SAMS South African Menopause Society

MENOPAUSE Matters

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The menopause and the human microbiome

Probably the most unexpected discovery associated with the sequencing of the human genome two decades ago, was not the actual structure of our genes and the code they carried, but something altogether different, the microbiome.

Our human microbiome consists of trillions upon trillions of microbes that live on us and in us.

Different micro-organisms exist in every system and every orifice we possess, and perform vital functions that keep us healthy – or not. These fellow travellers are called microbiota and are collectively known as a microbiome. There are microbiomes peculiar to various regions of our skin, hair, ears, nose, throat, genitourinary tract – even our eyes and brain, but by far, the largest is the gut microbiome which weighs about 2kg and contains bacteria, viruses, fungi and other micro-organisms Our combined microbiomes have at least 150 times more genes than our human genome.

Human Genetics 101

It was found that humans do not have a very different set of gene sequences compared with other species, either in number or complexity. Also, that our risk of disease is related to the interplay between large numbers of gene variations rather than a few aberrant single genes and their malfunction. These were not unexpected revelations since conditions such as hypertension, diabetes, and all non-transmissible disorders depend on the balance across systems, plus specific dynamics within and between these physiological interactions that are "gene dependant".

For a disease to be called genetic, a set of variations have to be present simultaneously, creating "patterns". These patterns are groups of single-nucleotide variants (SNVs).

The correct name for a set of abnormal genes is a polygenic risk score (PRS). Another way of looking at it is thinking of a person's PRS as their susceptibility to suffer from a genetic disorder. By measuring a person's PRS it is possible to predict the likelihood of a disorder appearing , or that person's likely response to treatment (Shah *JAMA Netw Open* 2021;4:e2119333). This is the basis of "precision medicine" with tailored management to a particular patient, based on their genetic makeup which includes their PRS for that condition.

Genetics and breast cancer

The best illustrations of genetics assisting clinical medicine are in breast cancer. The BRCA I and II are prime examples of genetically inherited variations which considerably increase the woman's chances of breast (and other) cancers and allow her to react accordingly.

Another genetic advance in breast cancer therapy is the "21 gene assay" which can inform those undergoing treatment whether they will benefit (or not) from adding adjuvant chemotherapy to their schedules (Kalinsky et al *NEJM* 2021;385:2336-47). A second example is the genetic characterisation of women who may (or may not) benefit from sustained tamoxifen medication (Burton *JAMA Netw Open* 2021;4:e2115227).

The gut & the brain

The microbiome of the gut is integral to the enteric nervous system. The enteric nervous system is a complex integration of nerves (for examples the vagus nerve) and hormones (neurotransmitters) that feedback in both directions creating the "gut-brain axis". The gut microbiota thus have a direct effect on our cognitive function, which may be important in dictating susceptibility to dementia in later life (Meyer et al *JAMA Netw Open* 2022;5:e2143941).

Basically, we need a diverse mix of microbes in our gut to maintain health and homeostasis throughout our bodies. This diversity is described as a "richness" or variation, whereas a paucity of variation or dominance of any set of flora is harmful, and it is called dysbiosis. There are specific short-chain fatty acids produced by normal gut microbes that are essential to normal brain function and the lack of these microbiome products is implicated in accelerated cognitive decline.

Editorial comment: Biochemists are exploring blood-based biomarkers to track the function of the nervous system. If these markers can monitor the brain's neurodegeneration, then it may be possible to follow the progress of interventions in slowing the course of conditions such as Alzheimer's Disease.
One such biomarker is a neurofilament light chain (NfL) which is present in varying concentrations the plasma.

NfL reflects neuronal injury and degeneration and can be used to show the benefits of physical activity in slowing cognitive decline (Simrén & Gustafson JAMA Netw Open 2022;5;e223602). Maybe it could be used to show beneficial effects of MHT in restoring the gut microbiome and thus benefiting brain function?

Microbiome changes through the menopause

The decline in estrogen status through the menopause transition leads to changes in the vaginal, urinary tract, oral, gastro-intestinal plus many other microbiomes. The question now being asked is whether menopausal hormone therapy affects the microbiota in these systems and, if so, do the changes reflect any benefit or harm (Pru *Menopause* 2022;29:253-4).

Research sampling duodenal micro-organisms from a variety of pre- and postmenopausal women has shown that taking estrogens and progesterone change the microbiome to approximate that of premenopausal women (Leite et al *Menopause* 2022;29:264-75).

Postmenopausal participants (not on MHT) had less diversity in their duodenal microbiota, higher fasting glucose levels and lower testosterone levels. This is an example of dysbiosis that is linked to metabolic dysfunction. Those taking hormones had microbiomes associated with superior cardiovascular prognostic indicators which may in turn be related to future improved cognitive function.

Microbiome manipulation

Given the new knowledge accumulating about the gut microbiome, the possibilities of manipulating its make-up are being energetically explored. It is clear that antibiotics can profoundly affect the balance of its flora and, in extreme cases, lead to the overgrowth of intractable and resistant microbes such as *Clostridiodes difficile* (Slomski *JAMA* 2022;327:1118).

The track record of probiotics in rectifying such bacterial imbalances is inconsistent and where rigorous trials are carried out, evidence of their usefulness in the clinical situation is lacking (Johnstone et al *JAMA* 2021;326:1024-33). Microbial dysbiosis is a topic which will increasingly be investigated, but thus far, faecal replacement therapy has proved more effective than probiotics in practice, so it appears science has a long way to go in unravelling this complex topic.

The menopause & technological advances

Technology advances informing clinical menopause medicine:

- The human genome was sequenced and human microbiomes discovered
- The vastness of the microbiome variety was unanticipated (Camarillo-Guerrero et al *Cell* 2021 doi 10.1016/j.cell.2021.01.029)
- Observing how hormones change a woman's microbiome helps explain "knock-on" effects of MHT changing clinical patterns
- Defining an individual's polygenic risk score (PRS) will allow targeted precision medicine

- Biobanks have been created in which hundreds of thousands of person's genetic codes can be linked to clinical outcomes – for example, the UK Biobank, the Chinese Kadoorie Biobank, and the US Nurses' Health Study.

The following are some clinical applications of technological advances:

MHT & venous thromboembolism

A woman's PRS of her propensity/risk of developing a venous thromboembolism on MHT has been defined and can inform about its use (Kim et al *Menopause* 2022;29:293-303 Nurses' Health Study).

Menopause timing & dementia

A woman's age at menopause is linked to her risk of developing presenile dementia. If she experiences a premature menopause (prior to age 40 years) her chances of having all-cause dementia before the age of 65 years increase by a third (Hoa et al *Am Heart Assoc* 2022 UK Biobank).

Stroke risk and lactation in postmenopausal women

Data collection and correlation from the Chinese Kadoorie Biobank has shown that women who breast-fed their offspring are less likely to suffer a stroke than their sisters who did not lactate (Ren et al *JAMA Netw Open* 2022;5:e220437).

A large number of participants (more than 100 000) with detailed history of pregnancies, suckling and subsequent cerebral events allowed risk calculations to be made about the protective effects of breast-feeding and later cerebro-ischaemic events. This is a situation where complex "number-crunching" supports basic health and nurturing routines.

Hormone therapy and bone turnover

The tightly coupled balance between bone formation and resorption changes with the lowering of estrogen levels starting at the time of the menopause transition. The resultant negative effects on skeletal architecture can lead to osteoporosis from decreased bone mineral density and is reflected by increased markers of bone turnover.

The Replenish trial of estradiol and progesterone therapy for women within five years of their menopause, confirmed its primary premise of effectively reducing the frequency of moderate to severe vasomotor symptoms (McClung et al *Menopause* 2022;29:304-8). Concomitant reductions in bone turnover markers, which measure collagen breakdown products, suggest skeletal benefit from the use of even short-term menopausal hormone therapy.

Menopause transition markers

Apart from the reduction of vasomotor symptoms, there appears to be an increasing range of beneficial side effects of using menopausal hormone therapy, including improvements in cardiovascular, cognitive, and skeletal markers. If these are confirmed, and if the "timing hypothesis" of early commencement for maximal benefit is also accepted, then early MHT intervention seems sensible. Simply taking a menstrual history is a "post-hoc" diagnosis and direct hormone levels can fluctuate during the transition, so the quest for markers of the precise onset of a woman's perimenopause status continues.

Biochemical markers may prove helpful in defining the chronological premenopausal to postmenopausal stages and this could be where immunoglobulin levels are useful (Deris et al *iScience* 2022 doi 10.1016/j.isci.2022.103897). Liquid chromatography can measure the biochemistry of IgG metabolism which is sensitive to gonadal hormone effects and can thus track ovarian senescence.

An early perimenopause diagnosis could allow more expedient intervention with MHT and its potential benefits. Scientific evidence can move clinical applications forward so further laboratory data are awaited to assist real-world management.

Editorial comment – Scientific advances offer logical (biological) explanations for physiological events. They help us understand the mechanisms which underpin the clinical features we observe and allow us to judge whether these changes are detrimental or not, and how interventions work.

These explanations may allow changes of attitudes to management. Perhaps using hormones perimenopausally will be viewed through a different lens. Rather than being seen as "imposing non-natural laboratory products" they could be perceived as "restoring natural gut flora" and re-establishing a desirable symbiosis.

Maybe hormone therapy will have a series of physical and neurological benefits that will be rationally added to their relief of vasomotor symptoms? The benefit/harms ratio could be judged in a less negative way as more understanding leads to less suspicion, and less fear.

I look forward to the day when MHT is accepted in the same way that oral contraceptives are. Very good at their primary function but with advantages associated with their use which improve the quality of the woman's life.

Medication	**Oral contraceptives**	**Menopausal Hormone Therapy**
Primary indication	Prevention of pregnancy	Prevention of vasomotor symptoms
Beneficial effects	Decreased menstrual loss Decreased dysmenorrhoea Improved iron stores	Improved mood & sleep Fewer night sweats Decreased bone loss

	Treatment of PCOS and Endometriosis Less acne Lower ovarian cancer risk	Healthier CVS function Healthier metabolic function Fewer wrinkles Reduced GUSM symptoms Less libido loss
Harmful effects	Raised thrombotic risk	Raised thrombotic risk Raised breast cancer risk

In summary – MHT is not a capitulation – it is a smart option.

Postmenopausal hair loss

Half of all women experience hair loss within the first decade after their menopause. Research reveals that if female pattern hair loss does occur, then it transpired that two thirds had mild loss, one third moderate loss, and 5% severe loss. This form of alopecia was strongly related to a lowering of the woman's self-esteem (Chaikittisilpa et al *Menopause* 2022 doi 0.1097/GME.0000000000001927). Hair loss was strongly correlated with being overweight (BMI greater than 25) and the findings were not linked with hormone levels, nor were there any stressor or intervention comparisons. Is this another avenue of exploration for MHT therapies?

Follow-up of previous reports

Addiction therapy Last month, *Menopause Matters* covered the topics of love, addiction and hormonal changes in the brain whereby humans become enslaved to products or processes. This month an article has appeared in which these insights described have been put to good use.

Cocaine use disorder is one of the most intractable addictions, so it was encouraging to find that, under research conditions, oxytocin administered intranasally to people dependent on cocaine was helpful in attaining abstinence (Raby et al *Drug & Alc Dep Reports* 2022;2:100016). The chances of weekly abstinence were increased compared with placebo during the 6-week trial so at least the proof-of-concept aim was achieved which may inspire other hormonal approaches in people with substance use disorders.

Vaginal laser treatment. In a previous issue of *Menopause Matters*, I reviewed the use of transvaginal laser therapy as treatment for Genito-Urinary Syndrome of Menopause. Now a blistering critique has appeared in the Australian **Friends of Science in Medicine**, *Newsletter 31* of 18th March 2022 by MacLennan. He asks, is it "A burning question or a commercial sting?" and states that, in his view "There is no physiological mechanism by which burning atrophic vaginal epithelium will magically rejuvenate it."

He notes "Burns, infection, increased dyspareunia and scarring have been reported" and warns that complications of its use "outside of ethical trials could become the next medico legal minefield."
I presume here he is referring to the mesh/tape debacle. He is one of the most distinguished leaders in O&G and I believe his words of caution should be heard by everyone considering using this therapy.

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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. Any clinical decisions made on the data presented are at the reader's discretion.