education

RESEARCH REVIEWS Fortnightly round up from the leading medical journals

Filtering the evidence on air filters

When the world was reopening after the covid-19 restrictions eased, many schools, offices, and healthcare facilities invested in air filters and other engineering solutions that claimed to reduce the spread of respiratory infections—such as covid-19—that can spread through the air. A scoping review in *Annals of Internal Medicine* describes the challenges of building an evidence base for these: it found studies involving 1073 different interventions, from negative pressure ventilation, to high efficiency particulate air filters and photocatalytic oxidation. Most studies assessed the surrogate outcome of air quality (eg, the quantity of viable non-pathogenic organisms from air samples) and only 57 of 672 studies included human participants.

Ann Intern Med doi:10.7326/ANNALS-25-00577

High tibial osteotomy for knee osteoarthritis

Being unable to remember the difference between varus and valgus at medical school should have prompted me to consider a career outside of medicine—although I suspect many of the class of 2006 would have said that becoming a general practitioner was the next best thing. A new trial suggests that people with symptomatic medial compartment knee osteoarthritis and varus alignment (where the distal segment is angled towards the midline, but don't take my word for it) may benefit from high tibial osteotomy, which aims to redistribute the load on the knee and thereby preserve joint structure. Although this was only a single centre study, improvements on magnetic resonance imaging and pain scores were seen in the surgery arm of the study after two years compared with the control group.

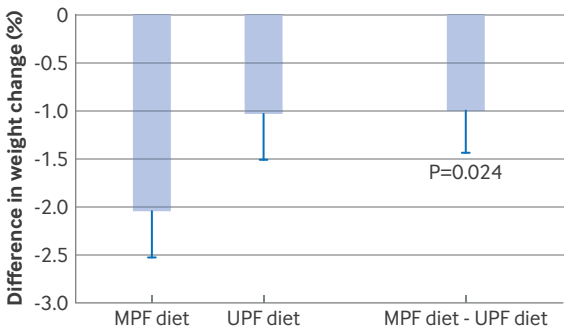
Ann Intern Med doi:10.7326/ANNALS-25-00920

Eating well with UPFs

The Eatwell Guide follows recommendations by the Scientific Advisory Committee on Nutrition (SACN), and focuses on macronutrients such as carbohydrates and fat, and food types, such as fruit, dairy, and starchy food. Many think that guidance on ultraprocessed foods (UPFs) should be added, but the SACN has called for more evidence from randomised trials. The UPDATE trial provides some evidence, but will it persuade the SACN to change its position?

The study randomised 50 people with a body mass index (BMI) between 25 and 40 to follow one of two diets for eight weeks, each based on the Eatwell Guide. One diet consisted of UPFs and the other contained minimally processed foods (MPFs). After a washout period the groups switched diets. The MPF diet led to average weight loss of 2%, compared with 1% for the UPF diet (fig 1)—a statistically significant, but perhaps underwhelming difference, in the age of tirzepatide. Several of the secondary outcomes, such as systolic blood pressure and food cravings, were also lower with an MPF diet.

Nature Med doi:10.1038/s41591-025-03842-0



Percentage weight change on MPF and UPF diets

CREDIT: DICKEN SJ, JASSIL FC, BROWN A, ET AL. NAT MED 2025 HTTPS://DOI.ORG/10.1038/S41591-025-03842-0

CLINICAL PICTURE

Reticular pallor of the buccal mucosa

This man in his 20s presented with a three month history of a burning sensation in his mouth, associated with mildly restricted mouth opening. He had no medical history, but reported chewing betel (areca) nuts daily for the past two years. Examination showed reticular marble-like pallor to the soft palate and buccal mucosa bilaterally, which was firm to palpation. Histopathology of a biopsy taken from the right buccal mucosa showed epidermal atrophy, vacuolar interface alteration, and excessive collagen deposition with chronic inflammatory infiltration below the mucosa. He was diagnosed as having oral submucous fibrosis (OSF).

OSF is a potentially malignant oral condition associated with chewing betel nuts and products containing betel nuts such as paan.[1 2] Betel nuts, classified as carcinogenic, are widely chewed, particularly in South and South East Asia, for the stimulant effect of the compound arecoline, which

The noble path to Everest

The mountaineering world is in a "frenzy" over the use of inhaled xenon, according to a letter in the *New England Journal of Medicine*, after four British mountaineers completed the ascent and descent of mount Everest in just 7 days—a trek that typically takes 6-8 weeks. Thankfully for GPs, tired of signposting trekkers seeking acetazolamide to travel clinics, xenon is in fact one of the noble gases (Xe, atomic number 54), and not anything available on prescription. The correspondence casts doubt on the benefits of xenon, saying the achievement "probably had little to do with the xenon effects" and was more a product of the experience of the climbers and "the luck of good weather, helicopter and Sherpa support, and most importantly, sleeping in altitude tents over a period of several weeks before their climb"—not to mention the full oxygen support for the final ascent to 8849 m.

N Engl J Med doi:10.1056/NEJMc2507671

Expanding the evidence for semaglutide in East Asia

Although the days when people wanted to take oral semaglutide for weight loss seem like a lifetime ago, a new trial fills an evidence gap in a population who are more susceptible to weight related complications at lower BMI and are often overlooked by drug trials. The study randomised 201 people in Japan and South Korea with a BMI of 27.0 or greater and two or more related complications or a BMI of 35.0 or greater and one or more related complications. Those allocated to take oral semaglutide for 68 weeks had similar levels of adverse events to those seen in other populations, and had a mean body weight reduction of 14.3% versus 1.3% in the placebo group.

JAMA Intern Med doi:10.1001/jamainternmed.2025.3599

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has been implicated in the pathogenesis of OSF.[2] Cessation of betel nut chewing is the most effective preventive measure against OSF,[2] highlighting the importance of asking about betel nut use in patients presenting with intra-oral lesions.

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Patient consent obtained.

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MINERVA From the wider world of research

Sex distribution in newborn babies

The orthodox view that, in every singleton pregnancy, there is a more or less equal chance of the baby being a boy or a girl may not be right. An analysis of the sex of children born to 60 000 nurses in the United States between 1956 and 2015, finds that families where all the offspring are of one sex are commoner than one would expect from a simple binomial distribution (*Sci Adv* doi:10.1126/sciadv.adu7402). Among families with three boys or three girls, the chances of the next sibling being of the same sex were around 60%.

Anisogamy and the definition of sex

The most fundamental definition of sex in both plant and animal kingdoms depends on gamete size (UnHerd https://unherd.com/2025/08/why-men-are-different-from-women/). In all species, except for a few algae, gametes from different sexes come in strikingly different sizes—a phenomenon known as anisogamy. Female gametes are always much larger than male gametes. A human egg contains at least ten thousand times as much matter as a human sperm. In many species (think ostriches), the discrepancy is even greater.

Lifestyle modifications to treat atrial fibrillation

Obesity is a risk factor for atrial fibrillation. A randomised trial in patients with paroxysmal or persistent atrial fibrillation and a body mass index greater than 30 reports that a combination of drugs and a lifestyle intervention to promote weight loss and increase physical activity rendered a third of patients free of arrhythmias (*J Am Coll Cardiol* doi:10.1016/j.jacc.2025.04.042). Mind you, this combination wasn't as effective as catheter ablation, which did the same thing in nearly three quarters of patients.

Long term oxygen therapy

Long term oxygen therapy improves survival in patients with chronic hypoxaemia from obstructive pulmonary disease, interstitial lung disease, or pulmonary hypertension. It also reduces numbers of hospitalisations, according to a large observational study from Sweden (*Thorax* doi:10.1136/thorax-2023-221063). The presence or absence of hypercapnia made no difference.

Eggs

Once considered the cornerstone of any nutritious breakfast, eggs became dietary villains during the epidemic of coronary heart disease in the second part of the 20th century. Now they're being exonerated. A randomised trial in South Australia reports that eating two eggs a day, as part of a low saturated fat diet, led to a reduction in plasma low density lipoprotein cholesterol concentrations (*Am J Clin Nutr* doi:10.1016/j.ajcnut.2025.05.001).

Adipose tissue biology

Losing body fat improves insulin sensitivity in people with obesity. This isn't simply a matter of decreasing the volume of adipose tissue because liposuction carries no metabolic benefits. A detailed investigation of 10 adults with obesity, before and after substantial weight loss, shows a complex story of adipose tissue biology involving altered expression of genes controlling extracellular matrix formation and changes in circulating levels of leptin and adiponectin (*Diabetes Care* doi:10.2337/dc24-2739).

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CHOOSING WISELY

Initial assessment of infertility in primary care

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The World Health Organization (WHO) defines infertility as the lack of a pregnancy after at least 12 months of regular unprotected intercourse.[1] WHO estimates that one in six people is affected by infertility globally (data obtained between 1990-2021).[2] Infertility has been increasing over time.[3 4]

CPD READING

0.5 HOURS

LEARNING MODULE

See learning.bmj.com for linked learning module

What to consider when discussing infertility with patients

Experiencing infertility can be stressful, potentially contributing to emotional, physical, financial, and social stress.[5] Fertility treatment can be time consuming and expensive, and navigating the required tests and appointments can be challenging. Infertility care should be tailored to patients' preferences, needs, and values.[6] This means that care processes go beyond clinical considerations to include patients' emotional, social, financial, and spiritual perspectives.

Based on our experience, we suggest considering the following:

- Referral for counselling with a psychologist or other experienced care provider to manage symptoms of depression and improve social support for patients having difficulties navigating the complex challenges associated with fertility care.[8]
- Consider cultural norms and expectations associated with fertility and aim to address any stigma and shame faced by patients with infertility.[9] Infertility stigma is high in low and middle income countries where childless women may be socially isolated.[10]

WHAT YOU NEED TO KNOW

- Offer pre-conception counselling that encompasses lifestyle factors and management of any pre-existing medical conditions to increase the likelihood of a healthy pregnancy
- Initial investigations in primary infertility include testing for tubal obstruction, a semen analysis, and confirmation of ovulation with either urinary ovulation predictor kits or mid-luteal phase serum progesterone test
- Avoid tests and treatments that are not evidence based and do not add clinical value

What to consider when ordering tests

The most comprehensive guidelines on the initial assessment and management of infertility were published by the National Institute for Health and Care Excellence (NICE), last updated in 2017.[11-16]

Since the NICE guidelines were updated, the average age and rate of people presenting with infertility, as well as the number and complexity of tests and treatments for infertility, has continued to increase.[17] Many countries around the world have seen a substantial decrease in total fertility rates over time, particularly during the 2021-22 post-pandemic years.[20] In the UK, the rate of testing female sex hormones for all indications has increased from 68.3 per 10 000 person years in 2000 to 140.5 per 10 000 person years in 2015, with a similar increase in oestradiol testing.[21]

The initial assessment of infertility and decision on when to refer for specialist care can be challenging for primary care providers and varies by location based on access to testing and fertility specialists. While some patients do not receive important tests for infertility, others may undergo multiple repetitive and sometimes unnecessary tests while awaiting consultation with a specialist. Here, we describe a suggested approach to the initial assessment of primary and secondary infertility. We highlight points from guidelines by NICE, the American Society for Reproductive Medicine (ASRM), and the European Society of Human Reproduction and Embryology (ESHRE) that are relevant for primary care providers.[13-16]

What are potential causes of and risk factors for infertility?

Risk factors and causes of infertility can be categorised into the following groups: ovulatory (21.8%), tubal and utero-cervical (23.5%), male factor (23.9%), and unexplained (30.7%).[25] These are detailed in table 1 on bmj.com. Key points to elicit on history to identify potential causes of infertility are summarised below.

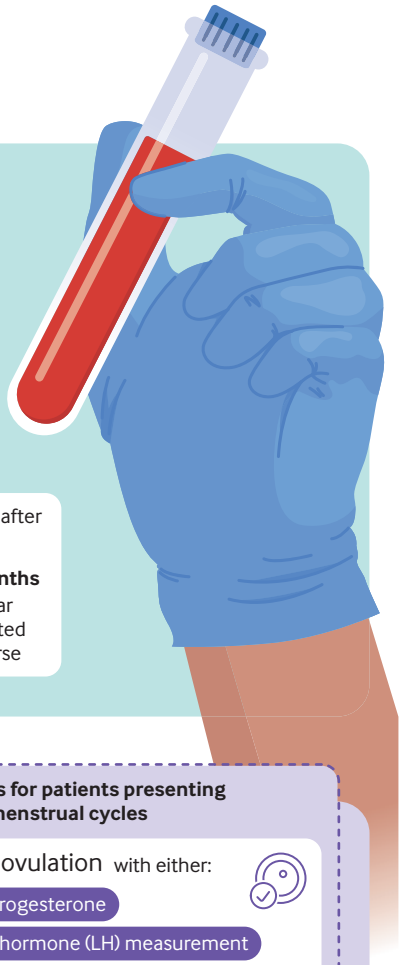
Ovulatory dysfunction—A typical menstrual cycle ranges from 24 to 35 days. Home ovulation predictor kits can be bought from pharmacies and easily interpreted by patients to confirm ovulation when there is uncertainty. Confirmation of ovulation is not recommended for women with regular menstrual cycles but can be useful to diagnose ovulatory dysfunction in women with irregular menstrual cycles or in whom home ovulation prediction testing does not clearly show a surge in luteinising hormone (LH), suggesting a lack of ovulation that cycle.[13 16]

thebmj Visual summary

Infertility testing

Initial investigation and referral

If pregnancy has not occured after optimisation of patient health and timing of intercourse, further investigation may be required. This graphic presents a suggested approach to the initial assessment of infertility, with consideration given to providing the most important and clinically relevant tests



When should patients be investigated?

Regular menstrual cycle

- **Age ≤35 years AND No risk factors** → Investigate after **12 months** of regular unprotected intercourse
- **Age >35 years OR Important risk factors** → Investigate after **6 months** of regular unprotected intercourse

Prior

- Chemotherapy, substance or anabolic steroid use
- Pelvic infections, sexually transmitted infections or tuberculosis
- Pelvic or testicular surgery

Endometriosis, large uterine fibroids, endometrial polyps, endometrial hyperplasia or malignancy or suspected Müllerian anomalies

Irregular menstrual cycle

Defined as <24 days or >35 days between menstruation

→ Investigate after **6 months** of regular unprotected intercourse

Which tests should be performed?

Tubal patency testing

with one of

- Hysterosalpingography (HSG)
- Sonohysterogram (SHG) / Hysterosalpingo contrast sonography (HyCoSy)

Cause of infertility found?

- No → Transvaginal ultrasonography
  - Can be obtained at time of SHG/HyCoSy
- Yes → Refer to specialist

Semen analysis for partner

If abnormal repeat in **1 to 3 months**

Repeat test abnormal?

- Yes → **Check**
  - Physical exam of testes for masses and varicocoeles
  - Measure serum FSH* to distinguish hypothalamic, obstructive, and testicular causes
  - → Refer to specialist
- No → Refer to specialist

Additional tests for patients presenting with irregular menstrual cycles

Confirmation of ovulation with either:

- Mid-luteal serum progesterone
- Urinary luteinising hormone (LH) measurement
- Ultrasound monitoring for follicular development

Ovarian reserve testing

with day 3 follicle-stimulating hormone or anti-Müllerian hormone to help establish a diagnosis of:

- Polycystic ovary syndrome
- Premature ovarian insufficiency

Other endocrine testing Based on symptoms eg,

- Thyroid stimulating hormone
- Prolactin
- Androgens
- Screening for diabetes

Investigate after **6 months** of regular unprotected intercourse

Ovulation restored?

- Yes → Investigate after **6 months** of regular unprotected intercourse
- No → Refer to specialist

*Follicle-stimulating hormone

Tubal disease—Tubal dysfunction results from scarring of the fallopian tubes, most commonly as a result of an inflammatory or infectious process.[27] One episode of pelvic inflammatory disease confers a 12% risk of tubal infertility, increasing to 23-35% and 54-75% with second and third infections, respectively.[28] Tubal disease and risk factors for tubal disease also increase the risk of ectopic pregnancy.[29] Assess for tubal factor infertility in patients presenting with infertility when there is a history of postpartum infection, unsafe abortion, and sexually transmitted infection.[30]

Utero-cervical factors—Utero-cervical disease can lead to infertility if it causes significant distortion of pelvic anatomy or affects the endometrium. Uterine fibroids are more likely to contribute to infertility in African populations.[31] Incidence of cervical cancer has declined globally, but has been increasing in countries that lack well developed screening and vaccination programmes, particularly in eastern Africa and eastern Asia where cervical cancer remains an important consideration in the assessment of infertility.[32]

Male factor—Male factor infertility can be classified into four categories: hypothalamic-pituitary disorders, primary gonadal disorders, disorders of sperm transport, and idiopathic.[29 33]

Unexplained infertility—In some cases, no clear cause for infertility is found. These couples are considered to have unexplained infertility, which is a diagnosis of exclusion.[13]

Key points to address in history taking

Eliciting a thorough history will help guide how to best investigate and care for patients with infertility.

For female partner

- What is the average number of days from the first day of your period to the first day of the next period? What is the shortest time and what is the longest time?
- Have you ever been told you have a gynaecological condition such as fibroids, polyps, or endometriosis?
- When was your most recent cervical cancer screening (eg, pap smear or HPV test)? What were the results? Any history of abnormal results? Have you been vaccinated against HPV?

For both partners

- How often do you have vaginal intercourse? Have you tried timing intercourse to the fertile window with a fertility application or urinary ovulation sticks, and have you had any difficulty with interpreting the information? Do you have problems having intercourse—for example, owing to difficulty with erection or ejaculation or pain during intercourse?
- Have you had any previous pregnancies? Have you had any pregnancy losses?
- If you have children, do they have any health concerns?
- Have you ever had a sexually transmitted infection such as chlamydia or a pelvic infection such as ruptured appendicitis or pelvic inflammatory disease?
- Do you have any medical conditions such as autoimmune disease, inflammatory conditions, or other systemic medical conditions?
- Have you had any previous surgeries, including any in the abdomen, pelvis, or genitalia?
- Are you currently taking any medications? Are you taking any steroids or hormones such as testosterone or anti-androgens, chemotherapy agents such as methotrexate, antipsychotic or antidepressant medications, medications for kidney disease, or herbal supplements?
- Are you aware of any conditions that run in the family—for example, abnormalities from birth, genetic conditions, infertility, or pregnancy complications?
- Are you and your partner related to each other?
- Do you drink alcohol, smoke cigarettes, or use cannabis or any illicit drugs?

How can a patient's health be optimised for pregnancy?

Optimisation of health before conception can significantly reduce the risk of pregnancy morbidity and mortality for women and their babies. Based on guidance from the American College of Obstetricians and Gynecologists, optimisation may include:

- Adequate diet and supplementation of vitamin D and folic acid to reduce risk of neural tube defects and nutritional deficiencies in pregnancy[36]
- Encouragement of exercise and weight management to reduce risks of gestational diabetes, hypertensive disorders of pregnancy, caesarean section, and related complications[36]
- Pre-conception health screening and intervention to reduce vertical transmission of HIV with the use of antiretroviral therapy, incidence of babies affected with fetal alcohol syndrome through alcohol cessation, maternal death from postpartum haemorrhage associated with anaemia, and fetal abnormalities from known teratogenic medications[36]
- Screening for risk factors for adverse pregnancy outcomes. Refer for genetic counselling when both partners are known to be carriers of an autosomal recessive condition, if there is a strong family history suggestive of a genetic disorder, or if carrier screening is available based on ethnic or regional risk factors.[34]

What tests should be ordered for initial assessment of infertility?

Initial investigations for infertility include assessment of ovulation (if required), tubal patency and uterine abnormalities for the female partner, and semen analysis for the male partner.

Tubal patency testing and semen analysis are the two most important investigations to identify causes for infertility and can be arranged by primary care providers where resources are available (see infographic). Providers may feel compelled to order tests and interventions without any evidence of benefit when standard testing has not revealed a cause. This can potentially lead to patient harm through false positive or negative results that require follow-up and cause additional psychological and financial burdens for patients, as well as using healthcare resources.[13 39]

Points to note

- Testing for ovulation or ovarian reserve is not recommended in women with a normal menstrual cycle history.[13 16]
- When there is a high suspicion for ovulatory dysfunction and PCOS on history, further hormone testing, screening for thyroid disease and diabetes, and referral to an endocrinologist or reproductive endocrinologist may be indicated.
- Specialists may consider diagnostic laparoscopy for patients with risk factors for tubal disease, such as previous pelvic inflammatory disease with tubo-ovarian abscess[13 16]
- When risk factors for tubal disease are identified on history, a test for chlamydia antibody can be performed to screen for patients who may benefit from referral for laparoscopy.[13]

Reducing unnecessary testing for infertility

In routine evaluation of infertility, we have observed that tests not supported by evidence are often performed, or that indicated tests are repeated unnecessarily. Repeat hormone testing is rarely indicated unless to follow a change in hormones with initiation of management; for example, re-testing TSH after initiating levothyroxine for hypothyroidism or re-testing prolactin after initiating a dopamine agonist for hyperprolactinaemia. Repeat testing of day 3 gonadotrophins and oestradiol does not affect the likelihood of pregnancy in the next 6-12 months for women with regular menstrual cycles and has no impact on the likelihood of pregnancy for those undergoing fertility treatment, but is commonly repeatedly performed by practitioners to assess for elevations of FSH and LH in perimenopause as a means of advising patients on the poor prognosis of fertility treatment.[40-44] Anti-Müllerian hormone (AMH) can be a helpful test in predicting both over-response and under-response to gonadotrophins in patients considering IVF and can be used to assist in distinguishing between high ovarian reserve of PCOS when AMH is elevated and diminished ovarian reserve when AMH is low in patients presenting with irregular menstrual cycles. However, it is not useful in the initial assessment of infertility for women with regular menstrual cycles, since ovarian reserve testing does not predict spontaneous conception over the subsequent 6-12 months.[13 42]

All tests have associated risks and can incur additional costs and inconvenience for the patient. Waiting for results of unnecessary tests can create additional stress and anxiety. Unnecessary tests take resources and time away from more efficient and effective fertility treatment, creating costs for patients, clinics, and healthcare systems.[46]

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

One of the authors (KB) has lived experience with infertility. KB was involved in all stages of the article's development, including conception, drafting, and subsequent revisions to ensure that a patient perspective was present throughout. One of the authors (PK) in particular shared her perspective as a clinician on unique patient experiences of infertility in the Indian context related to gender norms and expectations that are relevant to other low and middle income countries.

EDUCATION INTO PRACTICE

- How would you identify risk factors for infertility in a patient's history? How might these factors inform testing decisions?
- What lifestyle factors could you counsel patients experiencing infertility about to optimise the chances of having a healthy baby?
- How are you able to offer or connect patients to psychosocial support to help manage the stresses associated with infertility and to ensure patient centred care?

How is infertility managed?

Lifestyle advice

Clinicians can offer advice on modification of lifestyle factors to optimise conception and a healthy pregnancy. Advise patients to have frequent or well timed intercourse at least every two to three days during the fertile window, defined as the six most fertile days finishing on the day of ovulation.[47] Ovulation can be estimated by subtracting 14 days from the average menstrual cycle length. The fertile window can be estimated from menstrual cycle length, or with the use of urinary ovulation predictor kits or a fertility application. Not having conceived despite regular intercourse, difficulty in predicting the fertile window owing to irregular menstrual cycles, or difficulty in achieving regular intercourse because of coital dysfunction are reasons to investigate further.

When to refer

Referral to a fertility specialist team can result in improved patient satisfaction and treatment efficiency for patients experiencing infertility and is recommended for the management of tubal factor, male factor, and unexplained infertility, when a patient has not conceived after six months of ovulation induction in which ovulation has been documented or earlier for ovulatory dysfunction. These patients may need advanced care such as gonadotrophins, surgery, intrauterine insemination, or in vitro fertilisation.

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EDITORIAL

Menopause misinformation is harming care

Symptoms should be prioritised ahead of testing

A societal transformation of attitudes and beliefs surrounding menopausal hormone therapy (MHT) has outpaced provider education, leaving primary care specialties unprepared to deliver this care.[1] In the UK, MHT is more commonly referred to as hormone replacement therapy (HRT). Internationally, however, the term MHT is increasingly preferred because it more accurately reflects the full range of treatments used to manage symptoms and health effects of menopause, emphasising the importance of individualised care.[2]

As women are increasingly empowered to seek relief for menopausal symptoms, there has been a sharp rise in services that aim to address this growing demand. Digital health technologies that are available direct to consumer (such as mobile applications, telehealth clinics, podcasts, and websites) have targeted menopause management, raising concerns about the reliability and potential commercial bias of the information.[10,11] A decade ago, the global "femtech" market was valued at $500m (£375m; €430m); today, it is estimated at $28bn and is continuing to grow.[12] One of the most troubling trends arising from this surge is the promotion of routine hormone panel testing for the evaluation of menopausal symptoms—often including serum, salivary, or urine assays for oestradiol, progesterone, testosterone, and even cortisol. These tests can cost hundreds of dollars and are marketed to patients and clinicians as necessary for "individualising" hormone therapy.[13,14]

Beyond questions of clinical validity, the utility of hormone testing is constrained by the physiology of the menopause transition. Perimenopause is characterised by highly variable day to day fluctuations in oestradiol and follicle stimulating hormone levels that contribute to vasomotor symptoms, sleep disturbance, mood changes, and cognitive concerns. Observance of "normal" hormone levels can lead to underdiagnosis and undertreatment of women with symptoms. Postmenopause is defined by a predictable drop in oestradiol and rise in follicle stimulating hormone; however, there is no definitive test to differentiate this from perimenopause. The principle of evidence based practice is that a test should only be done if the result will directly guide patient care. Clinical guidelines from the British Menopause Society, National Institute for Health and Care Excellence, American College of Obstetricians and Gynecologists, The Menopause Society, and Endocrine Society agree: in women over age 45 presenting with validated symptoms of menopause, including menstrual irregularity, menopause is a clinical diagnosis, and hormone testing is unnecessary.[17-21]

Routine hormonal testing is not supported by current evidence

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Despite this, many women now present with detailed hormone panels from wellness providers or online services. In our experience, these panels are often used to justify taking compounded hormone regimens or supplements based on marginal deviations from hormone thresholds that are not grounded in evidence.[16,23] Compounded bioidentical hormone therapy lacks standardisation and regulatory oversight and has not been tested for safety or efficacy.[23] There is concern that inconsistencies in the quantities of oestrogen or progestogen in compounded bioidentical hormone therapy regimens can result in endometrial hyperplasia or carcinoma, particularly in women with an intact uterus who are receiving inadequate progestogen.[24]

Symptom driven approach needed

There is a growing recognition that menopause care is most effective when grounded in an approach that is symptom driven and patient centred. Vasomotor symptoms, insomnia, mood changes, and vaginal dryness are best assessed by a thorough clinical history rather than by hormone levels. For women under 60 or within 10 years of menopause onset, MHT is the most effective treatment for vasomotor and genitourinary symptoms, with a favourable safety profile in appropriately selected patients.[25]

Routine hormone panel testing in the management of menopause symptoms is not supported by current evidence and does not improve care—whether before starting MHT, or to titrate dosing.[26] Until we can establish individualised target hormone levels by accounting for pharmacokinetics, receptor specific pharmacodynamics, and differentiating between endogenous and exogenous hormones, there is no role for commercial hormonal panel testing to guide therapy. In the meantime, such testing offers only a false sense of precision. Although innovation is needed, the normalisation of hormone panel testing could be a symptom of a larger problem: the commercialisation of women's health and a movement away from evidence based practice. For midlife women, effective treatment begins not with numbers, but with listening.

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STATE OF THE ART REVIEW

Advances in the management of osteoporosis

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This is a summary of Clinical Review Advances in the management of osteoporosis. The full version can be read here: https://www.bmj.com/content/389/bmj-081250

CPD READING
0.5 HOURS

Osteoporosis is a chronic disease mainly prevalent in older people. A hip fracture is associated with a one in five chance of mortality in the first year.

Recognition of emerging risk factors for skeletal fragility, such as diabetes and sarcopenia, coupled with the introduction of advanced imaging to analyse bone microarchitecture, has led to refinement in fracture risk assessment models and deepened our understanding of the pathophysiology behind skeletal frailty. Furthermore, major advances in therapeutic approaches to osteoporosis allow for individualised approaches to reduction of fracture risk.

Epidemiology

Globally, the prevalence of osteoporosis in people aged 50-85 is as high as 21.7%, as reported in a meta-analysis of 40 studies.[8] Osteoporosis associated fractures account for 8.9 million fractures worldwide annually and resulted in 25.8 million years lived with disability in 2019.[9 10]

A study across 204 countries estimated the annual incidence of hip fractures to be 681 per 100 000 in people above age 55, with a male-to-female ratio of approximately 0.6.[11] The past two decades have seen an increasing trend in incidence of hip fracture by 24%, mostly owing to population growth and an aging population.[11]

WHAT YOU NEED TO KNOW

- The management of osteoporosis has seen large advances in the last decade, mainly driven by the advent of osteoanabolic agents and discussions around sequential and combination therapy.
- The evolution of clinical and imaging tools for risk stratification will guide identification of the highest risk groups, facilitating an individualised treatment approach.
- Despite major advances in knowledge, gaps in care delivery remain, with substantial parts of the population remaining at risk. Fracture liaison services along with education for patients and clinicians are required to bridge this gap and ensure effective implementation of care models.

A multifaceted approach to osteoporosis management

Reduction of fracture risk requires a multifactorial approach: tackling risk factors, preventing falls, encouraging weight bearing exercise, ensuring adequate calcium and vitamin D supplementation, timely initiation of drug therapy, and continuous re-evaluation of fracture risk.

Emerging risk factors

In recent years, risk factors have been identified that are not fully accounted for in clinical risk tools such as the Fracture Risk Assessment Tool (FRAX) and Garvan risk calculator. Recurrence, site and recency of previous fracture, recency and dose of glucocorticoid treatment, type 2 diabetes mellitus, bariatric surgeries, frailty, sarcopenia, and falls all add significant variability to risk estimates.[16]

Type 2 diabetes

Type 2 diabetes is increasingly recognised as an important risk factor for fracture independent of FRAX or bone mineral density (BMD).[17 18] The Rotterdam study showed a 33% increase in risk of non-vertebral fractures despite elevated BMD in men and women above age 55.[18] The risk remained significant even after correction for age, body mass index, fall risk, and disability status.[18] These findings were confirmed in multiple other longitudinal studies, with risk particularly elevated for insulin treated, poorly controlled type 2 diabetes with longer duration beyond 10 years and primarily seen in hip and total fractures but not vertebral fractures.[17 19 20] FRAX calculations unadjusted for diabetes status result in underestimation of fracture risk.

Sarcopenia

Sarcopenia is defined by low muscle strength; other features include low muscle quantity or quality and low physical performance.[22] Sarcopenia, osteoporosis, frailty, and falls are strongly correlated.[23 24] In a population based, cross sectional study, the coexistence of osteoporosis and sarcopenia had a synergistic effect on the odds of frailty compared with either osteoporosis or sarcopenia alone.[25] Sarcopenia is negatively associated with BMD.[26 27] As shown in the Healthy Aging Initiative population study in Sweden, patients with sarcopenia had lower areal BMD and impaired microarchitectural parameters on high resolution peripheral quantitative computed tomography than those without sarcopenia, with an increased likelihood of incident falls.[26]

Recency of fracture and imminent risk

The first two years after an index fragility fracture represent a period of imminent re-fracture risk, occurring in 7.58% in the first year and 11.58% in the first two years.[28] These account for nearly half of all re-fractures over a 10 year period.[29] The effect of imminent fracture risk was most marked with an index vertebral or hip fracture and more pronounced in younger populations; it is less important in the case of index humerus or distal forearm fracture.[30 31] This has been emphasised in recent guidelines to define a "very high risk" population for fractures,[32 33] warranting immediate evaluation and prompt initiation of therapy.

Advances in risk assessment

Dual energy x ray absorptiometry (DXA, or DEXA) imaging, supplemented with spinal imaging, should be done in accordance with clinical guidelines. Fracture risk is then typically estimated via available tools such as FRAX or the Garvan Institute fracture risk calculator.[32 34]

FRAXplus

The FRAXplus calculator offers a refinement of FRAX predicted risks, taking into account recency and site of previous fragility fracture, presence and duration of type 2 diabetes mellitus, number of falls, lumbar spine-femoral neck discordance, trabecular bone score (TBS), and hip axis length. However, as the accuracy of multiple adjustments has not been validated, clinicians are advised to select the dominant factor likely to produce the greatest effect in modification of estimated risk.

Trabecular bone score

Trabecular bone score uses grey level textural measurement derived from DXA images of the lumbar spine and provides an indirect indication of bone microarchitecture, which contributes to bone strength.[37] A large meta-analysis of more than 17 000 patients from 14 prospective cohort studies showed that trabecular bone score improves fracture risk stratification independently of BMD and FRAX probability,[38] with trabecular bone score adjusted T-scores showing superior risk predictions compared with unadjusted T-scores.[39] Its benefit is seen not only in postmenopausal women and older men but also in secondary causes of osteoporosis such as type 2 diabetes, glucocorticoid induced osteoporosis, and possibly primary hyperparathyroidism.[38 40-43]

Radiofrequency echographic multi-spectrometry

Radiofrequency echographic multi-spectrometry uses radiofrequency ultrasound signals for the analysis of spine and hip bone density based on comparisons of reflected signals with reference spectral models. Validation studies in more than 4000 women show good concordance with BMD obtained by DXA.[44 45] A prospective observational study over 3.7 years found better sensitivity for predicting incident fragility fracture with lumbar spine T-scores derived by radiofrequency echographic multi-spectrometry than with DXA,[46] but the fracture prediction from femoral neck T-scores was similar. This is proposed to be attributed to the ability of radiofrequency echographic multi-spectrometry to automatically remove artifact signals commonly found in the lumbar spine, which limit the accuracy of DXA. As a portable bedside device, radiofrequency echographic multi-spectrometry can be a good alternative in low resource settings without access to DXA.

Non-drug interventions

Exercise and fall prevention

Osteoporosis and sarcopenia guidelines both stress the need for regular weight bearing, resistance, and balance training exercise for reducing the risk of falls and fractures.[32 47] A randomised clinical trial in 162 adults above age 60 found that multicomponent exercise over 12 months comprising resistance, weight bearing, and balance training improved lumbar spine and femoral neck BMD by 1-1.1% (P=0.025 and P=0.042 versus controls) and muscle strength by 10-13% (leg and back; both P<0.001 versus controls) compared with usual self-care.

Resistance exercise training is the cornerstone of sarcopenia management. A framework proposed for the typical older adult with sarcopenia involved a focus on lower body exercise for two sessions a week, progressing in intensity based on maximum repetition or rate of perceived exertion, repeating six to 12 times in one to three sets with clearly defined rest periods within and between sessions.[50]

Barriers such as fear of falls, access shortage, and sustainability of long term participation in maintenance exercise are commonly cited reasons impeding the effectiveness of fall prevention strategies.[53 54] Chair based exercises or Tai chi in the early stages of exercise programmes may help with fear of falls, improve postural control, and reduce falls in older adults.[54 56 57]

Vibration therapy

Whole body vibration has shown efficacy in preventing bone loss at the lumbar spine in postmenopausal women.[62] Interventions showing a positive impact include those that use high frequency and low magnitude vibrations and those with high cumulative doses.[62] RCTs were mainly conducted over short periods ranging from six to 12 months and in women with normal or near-normal BMD, so longer term efficacy is unknown.

Nutrition: calcium, vitamin D, protein intake, and vitamin K supplementation

Calcium and vitamin D supplementation are widely recommended for bone health. Guidelines suggest an elemental calcium intake of 800-1200 mg/day, primarily from dietary sources, as excessive intake may lead to adverse effects such as constipation and cardiovascular problems.[63 64] Vitamin D

Summary of interventions in osteoporosis

Non-drug interventions

- Exercise and fall prevention:
  Weight bearing, resistance, balance training
  2-3 sessions per week, for at least 12 weeks
  Progressive in intensity
  Reduces fracture risk via fall prevention and small increase in BMD
- Concomitant calcium and vitamin D:
  Target 25-hydroxyvitamin D >20 ng/mL
  For postmenopausal women and older men, aim for total elemental calcium 1000-1200 mg/day and vitamin D 800-1000 IU/day
  Avoid large intermittent bolus dosing
  Avoid doses ≥4000 IU/day
  Stronger evidence for institutional setting than community based setting
- Protein intake:
  Aim for >1.0 g/kg/body weight/day in adults >65 years (expert recommendation)
  Avoid malnutrition
- Vitamin K supplementation:
  Vitamin K2 supplementation has some evidence in Asian populations, but overall insufficient evidence for routine supplementation
- Fracture Liaison Service:
  Bridges gap in delivery of care
  Cost effective intervention
  Covers imminent fracture risk

Drug therapy

- Drugs available:
  Anti-resorptives first line for most people at high risk: alendronate, risedronate, zoledronate, denosoumab
  Osteoanabolic agents preferred first line for people at very high risk: teriparatide, abaloparatide, romosozumab
  Second line therapies: HRT for postmenopausal women <60 years with vasomotor symptoms, SERMs if high risk of breast cancer, SERMs and ibandronate for vertebral fracture prevention only
- Sequential therapy:
  Strongest efficacy for osteoanabolic-first approach, with transition to denosumab
  Transition from osteoanabolic to bisphosphonates also effective
  Denosumab should be followed with a potent bisphosphonate to prevent bone loss
  Denosumab-to-teriparatide transition should be avoided owing to hip bone loss at 12 months. Romosozumab is favored after denosumab if an osteoanabolic is needed, or adding teriparatide to denosumab
- Treat-to-target approach:
  Defines a goal at start of therapy, usually defined by T-score
  Personalised target T-score based on individual risk profile, usually ranges from T −2.5 to −2.0 at total hip or 1.0 standard deviation increase
- Monitoring therapy:
  BMD every 1-3 years on therapy
  BTMs to monitor treatment response and compliance: P1NP and CTX most well validated. On anti-resorptives, aim for suppression of P1NP and CTX below mean/median of healthy adult or change greater than LSC. On teriparatide or abaloparatide, aim for P1NP above reference range or change greater than LSC
  Pre-analytical variations in BTMs should be considered

BMDf=bone mineral density; BTM=bone turnover marker; CTX=C-terminal telopeptide; HRT=hormone replacement therapy; LSC=least significant change; P1NP=procollagen type 1 N-terminal propeptide; SERM=selective oestrogen receptor modulator

supplementation typically ranges from 400 IU/day to 2000 IU/day, with most guidelines recommending 800-1000 IU/day. Fracture prevention is most effective when calcium and vitamin D are combined, as evidence for benefit from either alone is limited.[65 66]

The role of protein intake in osteoporosis is less established. Low protein intake has been linked to bone loss, particularly in older adults, with limited evidence supporting its role in preventing hip fracture. Given the strong association of sarcopenia with fracture risk, experts recommend >1.0 g/kg/day of protein for adults over 65, potentially increasing to 1.5 g/kg/day for those at risk of malnutrition.[83-85]

Vitamin K, essential for osteocalcin activation, is primarily found as K1 in green leafy vegetables and K2 in fermented foods. Its role in osteoporosis treatment remains controversial owing to conflicting evidence from studies on BMD and fracture risk.[86 87] Some data suggest that vitamin K2 (menaquinone-4) may benefit bone health, particularly in Japan, but methodological limitations, such as small sample sizes and bias, weaken the conclusions.[88-92]

Bridging the gap between recommendations and delivery of care

Despite remarkable pharmacological advances for effective anti-osteoporotic treatment and a growing older population, a significant proportion of people remain undertreated.

Fracture liaison service is an organisational system of delivering care to close this treatment gap. Evidence from meta-analysis of 57 RCTs shows a 21% increase in treatment initiation and 10% reduction in re-fracture rate compared with standard care,[104] with its cost effectiveness demonstrated across a range of types of fracture liaison service including low intensity, low cost programmes.[105]

Drug therapy

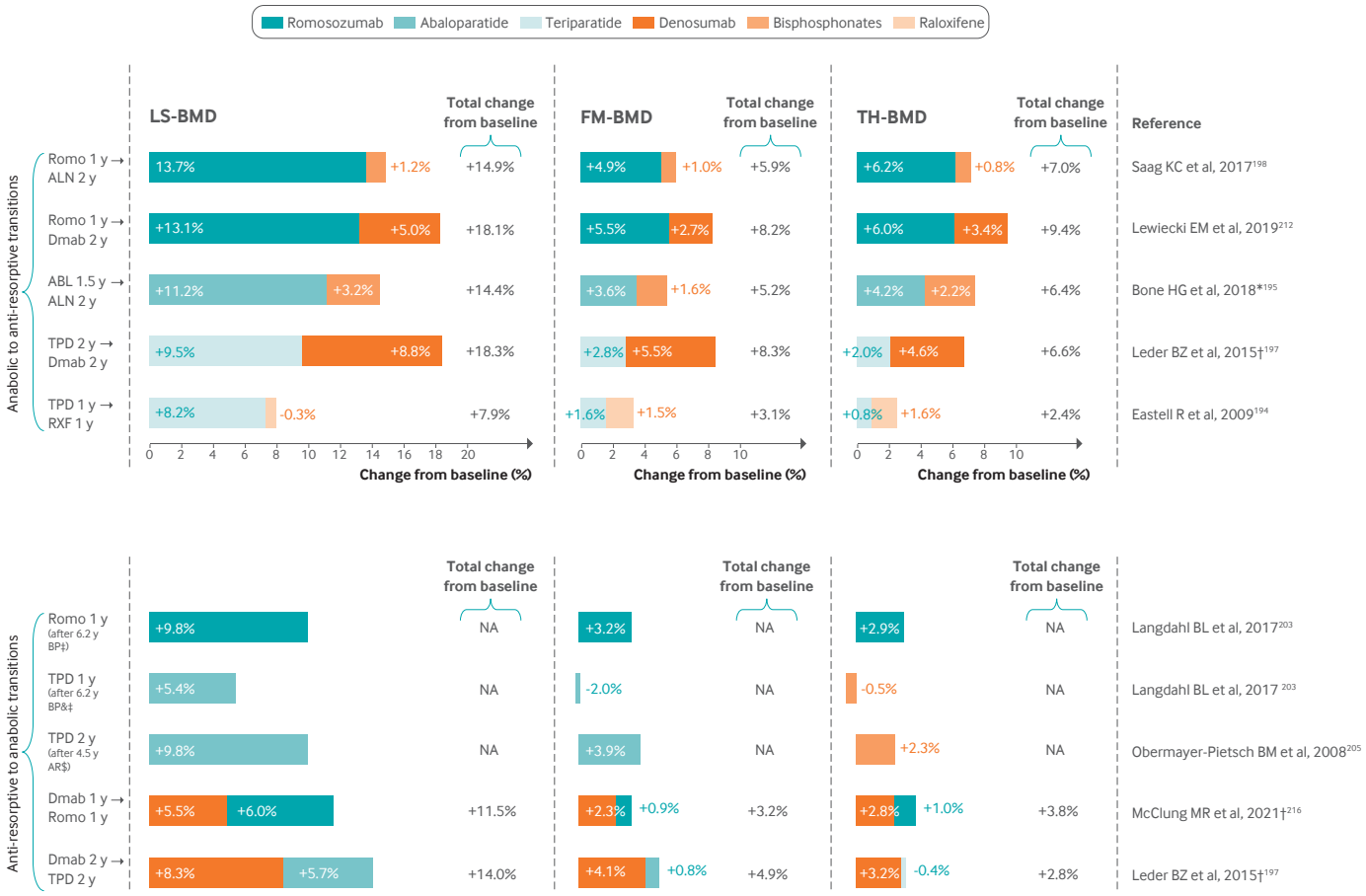
The box summarises the drug and non-drug interventions in osteoporosis.

Menopausal hormonal therapy and selective estrogen receptor modulators

Oestrogens have potent anti-resorptive properties in bone and reduce vertebral and non-vertebral fracture risk by 34% and 13%, respectively, in postmenopausal women.[109] Following release in 2002 of the Women's Health Initiative, its use dramatically declined.

Further analyses of the Women's Health Initiative and many other studies found attenuated risks in women menopausal for less than 10 years, and in fact showed a trend toward a protective effect on cardiovascular events and all cause mortality.[112-115] In the past decade, the availability of 17β-estradiol, transdermal oestrogens, and ultra low dose formulations has further mitigated risks of thromboembolism while maintaining gains in BMD.[116 117]

Selective oestrogen receptor modulators (SERMs) such as raloxifene and bazedoxifene have the additional benefit of exerting oestrogen receptor antagonistic or neutral effects in the breast and endometrium. However, raloxifene and bazedoxifene prevent the occurrence only of vertebral fractures but not of non-vertebral fractures.[120]



Percentage change in bone mineral density (BMD) compared with baseline. For full description see bmj.com

Anti-resorptive effects of SERMS are relatively mild. Reduction in vertebral fracture risk is approximately 30-40% over three to five years,[122 123] compared with 40-50% over three to four years with oral bisphosphonates.[124-126]

Reductions in breast cancer risk have to be balanced against the increased risk of venous thromboembolism and fatal (but not total) stroke in postmenopausal women at risk of or with pre-existing cardiovascular disease.[127 128]

Bisphosphonates

Bisphosphonates have been the cornerstone of osteoporosis management owing to their efficacy, availability, and cost effectiveness. Data from 193 987 postmenopausal women across 107 trials with median follow-up of 28 months found that compared with placebo, zoledronate, alendronate, and risedronate reduce the risk of hip (relative risk 0.60, 0.61, and 0.73, respectively), non-vertebral (0.79, 0.84, and 0.78, respectively), and vertebral fractures (0.38, 0.57, and 0.61, respectively) in descending order of efficacy, whereas ibandronate prevents only vertebral fractures.[129] Gastrointestinal side effects and adherence to weekly dosing are the main limitations with oral alendronate and risedronate, which may make intravenous yearly zoledronate a suitable alternative. All bisphosphonates should be avoided in people with creatinine clearance below 30-35 mL/min owing to their potential for accumulation and the risk of nephrotoxicity with intravenous bisphosphonates.[32 119]

Denosumab

The FREEDOM trial and its 10 year extension study confirm the potent effects of denosumab on fracture prevention and its favourable risk-benefit profile.[154 155] Unlike bisphosphonates, long term denosumab use induces progressive BMD gains of 21% at the lumbar spine and 9% at the femoral neck and total hip, improvements in bone microarchitecture, and continued reduction of vertebral and non-vertebral fracture risk for up to 10 years.[155]

Parathyroid hormone based therapy

Osteoanabolic therapy with teriparatide (parathyroid hormone 1-34 analogue) and abaloparatide (parathyroid hormone related peptide 1-34 analogue) strongly induces both bone formation and resorption.

Parathyroid hormone based therapies show greater efficacy for reduction of fracture risk than do anti-resorptives.[179] In a meta-analysis of RCTs, the parathyroid hormone receptor agonists teriparatide and abaloparatide have hazard ratios of 0.62 and 0.51, respectively, for non-vertebral fractures compared with placebo.[129] They reduce vertebral fracture risk even more dramatically, with hazard ratios of 0.27

and 0.14, respectively.[129] Wrist fracture risk is reduced with abaloparatide (hazard ratio 0.39) but not teriparatide.[180-182]

Romosozumab

The anti-sclerostin monoclonal antibody romosozumab exerts potent anabolic effects via modelling based bone formation and mild anti-resorptive effects. Procollagen type 1 N-terminal propeptide (P1NP) increases rapidly within two weeks and peaks within one month, and it is coupled with suppression of C terminal telopeptide (CTX) maintained over 12 months.[198 199] Further BMD increments are attenuated after 12 months, likely owing to the return of P1NP to below baseline within six to nine months.[199]

As the most potent anti-osteoporotic drug to date, a network meta-analysis found that romosozumab shows relative risks of 0.44, 0.67, and 0.33 for hip, non-vertebral, and vertebral fractures, respectively, compared with no treatment.[129] Compared with placebo and teriparatide, romosozumab has shown significantly greater improvements in both cortical and trabecular volumetric BMD in the spine.[201] BMD gains are reversed nearly to baseline over one year following discontinuation of romosozumab and should be prevented by transition to anti-resorptive therapy.[202]

Until the cardiovascular risks with romosozumab are clarified with appropriately powered trials for cardiovascular events and/or large real world post-marketing data emerge, experts recommend avoiding its use in people with the highest cardiovascular risk.

Testosterone replacement

In younger men with primary or secondary hypogonadism, testosterone replacement leads to initial improvement and subsequent stabilisation of BMD.[209] The evidence for improvement in bone health with testosterone replacement in older men with low testosterone is equivocal.[209]

Sequential and combination therapy

With limitations on prolonged anti-resorptive and osteoanabolic therapies, many patients need sequential treatment. Evidence suggests that starting with an osteoanabolic agent followed by an anti-resorptive agent provides optimal BMD gains (figure).

Studies show that transitioning from teriparatide or romosozumab to denosumab leads to continued BMD increases, with the romosozumab-to-denosumab sequence yielding gains equivalent to seven years of denosumab alone, as seen in the FRAME (romosozumab versus placebo) and FREEDOM (denosumab versus placebo) studies.[197 200 219] This was associated with significant reductions in fracture risk at all sites in the FRAME extension study.[212] Bisphosphonates also help to maintain or increase BMD after osteoanabolic therapy, as observed in the ACTIVExtend and ARCH trials.[213] Compared with bisphosphonates, a transition to denosumab has been shown to yield greater additional gains in the lumbar spine.[214]

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

The development of this manuscript included an interview with an osteoporosis patient advocate to incorporate patients' perspective into osteoporosis management. The patients highlighted real world challenges with osteoporosis medications, including common side effects and long term safety concerns, and raised frequent questions about diet—particularly protein and vitamin K. In response, the manuscript was updated to cover these concerns and now includes guidance on protein intake and vitamin K supplementation.

Combination therapy has been explored. The most effective combination seems to be teriparatide with denosumab, as shown in the DATA trial.[223] Despite the efficacy of this combination, the small added benefit may not justify the high cost.

Personalised and treat-to-target approach

Goal directed treatment for osteoporosis has been the subject of ongoing discussions, with experts advocating for an individualised "treat-to-target" approach. A traditional "step-up" approach advises starting with oral bisphosphonates, progressing to parenteral anti-resorptives and subsequently to osteoanabolics in patients with a poor response. A treat-to-target strategy defines a goal at the start of therapy and refines therapy according to continuous reassessment of progress.

BMD has been identified as the best specific target in a treat-to-target approach as a surrogate for fracture risk.[226] With regard to site of BMD monitoring, treatment related change in total hip BMD was the most strongly correlated with fracture reduction at both vertebral and non-vertebral sites, explaining 44-67% of the reduction in events, validating its use in monitoring therapy.[36]

Guidelines

Table 2 (see online) compares osteoporosis treatment recommendations from leading international societies. The North American based (American Association of Clinical Endocrinology, Endocrine Society, and Bone Health and Osteoporosis Foundation (BHOF))[32 33 119] and European based (National Osteoporosis Guideline Group, IOF/ESCEO)[231 249 250] guidelines diverge on their thresholds for starting therapy, with the North American societies selecting a fixed threshold and the Europeans adopting an age dependent threshold. They also differ in their recommendations for BMD monitoring while on therapy. All recommend anti-resorptives as first line therapy for patients at high risk and osteoanabolics for those at very high risk. Sequential therapy with an osteoanabolic-first approach is recognised to be effective for the patients at highest risk in the BHOF and IOF/ESCEO guidelines.

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Uncovering my hidden autism

CPD READING
0.5 HOURS

This author shares their experience of being diagnosed with autism as an adult and how this enabled them to get support

I have recently received a diagnosis of autism at the age of 46. I discovered my condition following a breakdown in coping skills that came with a change in job and office base. I experienced overwhelm, stress, and exhaustion, symptoms I now understand to be autistic burnout, as named by the autistic community. Fortunately, I was seeing a private psychologist who was able to guide me towards specialist diagnostic assessment. My quest for the truth felt too pressing to join a three year waiting list.

I believed my identity to be in flux, and the outcome of the assessment was all consuming. For 23 years I have lived with a diagnosis of emotionally unstable personality disorder (EUPD, formerly known as borderline personality disorder). The EUPD diagnosis was made by a psychiatrist when I was 23 because I self-harmed. I became stuck with this highly stigmatised diagnosis which is still revived by any contact with health services, even for physical concerns. I lost trust in doctors to see me in a way that was unbiased and I felt blamed for my failure to achieve recovery.

Power of a diagnosis

During the diagnostic assessment for autism, I recalled examples of autistic traits in my childhood, such as walking on tiptoes, poor handwriting, and fainting because of social discomfort. I talked about my father who most likely was autistic but never saw a doctor for 33 years until his final illness. I reframed my past through an autistic lens and everything made sense.

The autism diagnosis brought validation and hope. Elation then gave way to depression as I felt grief about how my life could have been if I had known I was autistic as a young woman. I may have avoided years of confusion, self-harm scars, psychiatric drugs, severe anorexia, mental health sections, and expensive private therapies. I still didn't feel understood, as a few well meaning people suggested I must only be "ever so slightly autistic" as I had managed to hold down a job and never threw chairs around at school. These assumptions miss the point, given how conditioned autistic girls and women can be to internalise their distress.

Finding myself again

Six months on, I am settling into my diagnosis. I finally have answers about my quirks, such as why everyday noise disturbs me as a result of sensory processing difficulties. I get upset by changes of routine and lack of structure. I calm myself through self-stimulatory behaviour, rubbing my feet together, hugging my knees, tapping my lip, and shaking my hand. I need to decompress after meeting people.

I feel like I no longer need to justify my life choices. I can ask for reasonable adjustments at work which help to avoid miscommunications. I can talk to my GP about health issues which are interconnected with autism such as gut inflammation and anxiety. I know other autistic women through online communities and local support forums. I forgive myself for past mistakes using my newly developed self-compassion.

Anonymous patient author

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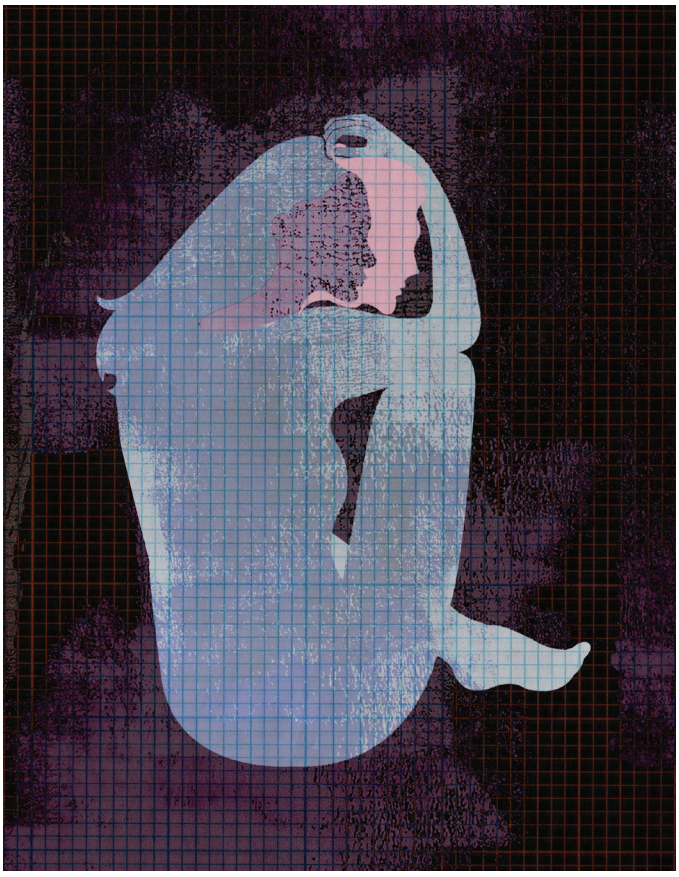

PRIYA SUNDRAM

WHAT YOU NEED TO KNOW

- Many women with autism struggle to get a diagnosis because of historic underdiagnosis and overlapping mental health conditions.
- Masking (suppressing autistic traits) takes a lot of physical and emotional resources to maintain and contributes to autistic burnout
- Getting a diagnosis of autism can bring freedom to ask for adjustments from society

EDUCATION INTO PRACTICE

- How could you support someone with a previous diagnosis of EUPD to explore assessment for autism?
- What adjustments can you make to support someone who is late diagnosed or self-identifying with autism?

ADDITIONAL INFORMATION

- https://www.autism.org.uk/advice-and-guidance/what-is-autism/autistic-women-and-girls
- Tamilson B, Eccles JA, Shaw SCK. The experiences of autistic adults who were previously diagnosed with borderline or emotionally unstable personality disorder: A phenomenological study. *Autism* 2024;29:504-17.
- https://squarepeg.community/

CASE REVIEW

Cutaneous upper limb nodules

A right hand dominant man in his 50s who, six weeks previously, had undergone washout of a volar thumb wound, presented to the plastic surgery clinic with a one week history of erythematous cutaneous nodules over the left thumb and dorsoradial forearm (figure). The wound, which was painful and swollen, had been attributed initially by the patient to an infected splinter, but no foreign body had been found on surgical exploration and routine microbiological wound cultures were negative. The patient did not report systemic symptoms such as fever, and there was no palpable lymphadenopathy on examination.

Medical history was unremarkable, but history taking focused on infectious disease revealed recent maintenance of a tropical fish tank. On the advice of microbiology colleagues, an incisional tissue biopsy was performed that revealed cutaneous inflammatory change without without caseating granuloma. Microbiological culture of the biopsied tissue demonstrated acid fast bacilli. Chest and upper limb radiographs did not show any findings suggestive of pulmonary tuberculosis and osteomyelitis respectively.

1 **What is the most likely diagnosis?**

2 **What investigations are required?**

3 **How would you treat this condition?**

Clinical photographs demonstrating the erythematous cutaneous nodules over the left dorsoradial thumb interphalangeal joint, distal and proximal radial forearm

Submitted by Joseph A Ward, David Bodansky, and Rikki Mistry

Patient consent obtained.

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answers

CASE REVIEW **Cutaneous upper limb nodules**

1 What is the most likely diagnosis?

Mycobacterium marinum infection.

M marinum is an opportunistic non-tuberculous mycobacterial infection contracted through exposure of open wounds to contaminated aquatic microenvironments. Incidence in the US population is reported to be ~0.27 cases per 100 000 individuals, and the disease causes granulomatous nodules that disseminate in a linear distal-to-proximal fashion along cutaneous lymphatic channels in a similar manner to sporotrichosis.

Termed "fish tank granuloma," *M marinum* is hosted by fresh or saltwater fish and propagates well in tropical water, but may also exist in plants or soil. Recognised risk factors include aquatic sports and occupational exposure to wet environments such as fish tanks, aquariums, or paddy fields.

2 What investigations are required?

Diagnosis necessitates tissue sampling and a high index of suspicion given that microbiological confirmation requires prolonged culture for about six weeks owing to its slow growth. The optimum mode of tissue sampling is an incisional biopsy. Tissue should be sent for histological analysis and mycobacterial, fungal, and bacterial culture, alongside any pus in the tissues. Acid fast bacilli staining may only be positive in <16% of cases, so positive polymerase chain reaction amplification of the *hsp65* gene will provide reliable diagnostic confirmation.

3 How would you treat this condition?

Only a limited evidence base exists to guide treatment, but the Infectious Disease Society of America recommends treatment with at least two antibiotics that include clarithromycin and another agent (ethambutol, rifampicin, or trimethoprim-sulfamethoxazole). *M marinum* is known to be intrinsically resistant to azithromycin, isoniazid, and pyrazinamide. Empirical antibiotic therapy is appropriate when there is high index of clinical suspicion while culture results are awaited. Prolonged antibiotic therapy is necessary to treat the bacteria but is effective and results in low rates of recurrence. Where delayed or inadequate antibiotic therapy is administered, deep seated infections with sequelae such as osteomyelitis, tenosynovitis, and disseminated disease can occur. Surgery is indicated only for diagnostic tissue sampling or to incise, drain, or debride suppurative infection.

LEARNING POINTS

- ***Mycobacterium marinum* is an opportunistic non-tuberculous mycobacterial infection that can occur when injured skin is exposed to contaminated aquatic environments**
- **The characteristic presentation is erythematous cutaneous nodules that disseminate distal-to-proximal in a linear fashion along cutaneous lymphatics**
- **Prolonged antibiotic therapy with at least two drugs (clarithromycin and another) is necessary to effectively treat the disease.**

PATIENT OUTCOME

The patient was treated with a course of high dose clarithromycin and ethambutol, and the nodules resolved after treatment for six months with no disease relapse.

CPD READING 0.5 HOURS

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

LEARNING MODULE

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