

MENOPAUSE MATTERS

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Metabolomics – What it is – and why you should know about it

- Metabolomics is the study of metabolites. Metabolites are the products of metabolism.
- In the process of living, organisms and cells metabolise substances and this involves the break-down of complex molecules into smaller molecules.
- Metabolites can be viewed as the waste-products of cells.
- These are “chemical fingerprints” which reflect the processes that have taken place.
- A collection of these small metabolites in a person’s blood gives a profile of the cellular activities which may be physiological or pathological.
- A cell’s or tissues’ complete set of metabolites is called its metabolome.

Where this becomes of interest is when pathological processes occur in a cell and abnormal metabolites are shed into the blood-stream. The detection of these pathological metabolites – whether singly or as a set making up a fingerprint – can indicate that a malignancy exists somewhere. With the advent of ever-more precise finger-printing and machine-learning algorithms, metabolites from specific organs can be identified.

The combination of malignant metabolites with their particular signature, plus learning algorithms, can pin-point the tissue from which these waste products arise. For example, it is possible to screen post-menopausal women for endometrial cancer by looking for specific metabolites in their serum.

In a pragmatic study, more than 1 500 women with a mean age of 68 years had blood samples taken and analysed through a machine-taught algorithm mechanism. Some were known to have a diagnosis of endometrial cancer but the vast majority were asymptomatic so the “ensemble” was tested to check-out clinically relevant information ([Troisi et al JAMA Netw Open 2020;3:e2018327](#)). The system performed well identifying all 16 actual cases of endometrial cancer plus 2 false positives and no false negatives giving a high degree of accuracy.

This proof of concept research showed robust outcomes with sensitivity, specificity and accuracy all greater than 99%. It is inexpensive and non-invasive so it could be used for population screening. One wonders what other malignancy detection could be amenable to this methodology? Are there other cancers which could be candidates for what might be termed a “liquid screening biopsy”? Is this the next screening frontier?

In obstetrics we have been exposed to “liquid biopsies” through our introduction to the topic using “Non-Invasive Prenatal Tests (NIPTs)” in which fetal DNA is analysed by sequencing molecules from the fetus shed into the maternal circulation. Add to that machine learning technology plus cheaper laboratory methods and molecular medicine is on our doorsteps.

This has set us up to accept technologically advanced screening but are we going to see liquid biopsies being used to search for a range of cancers as a means of screening?

I have my doubts as there is the danger of such investigations becoming “fishing trips”. They could cause all sorts of reactions if an otherwise healthy person turns out to have a “potential malignancy”. We deal with abnormal variations in our cellular reproduction all our lives and our immune system eradicates these non-identical (non-normal self) deviants – so when do we or our health systems go on the hunt for a supposed primary? Am I being a Luddite?

With the proven success of HPV vaccination in reducing cervical cancer in early reports from Sweden ([Lei et al NEJM 2020](#); 383:1340-8) and screening with HPV plus co-testing with cytology, there is hope for cervical cancer reduction in the future. Ovarian cancer rates are decreasing with longer use of oral contraceptives, more salpingectomies for permanent female sterilisation and potential tumour cell serum screening so there is hope on the gynaecological oncology front.

Chronic pelvic pain – is gabapentin the answer?

Up to a quarter of women suffer from chronic pelvic pain. This is primarily a problem in a woman's reproductive career but may affect postmenopausal women as well. It is described as continuous or recurrent pain that lasts longer than 3 months and has no discernible pathology as excluded by laparoscopic investigation.

Pelvic pain result in a loss of productivity, social and relationship stresses presenteeism from chronic and frequent consultations to the medical profession and alternate therapists. Because a reliable and safe medication is desirable to offer assistance to these women, a trial was conducted in the UK involving 39 hospitals and women were randomised to receive a titrated daily dose of gabapentin or placebo for 4 months ([Horne et al Lancet 2020](#); 396:909-17). Subjective pain scores (between 1 and 10) were reduced from baseline by a mean -1.1 points in the active ingredient group and -0.9 in the controls suggesting minimal medicinal or placebo effect and no statistical evidence of benefit. Those receiving gabapentin had more adverse effects.

The investigators conclude "Given the increasing reports of abuse and evidence of potential harms associated with gabapentin use, it is important that clinicians consider alternative treatment options..." An article comparing electroacupuncture and sham treatment for low back pain showed no difference in analgesic properties but improved mobility so some benefit may be derived through options ([Kong et al JAMA Netw Open 2020](#);3:e2022787).

While on the topic of pain, we may be called upon to prescribe medications for the relief of acute pain but evidence-based data are difficult to assess. A systematic analysis indicates little, if any, advantage of opioids for recurrent situations and comes down in favour of topical and oral non-steroidal anti-inflammatory agents and acetaminophen (paracetamol) with or without diclofenac ([Busse et al Ann Int Med 2020](#).doi.10.7326/M19-3601).

Paracetamol is one of the most widely used analgesics but a few months ago NICE revised the recommendation of its use for chronic pain relief and Switzerland showed an increase in poisonings with the introduction of 1 000mg oral dosages ([Martinez-De la Torre & Weiler JAMA Netw Open 2020](#) 3:e2022897).

Urinary incontinence therapy

In the previous issue of MM the data from individual and group therapy treatment of urinary incontinence were presented. The work showed equally satisfactory results with pelvic floor muscle training at one year either singly or as group participants ([Domoulin et al JAMA Int Med 2020](#) doi. 10.1001/jamainternmed.2020.2993). But what about adding electromyographic biofeedback?

Research from 23 centres in the UK used adjunct biofeedback both in formal classes and for patients at home in a randomised trial and assessed any differences after 2 years ([Hagen et al BMJ 2020](#);371:m3719). Using standardised questionnaires the outcomes were disappointing with the authors concluding "routine use of electromyographic biofeedback with PFMT for women with stress or mixed urinary incontinence does not provide additional benefit."

Premature menopause

Primary ovarian insufficiency or premature menopause, is a rare condition in young women but increases in incidence with age, afflicting 1 in 10 000 aged 20 years, 1 in 1 000 aged 30 years, 1 in 250 aged 35 years and 1 in 100 aged 40 years. The definition is oligo- or amenorrhoea for 4 months before the age of 40 years with 2 follicle stimulating hormone levels in the menopausal range 2 months apart ([Jiang Menopause](#) 2020;27:1101-3).

The condition carries a myriad of consequences, one of which is decreased bone mineral density and the treatment possibilities include low- or high-dose replacement hormone therapy or combined oral contraceptives. In a comparative trial the contraceptive pill consisting of ethinylestradiol 30 µg plus levonorgestrel given continuously was superior in terms of increased bone density measures ([Gazarra et al Menopause](#) 2020;27:1110-6).

Calcium intake – does it matter?

Intuitively, it feels logical to encourage osteopenic postmenopausal women to raise their dietary intake of calcium. Surely it is good for them to eat more calcium-rich foods or take supplements to prevent rapid or excessive bone loss? But is this deductive reasoning supported by data?

Evidently not, according to researchers who followed up a cohort 2 000 older women with hip T-scores between -1.0 and -2.5. They measured their bone mineral density a total of 3 times over 6 years and related bone loss to calcium intake ([Bristow et al J Clin End Met](#) 2019 2019;104:3576-84). Their conclusion was (quoted in full) “Postmenopausal bone loss is unrelated to dietary calcium intake. This suggests that strategies to increase calcium intake are unlikely to impact the prevalence of and morbidity from postmenopausal osteoporosis.”

and vitamin D supplementation?

Most advocates of vitamin D supplementation suggest 400 IU per day for people who are vitamin D deficient. But many people hope “more is better” and doses of 1 000 IU or even 4 000 IU per day are taken by those who believe in supplements, despite enjoying a healthy diet and normal serum levels of vitamin D. In women these high doses are detrimental to bone health ([Burt et al JBMR](#) 2020 doi. 10.1002/jbmr.4152). Bone density loss increased as the doses of vitamin D rose and the effect was much more marked in women. Primum non nocere.

Dare one think that the whole **calcium – vitamin D edifice** for “quality aging” in healthy older people is built on sand?

Hair dyes and cancer

Is there a relationship between the use of hair dyes and cancer?

In Western countries more than half of women use hair dyes that are classified as oxidative (permanent), direct (temporary) or natural dye with the oxidative type used by the majority of women. The exposure is through dermal contact but there is no evidence of carcinogenicity in a large cohort (more than 100 000 women) followed up for 36 years ([Zhang et al BMJ](#) 2020;370:m2942). Hair-colouring substances can be given a clean bill of health.

I have tried to avoid Covid in Menopause Matters because there is a surfeit of information “out there” but I have come across 2 articles that will be important going forward and an interview that I found genuinely helpful. These are:

1. By identifying a protein specific to SARS-CoV-2 researchers have pin-pointed antibodies that are created against Covid and the method holds promise. It is published in Science but sensitive readers are warned about the density of the scientific language used in the article ([Schrock et al Science](#) 2020 doi. 10.1126/science.abd4250).
2. Another approach to Covid diagnosis has become available using CRISPR technology that is “as specific as and more sensitive than qRT-PCR for detecting SARS-CoV-2 from clinical samples” ([Brandsma et al J Infect Dis](#) 2020 doi. 10.1093/infdis/jiaa641)
3. If you wish to be authoritatively updated about Covid by Tony Fauci then click on

<https://www.youtube.com/watch?v=3MH-3ICY-N4&feature=youtu.be>

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Menopause Matters is a monthly review of matters menopausal that have recently appeared in the journals. It is produced for the South African Menopause Society and the summaries concentrate on clinical issues although some underlying patho-physiology will be included to ensure a scientific basis for the work. These summaries and opinions do not necessarily reflect the views of the S A Menopause Society.

The idea is derived from the Journal Article Summary Service (JASS) which summarises general O&G articles. Information about this service can be obtained from Athol Kent (atholkent@mweb.co.za) or from the JASS website www.getjass.com