1

Hyponatraemia is the most frequently observed electrolyte abnormality.1 Mild hyponatraemia is associated with cognitive deficits and falls, but in hospitalised patients it is associated with increased mortality.2 In primary care, patients are often found to have hyponatraemia during chronic disease monitoring. This prompts a focused re-evaluation to consider underlying causes such as medication, cancer, or adrenal insufficiency.2,3 In this article we provide a framework to assess patients with hyponatraemia in primary care.

Defining hyponatraemia

Hyponatraemia is defined as a serum sodium value below the reference range (lower limit is usually 133-135 mmol/L). Hyponatraemia is often subdivided into mild, moderate, severe, and life threatening, using a combination of the presence of associated symptoms and the sodium value.1,4 There is, however, a poor correlation between symptomatology and serum sodium level, so both must be taken into account when considering urgency of referral and subsequent management. Hyponatraemia may be acute (arbitrarily defined as an onset within 48 hours), chronic (>48 hours), or unknown (where management should be as per chronic).

WHAT YOU NEED TO KNOW

- Mild hyponatraemia is associated with increased risk of falls and osteoporosis
- Assessing volume status helps to guide differential diagnosis and options for management
- Medications such as diuretics, antidepressants, antipsychotics, and anti-epileptics are common causes of hyponatraemia
- Older people are particularly at risk of developing and suffering consequences of hyponatraemia
- Check thyroid function and 9 am cortisol in all patients with hypovolaemic and euvoaemic hyponatraemia

Assessment in primary care

Patients with asymptomatic, mild hyponatraemia (130-135 mmol/L) may—at least initially—be managed in primary care (fig 1). In practice this involves taking a focused history to identify symptoms of an underlying cause, a medication review, and an examination of fluid status. Initial investigations (table 1) include urine osmolalities, urinary sodium, and further blood tests including 9 am cortisol.

Depending on the clinical scenario, initial management of medication changes and/or fluid restriction may be appropriate. Mild, well tolerated hyponatraemia may be clinically acceptable if the patient is stable on the medication. Plan to review the patient at an interval determined by the clinical context to determine whether the hyponatraemia has resolved and whether further referral is indicated. For instance, if the patient is clinically well but known to be taking a medication that causes hyponatraemia, consider withholding the medication if it is safe to do so and re-checking the sodium in two weeks. If initial investigations suggest SIAD (syndrome of inappropriate antidiuresis), the underlying cause should be considered, regardless of whether the sodium level improves. Common pitfalls in the management of hyponatraemia are discussed in table 2 (bmj.com).

Severe symptoms are caused by brain oedema and should be managed as severe hyponatraemia, irrespective of the actual serum sodium concentration. An apparently asymptomatic patient with profound biochemical hyponatraemia also requires careful management as over-rapid correction may lead to complications such as pontine myelinolysis. We recommend emergency referral for anyone with a sodium level <125 mmol/L, and discussion with an endocrinologist about admission or referral for those with a sodium level of 125-129 mmol/L.6
Look for signs of severe hyponatraemia

- Vomiting
- Cardiorespiratory distress
- Excessive drowsiness
- GCS <8
- Acute hyponatraemia (<48 hours)
- Seizures
- Sodium <125

If sodium 125-129, discuss with endocrinologist whether admission or referral is needed

Urgent referral
Immediate referral for emergency department assessment

Clinical assessment
Assessment of recent events, including collateral history if appropriate. Ask about:
- Intercurrent illnesses
- Food and fluid intake
- Urine output
- Falls
- Cognitive function
- Symptoms of underlying malignancy
  - such as unintentional weight loss

Review comorbidities and medication history, including recent changes in medication

Volume status assessment including lying and standing blood pressure and estimation of the jugular venous pulse

Clinical assessment of hyponatraemia

Medication and hyponatraemia
Pharmacotherapy is a common cause of hyponatraemia. Thiazide diuretics are the most frequent culprit. In an observational study in primary care, 13.7% of patients prescribed thiazides had documented hyponatraemia. Although their use is declining, there were more than 14 million prescriptions for thiazide and thiazide-like drugs in England in 2018. In a hospital case note review, 29% of inpatients with hyponatraemia (<125 mmol/L) were taking a thiazide. In older people, up to 75% of those with hyponatraemia are associated with thiazides. Thiazide-like drugs indapamide and hydrochlorothiazide are also implicated in hyponatraemia. Low cost and familiarity make them frequent choices for the treatment of essential hypertension and oedematous states, but they are often implicated in hospital admissions for severe hyponatraemia, which should be factored into clinical decision making and guideline drafting. Thiazide induced hyponatraemia usually recurs, so it is appropriate to avoid thiazides in such patients.

Table 1 | Investigations for hyponatraemia

<table>
<thead>
<tr>
<th>Test</th>
<th>Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum osmolality</td>
<td>In SIAD a low serum osmolality (hypotonicity) is typical (&lt;275 mosm/kg).</td>
</tr>
<tr>
<td>Isotonic or hypertonic</td>
<td>serum in the presence of hyponatraemia is indicative of excess osmoles or solutes such as glucose, triglycerides, cholesterol, proteins, or immunoglobulins that can cause analytical problems leading to a pseudohyponatraemia</td>
</tr>
<tr>
<td>Urine sodium</td>
<td>Urine sodium &lt;20 mmol/L is suggestive of reduced effective circulating volume with hyperaldosteronism. Urine sodium &gt;30 mmol/L is consistent with SIAD but also present in other disease states and following natriuretic therapy (e.g., diuretics). Urine sodium concentrations should be interpreted with a knowledge of the dietary sodium intake, as high intake may lead to high urinary sodium excretion</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>Estimate of vasopressin activity. The presence of an unexpectedly elevated urine osmolality (&lt;100 mosm/kg/H₂O) in the presence of hypotonic hyponatraemia is an essential criterion for SIAD. Urine osmolality &gt;100 mosm/kg/H₂O, in the presence of hyponatraemia is strongly suggestive of polydipsia</td>
</tr>
<tr>
<td>Serum urea</td>
<td>A marker of extracellular fluid volume (EFV) status. A raised urea may indicate dehydration. The trend in changes over time can be particularly useful as a marker of recent EFV shift</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Assessment for renal failure as a cause of hyponatraemia</td>
</tr>
</tbody>
</table>

Initial management (prior to work-up results)

Fluid restriction
Withhold any contributory medication if clinically safe to do so
Treatment of underlying cause

Fluid restriction
Withhold any contributory medication if clinically safe to do so
Ensure adequate sodium intake
Investigate for ACTH deficiency with 9am cortisol

Fluid resuscitation
Usually requires inpatient referral
Withhold any contributory medication if clinically safe to do so
Investigate for adrenal insufficiency with 9am cortisol

Distinguishing features

**Hypervolaemia**
- Elevated jugular venous pulse

**Euvolaemia**
- Normal fluid status examination

**Hypovolaemia**
- Low blood pressure
- Postural blood pressure drop >20 mmHg
- Jugular venous pulse not visible

Primary causes

- Heart failure
- Liver failure
- Renal failure
- Profound hypothyroidism

Medications

- Thiazide, thiazide-like diuretics
- SIAD
  - Syndrome of inappropriate anti-diuresis
    - May be caused by
      - Medication (commonly anti-depressants, anti-psychotics, anti-epileptics)
      - Malignancy (such as small cell lung cancer)
      - Respiratory infection
      - Central nervous system causes (infection, stroke, trauma, malignancy)

Primary polydipsia

Fluid restriction

Medications

- Thiazides, thiazide-like diuretics
- Loop diuretics, potassium sparing antihypertensives
- Gastrointestinal losses
- Primary adrenal insufficiency

See table 1 for initial biochemical work-up
Loop diuretics may also cause hyponatraemia, but this is more likely to occur when they are taken in combination with medications such as angiotensin converting enzyme inhibitors or spironolactone. It is rarely easy to stop loop diuretics completely in such circumstances as fluid accumulation may re-occur. Typically, a compromise is needed between fluid restriction and loop diuretic dose, and a degree of hyponatraemia may need to be accepted.

Antidepressants and antipsychotics may induce SIAD, leading to water retention and a reduction in plasma sodium concentration. The greatest risk appears to be with selective serotonin reuptake inhibitors and especially with citalopram (incidence rate ratio 7.8). Mirtazapine and tricyclic antidepressants are less likely to induce SIAD and may be considered where it is clinically appropriate.

Typical and atypical antipsychotics have been associated with hyponatraemia. Among anti-epileptic drugs, carbamazepine, oxcarbazepine, and eslicarbazepine are most frequently associated with hyponatraemia. We recommend seeking advice from specialist teams where hyponatraemia due to these medications is suspected.

Many other commonly prescribed medications are associated with hyponatraemia, particularly in older patients. We recommend checking the side effect profile for all medications (in, for instance, the British National Formulary) and consider withholding any that may be implicated.

Syndrome of inappropriate antidiuresis (SIAD)

In SIAD, excessive action of vasopressin produces a state of water excess without major sodium retention. The expanded fluid volume cannot be detected clinically and patients appear euvoalaemic, although distinguishing between euvoalaemia and mild hypovolaemia is often challenging in clinical practice. Together with this clinical finding, biochemical indicators are of an inappropriately concentrated urine (>100 mOsm/kg H₂O) or elevated urine sodium (>30 mmol/L). Importantly, SIAD may only be diagnosed in the absence of adrenal, renal, liver, or profound thyroid dysfunction.

SIAD can be caused by medication, respiratory infection, central nervous system disorders, or malignancy. The likelihood of malignant disease where SIAD is present is unknown. If a person presents with suspected malignant disease and hyponatraemia, SIAD should be suspected, and referral to the appropriate specialist via an urgent referral pathway is advised. Initial malignancy screening is usually with axial imaging of the brain and thorax, and depending on local services these may be best initiated in primary care, at a clinic of cancer of unknown primary, or as part of a comprehensive geriatric assessment. We recommend that people with unexplained SIAD, where malignancy has been excluded, be referred to an endocrinologist for further investigation.

The simplest method to treat SIAD is fluid restriction, aiming to reduce fluid intake to below insensible losses and urine output. Typically, our initial advice is to ask the patient to restrict their fluid intake to 500 mL a day. However, this can have a major impact on patients’ lives and is often difficult to achieve. Fluid restriction does not imply calorie or sodium restriction. A greater degree of restriction will correct hyponatraemia more rapidly but is often limited by the thirst response. Fluid restriction alone is often insufficient to restore normal sodium concentrations, particularly in those with urine osmolality >500 mOsm/kg H₂O.

Tolvaptan (a vasopressin-2 receptor inhibitor) is an effective, licensed medication for SIAD, but should be initiated in specialist hands as it may cause excessively rapid correction of hyponatraemia, particularly in older people. Major international guidelines recommend against the use of demeclocycline, a tetracycline antibiotic with the therapeutic side effect of nephrogenic diabetes insipidus.

A feature of chronic SIAD, which occurs most commonly in older patients, is reset osmostat syndrome. In this syndrome, normal renal concentration of plasma occurs around a new, lower set point. Fluid restriction is unlikely to be successful because of excessive thirst, and treatment should be directed to the underlying cause if it can be identified.

Other causes

Adrenocorticotropic hormone deficiency due to hypopituitarism leads to impaired ability to excrete water in a condition which mimics SIAD. Hypothyroidism is usually only associated with hyponatraemia in myxoedema when the fall in cardiac output leads to a rise in vasopressin levels. These can be excluded by checking a 9 am cortisol level and thyroid function tests.

Hyponatraemia associated with heart, renal, or liver failure is associated with a poor prognosis. Refer patients for specialist management of the underlying condition.

Polydipsia causes hyponatraemia when the ingested fluid volume exceeds the maximal filtration capacity of the kidney. It is frequently associated with an underlying mental health disorder, most commonly schizophrenia. Urine osmolality <100 mOsm/kg H₂O, in the presence of hyponatraemia is strongly suggestive of polydipsia. Supervised fluid restriction is usually effective alone but may require adjunctive furosemide, behavioural therapy, or psychopharmacology depending on the scenario.

Competing interests: None declared.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.l1774

EDUCATION INTO PRACTICE

- Do you routinely consider hyponatraemia as a potential factor in a falls assessment in patients on thiazide diuretics?
- How many of your patients on thiazide and thiazide-like diuretics have their sodium level checked in the first month of therapy and on an annual basis?
- Think about the last person you saw with frailty and mild hyponatraemia. Do you think that active management of hyponatraemia might help this person with their functional status?
Preventing medication-related osteonecrosis of the jaw

Lara Zebic, Vinod Patel

Osteonecrosis of the jaw is a severe adverse effect reported with certain drugs commonly used in the treatment of cancers and osteoporosis. Although rare, it can severely impair quality of life. The number and type of drugs associated with osteonecrosis of the jaw continue to increase, as do their indications. With greater life expectancy and more people living with cancer as a chronic disease, the pool of those “at risk” is increasing.

Management can be costly, invasive, and difficult. Clinicians can play a pivotal role in prevention of medication-related osteonecrosis of the jaw by informing patients of the risks when they prescribe these drugs and discussing ways to minimise the risk. In this article we describe the risks associated with different therapies and provide guidance on prevention for non-specialists.

How do patients present?

The jaw bone—the mandible or the maxilla—is exposed with necrotic tissue or it can be probed through an intra-oral or extra-oral fistula (fig 1). As well as exposed bone, patients may present with pain, swelling, pus, mucosal ulceration or erythema, loose teeth, and altered sensation in the regional nerve distribution. Symptoms can be constant or cyclical and can affect eating, drinking, talking, and routine dental care.

WHAT YOU NEED TO KNOW

- Osteonecrosis of the jaw is a rare but serious adverse effect associated with anti-resorptive and anti-angiogenic therapies used in cancers and osteoporosis
- Patients with cancer receiving intravenous infusion of these therapies or using a combination of therapies are at a higher risk
- Fewer than 1 in 1000 individuals taking oral bisphosphonates for osteoporosis will develop osteonecrosis of jaw
- Inform patients of the risks before starting treatment and offer referral to dental services for screening and remedial treatment
- Ask patients who are receiving treatment to report jaw pain or awareness of exposed bone and promptly refer suspected cases to dental or oral maxillofacial services in secondary care
**What medications can have this adverse effect?**

The table (right) lists drugs with safety warnings about the risk of osteonecrosis of the jaw issued by the Medicines and Healthcare Products Regulatory Agency (MHRA). The exact mechanisms leading to osteonecrosis remain unknown, and they are likely to be multifactorial (fig 2). The jaw bones are vulnerable to the effects of these drugs because of their relatively high bone turnover and remodelling rates. They are also readily exposed to bacteria from the oral cavity through the thin, easily breached oral mucosa or via the teeth. Dental diseases such as abscesses or periodontal (gum) disease provide direct access to the bone.

**Anti-resorptive therapies**

Anti-resorptive therapies reduce bone turnover by inhibiting osteoclast function. Bisphosphonates are the most common drug implicated in medication-related osteonecrosis of the jaw. Another anti-resorptive agent, denosumab, has also been associated with a risk of jaw osteonecrosis. Cases of jaw osteonecrosis have been observed in a phase 3 clinical trial of the novel sclerostin-inhibiting monoclonal antibody romosozumab.

Bisphosphonates bind to the skeleton with an estimated half-life of 10 years, so the risk of osteonecrosis of the jaw continues long after treatment cessation. In contrast, denosumab allows osteoclast reactivation within six months of treatment cessation, so its effect on bone could be considered reversible.

These drugs are prescribed for osteoporosis; non-neoplastic conditions such as Paget’s disease and osteogenesis imperfecta; multiple myeloma; hypercalcaemia of malignancy; and for prevention of skeletal-related events in cancers that metastasise to bone. Such cancers are commonly breast, prostate, and lung cancers and, to a lesser degree, renal, thyroid, and gastrointestinal cancers. A National Institute for Health and Care Excellence (NICE) guideline now recommends bisphosphonates as adjuvant treatment for breast cancer in postmenopausal women. This is likely to have a substantial impact on the UK population at risk of medication-related osteonecrosis of the jaw.

**Anti-angiogenic therapies**

These therapies disrupt new blood vessel formation through their actions on the angiogenesis-signalling cascade. Their use in metastatic cancer treatment often overlaps with the administration of anti-resorptive drugs.

**Other drugs**

Cases of jaw osteonecrosis have been reported with other drugs, but these are rare and the magnitude of risk is uncertain. The US Food and Drug Administration (FDA) has linked several cases to mammalian target of rapamycin (m-TOR) inhibitors (everolimus and temsirolimus) used in renal cell cancer. Other case reports include anti-tumour necrosis factor agents and immunosuppressants used in rheumatic conditions and radium-223, a radiopharmaceutical currently approved for castration-resistant prostate cancer with bone metastasis.

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**DATA SOURCES AND SELECTION**

We have drawn on the recommendations from the American Association of Oral and Maxillofacial Surgeons and the Scottish Dental Clinical Effectiveness Programme, with relevant citations identified from their content. We supplemented this with literature from our personal archive of references which includes randomised controlled trials, prospective and retrospective studies as well as case reports. In discussing the risk of medication-related osteonecrosis of the jaw, we have attempted to cite the highest level of evidence available.

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**Drugs issued with MHRA safety alerts about the risk of osteonecrosis of the jaw**

<table>
<thead>
<tr>
<th>Drug types</th>
<th>Route of administration</th>
<th>Common indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-resorptive drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisphosphonates:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoledronate, ibandronate, pamidronate</td>
<td>Intravenous</td>
<td>Multiple myeloma, metastatic cancer, Paget’s disease</td>
</tr>
<tr>
<td>Alendronate, risedronate, clodronate</td>
<td>Oral</td>
<td>Osteoporosis, Paget’s disease, bone pain</td>
</tr>
<tr>
<td>RANKL inhibitor monoclonal antibody:</td>
<td>Subcutaneous</td>
<td>Metastatic cancer, osteoporosis</td>
</tr>
<tr>
<td>Denosumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-angiogenic drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGF inhibitor:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Intravenous</td>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitor:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Oral</td>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Fusion protein:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aflibercept</td>
<td>Intravenous</td>
<td>Metastatic cancer</td>
</tr>
</tbody>
</table>

**Fig 2 Theories of medication-related osteonecrosis of the jaw pathogenesis (compiled from Ruggiero et al)**
What is the risk with these therapies?

The overall risk of osteonecrosis of the jaw with anti-resorptive or anti-angiogenic therapies is low but difficult to estimate in any patient. The box above lists factors that increase the risk.\(^{16}\)

**Risk in patients receiving therapy for cancer**

Cancer patients are usually treated with a high frequency of infusions of intravenous bisphosphonates such as zoledronate or subcutaneous denosumab. The risk of jaw osteonecrosis associated with these medications in oncology approximates 1% (level 1 evidence, two meta-analyses and five randomised trials) and is proportional to the duration and cumulative dose of the medication received.\(^{1,17}\)

**Dual therapy increases risk**

The incidence of jaw osteonecrosis in patients taking anti-angiogenic drugs alone is reported as 0.2% (2/1076 patients) in an analysis of two double-blind randomised trials (1309 patients, pooled), but dual therapy with bisphosphonates increases the incidence to 0.9% (2/233).\(^{18}\) There are further case reports of spontaneous jaw osteonecrosis associated with dual therapy.\(^{7}\)

A cohort study of cancer patients diagnosed with medication-related osteonecrosis of the jaw (42 cases) found that the time from treatment onset to diagnosis of necrosis was shorter in those treated with intravenous zoledronate and bevacizumab in combination (12.4 months) than in those given bevacizumab alone (22.9 months, \(P<0.05\)).\(^{19}\)

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**Sources of further information**


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**Risk factors for medication-related osteonecrosis of the jaw**

<table>
<thead>
<tr>
<th>Medication-related factors</th>
<th>Dental factors</th>
<th>Concomitant medications</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Those being treated for cancer are at higher risk than those treated for osteoporosis</td>
<td>Dental surgery (tooth extraction) is a major risk factor</td>
<td>The risk is higher with dual therapy (anti-resorptive plus anti-angiogenic drugs)</td>
<td>Anaemia, diabetes, and HIV infection among cancer patients are inconsistently reported risk factors</td>
</tr>
<tr>
<td>Risk increases with the duration of anti-resorptive therapy</td>
<td>Dental infection, periodontal (gum) disease, or trauma from poorly fitting dentures may increase the risk</td>
<td>Corticosteroids and immuno suppressants such as methotrexate and azathioprine are associated with increased risk</td>
<td></td>
</tr>
</tbody>
</table>

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**Dental extraction is an important risk factor**

Osteonecrosis of the jaw can occur with no obvious induced cause in both therapeutic groups, but dental extractions increase this risk. A recent tooth extraction was reported by 52-61% of patients who developed medication-related osteonecrosis of the jaw in a range of studies including longitudinal cohort, retrospective studies, and analysis of three phase III trials.\(^{1,17}\)

The risk of jaw osteonecrosis after tooth extraction seems to be greater for patients being treated for cancer than for those treated for osteoporosis, with reported rates of 3.2% (95% confidence interval 1.7 to 4.7) and 0.15% (0.0 to 0.36) respectively (\(P<0.0001\)), according to a systematic review and meta-analysis (13 prospective studies, 2662 patients).\(^{20}\)

**How can it be prevented?**

Prevention forms the main management approach for patients taking anti-resorptive or anti-angiogenic drugs.\(^{4}\) Patients are often unaware of the possible risk until it is discussed before tooth removal or when they present with symptoms.

When prescribing these medications, inform patients of the small risk of developing osteonecrosis of the jaw. They should not be discouraged from taking their prescribed therapies, however, as clear evidence exists on the effectiveness of these drugs in treating cancers or osteoporosis.\(^{7}\) Discuss steps they can take to reduce the risk, such as maintaining good oral hygiene, a nutritious diet, reduced alcohol intake, and smoking cessation (fig 3). Encourage patients to attend regular dental reviews and to report any jaw symptoms.\(^{7}\)

It is strongly advised that patients are referred to dental services for screening and remedial treatment before initiating these therapies, particularly in patients with cancer who are at higher risk.\(^{5,8}\) Referral provides the opportunity to liaise with dental services so they are informed of the patient’s medications and their risk of developing medication-related osteonecrosis, and can implement the appropriate preventive and remedial treatments early. A dental assessment...
can identify the presence and risk of caries (dental decay), periodontal (gum) disease, and any longstanding dental infection. A Cochrane systematic review reported that regular dental examinations and preventive treatment seem to lower the risk of jaw osteonecrosis, although the evidence was of low quality. Larger studies are required to detect meaningful effects of preventive measures on the incidence of medication-related osteonecrosis of the jaw.

The American Association of Oral and Maxillofacial Surgeons highlights weak evidence (level 5) that taking a “drug holiday” may decrease the risk of medication-related osteonecrosis of the jaw and, given the long half-life of these medications, probably does no harm. These guidelines suggest a two month drug-free period before invasive dental treatments for patients taking long term (>4 years) oral bisphosphonates. A decision to pause drug therapy is primarily made by the prescribing physician and balanced against the risk of adverse events. Medications may be discontinued by oncologists if osteonecrosis of jaw develops in cancer patients depending on both the oncology disease status as well as the extent and severity of the jaw necrosis.

What does treatment involve?
Promptly refer patients with suspected medication-related osteonecrosis of the jaw to dental or oral maxillofacial services in secondary care. Management tends to be palliative and supportive to control infection, bone necrosis, and pain. This may include dedicated oral hygiene regimens, often through mouthwashes and, when required, antibiotics. Surgery remains an uncommon option as it carries the risk of exacerbating necrosis, but it may be required in severe cases. Refer patients with symptoms of concern or a non-healing ulcer present for two weeks or more via the two-week-wait pathway under the differential diagnosis of oral cancer.

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Find the full version with references at http://dx.doi.org/10.1136/bmj.l1733

**Fig 3** Visual aid for discussing the risk of medication-related osteonecrosis of the jaw (MRONJ) with patients (compiled from Ruggiero et al1 and the Scottish Dental Clinical Effectiveness Programme)
A 10 year old boy presented to the paediatric emergency department with a one week history of a limp and increasing pain in his left thigh. He first noticed this while running at school. Over the following week his pain worsened and began to affect his knee. He had no history of hip, knee or lower back pain, was otherwise well and had no known medical conditions.

On examination he was able to weight bear fully but with an antalgic gait. Internal rotation of the left hip was limited to 10° and abduction to 20°. He was afebrile. Blood results revealed a normal white cell count and inflammatory markers. Pelvic radiographs (anteroposterior and frog lateral views) were taken (fig 1).

1 What is the diagnosis?
2 What further investigations are required?
3 How would you manage this condition?

Submitted by Adam M Ali, Ali Hani, and Htwe Zaw

Parental consent obtained.

Cite this as: BMJ 2019;365:l1349

LEARNING POINTS

1. Consider SUFE in children with hip or knee pain.
2. In situ fixation usually involves a single screw passed through the physis (growth plate) and into the femoral head, avoiding the risk of further displacement.
3. Consider pre-slip imaging in high risk patients to assess the risk of SUFE.
4. Consider medical comorbidities and obesity, which are associated with SUFE.

Fig 1

The area inside the circle shows the femoral head and neck. A line drawn along the superior border of the femoral neck (Klein’s line—dotted line in image) does not intersect the femoral epiphysis on the left side, indicating that this child has SUFE.

LEARNING MODULE

You can record CPD points for reading any article. We suggest half an hour to read and reflect on each.

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ENDGAMES
Musculoskeletal abnormalities in Down’s syndrome

Children with Down’s syndrome have a high prevalence of musculoskeletal problems and they may be slow to reach motor milestones. Examination of a large series of cases from Ireland reports that pes planus is the commonest abnormality, affecting nine out of 10 children (Arch Dis Child). Inflammatory arthritis, usually affecting the wrists and small joints of the hand, is also much more frequent than in children without Down’s syndrome, and there is often a delay in diagnosis and treatment.

Out-of-hospital cardiac arrest

The compelling advantage of compression-only cardiopulmonary resuscitation (CPR) over CPR with both compressions and mouth-to-mouth ventilation is that bystanders are far more likely to try it. A nationwide survey from Sweden reports a sixfold increase in numbers of people receiving CPR after an out-of-hospital cardiac arrest following the adoption of a policy of promoting and teaching the compression-only variation (Circulation). The chances of survival in people who received CPR from bystanders were twice as high as in those who had to wait for the arrival of emergency medical services.

A peculiar leg rash

A 57 year old woman had a four month history of a mildly painful rash on both legs and feet. The skin was extremely dry and rough, with small cracks and brownish flakes (figure). Her diet lacked fruit and vegetables and she consumed approximately 8 units of alcohol daily. The brown colouring made eczema unlikely. Pellagra was considered and later confirmed by a reduced serum vitamin B3 (niacin) level of 11 µmol/L (normal range: 20-50 µmol/L).

Excess alcohol and poor niacin intake contributed to this patient’s condition. Alcohol affects niacin metabolism by inhibiting the conversion of tryptophan to niacin. Pellagra typically affects the neck and/or the back of the hands, but in this case only the legs were affected.

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Autism spectrum disorder

Folic acid supplements taken before conception or early in pregnancy reduce the incidence of neural tube defects in the offspring. It looks as if they might reduce rates of autism spectrum disorder too. A Californian study investigated 300 families in which one child had already received a diagnosis of autism (JAMA Psych). Among children born subsequently, those whose mothers had taken vitamin supplements during the first month of pregnancy were half as likely to have autism.

Diet and colorectal cancer

During six years’ follow-up of the half million participants in the UK Biobank study, more than 2500 people developed colorectal cancer. The strongest dietary associations were with red and processed meat (Int J Epidemiol). People who ate these foods four or more times a week were 20% more likely to develop colorectal cancer than those who ate them less than twice a week. Intake of fish, poultry, cheese, fruit, vegetables, tea, and coffee had no effect on risk.

Waning protection from vaccines

A review in Science highlights some of the puzzles about the durability of protection obtained from vaccination. Why do vaccines for mumps, pertussis, and yellow fever lose their effectiveness more quickly than those for measles, diphtheria, and tetanus? Flu vaccine is a particular problem. Not only is it less effective than most vaccines, protecting only about 60% of vaccinated people, but the immune response it stimulates wanes within a few months. People who receive their flu vaccines at the end of September may have lost much of the protective effect by January and February, when rates of flu tend to peak.

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