The ongoing nosologic dilemma with the metabolic syndrome

A clinical syndrome is defined as a typical constellation of historical, physical and laboratory features that may be conceptualized as a manifestation of a common underlying pathogenesis. In the past, syndromes were most often named after the clinical pioneers, who recognized unique and recurrent clusters of symptoms and signs. One example is of James Parkinson describing the shaking palsy more than a century before the neuropathological basis was identified. But most of such syndromes did not include what taxonomically can be a disease entity. The features were not highly variable or absent. Unlike that definitions of metabolic syndrome (MS), include hypertension, visceral obesity, impaired glucose tolerance, etc. The paper in this issue of the journal, titled ‘Menopause and metabolic syndrome: A study of 498 women from western India’ has been perspicacious as to the definition of MS as well as of its risk relevance to postmenopausal women.

Earlier the same investigators have discussed the history, definitions and synonyms of MS in the Indian Menopause Society Digest. That balanced perspective is also visible in the current contribution.

The studies cited have shown a prevalence rate in premenopausal women varying from as low as 13% in a Korean study to 46.4% in the present study based on varying criteria of diagnosis of MS by National Centers for Environmental Prediction III (NCEP) and International Diabetes Federation (IDF) respectively. The present study is one of the few to employ both the IDF and the latest harmonized definition of MS as applied to menopausal women. The prevalence of MS in the postmenopausal women shows a value of 69.2% as per IDF criteria, similar to the Brazilian studies. However, the investigators are aware of the controversy of worsening of MS with age alone. The increase in cardiovascular disease (CVD) in the Framingham cohort has been cited. But is that relevant and transferable to India, based in the South Asian susceptibility to CVD even at premenopausal age?

The authors have attempted to adjust for age as a confounding variable and find the higher prevalence rate in postmenopausal women not statically significant. One wonders at this conclusion! Is not age a determining rather than a confounding variable?

There are some lacunae in the study. Particularly, the family history of CVD and heart rate/ blood pressure (BP) responses to sympathetic stimulation or vagal withdrawal could have provided better risk data in the subsets with high low density lipoprotein (LDL) and low high density lipoprotein (HDL). It is hoped that the ‘Maitreyi’ group of women are followed up to assess the longitudinal verity of the high prevalence of MS.

The understanding of MS needs to be explored at several levels of biological organization. The studies on the intrauterine programming of diabetes and MS have provided evidence on the impact of intrauterine nutrition and development on chronic metabolic diseases in adult life. There are, however, few if any studies relating intrauterine growth retardation (IUGR), and early over-nutrition with menopause and or age-related worsening of MS. This needs to be looked at in view of the comment whether age is a confounding or a determining variable for the severity of MS, based on developmental programming. CVD too would then be understood better in terms of the relative importance of estrogen deprivation vs. other risk factors.

Mitochondrial DNA, (mt-DNA) variations and analysis are emerging to be important in metabolic disorders. That can help us understand the pathophysiology of mt-DNA diseases, including modern bio-energetic disorders such as obesity, diabetes and senescence. Park et al., have shown that IUGR and protein malnutrition may cause Type 2 diabetes by a reduction in mt-DNA content and impaired pancreatic islet β-cell development. Whether MS too shows such a reduction in the peripheral blood mt-DNA needs to be studied in women of different age groups and diabetic relative cohorts.

The environmental and lifestyle influences can
significantly affect the markers of MS. There are reports on how west-resident migrant Indians have higher CVD risk factors. There are hardly any studies comparing MS in the menopausal and postmenopausal South Asian women resident in India with those who have migrated to affluent nations. Then the impact of lifestyle as a determining influence can be reasonably assessed for the diverse components of MS.

The contributions of the autonomic nervous systems, excessive sympathetic drive, and sensitivity to vasoconstrictors to MS have not been studied in depth. In view of the role of the $\alpha_2$-noradrenergic receptors in menopausal flush, the vascular aggravation of MS due to estrogen deprivation needs investigation. Endothelial dysfunction due to reactive oxygen species and pro-inflammatory cytokines are also relevant to the development of MS.

Visceral obesity has emerged as a very important feature of MS. We need refined and cost-effective measurement of visceral fat and the degree of its inflammation. In Ayurveda, Vapa, the omental fat is considered as a proclivity factor for Prameha-Madhumeha. The relative weightage needs to be evaluated for the role played by the visceral and intramuscular fat in MS. There is a need for understanding a large-scale, multiracial long-term and India-wide study of MS by the Indian Menopausal Society.

Ashok D. B. Vaidya
ICMR Advance Center of Reverse Pharmacology,
MRC- Kasturba Health Society, 17 K Desai Road,
Vile Parle (W), Mumbai - 400 056, India.
E-mail: ashokdbv@gmail.com

REFERENCES
1. Kempster PA, Hurwitz B, Lees AJ. A new look at James Parkinson’s Essay on the Shaking Plasy. Neurology 2007;68:482-5.
2. Pandey S, Srinivas M, Agashe S, Joshi J, Galvankar P, Prakash CP, Vaidya R. Menopause and metabolic syndrome: A study of 498 urban women from Western India. J Mid-life Health 2010;2:63-9.
3. Vaidya RA, Pandey SN, Srinivas M, Nabar N. Metabolic syndrome: History synonyms and definition(s) Ed. Parihar M, Published by IMS Education Committee, Mumbai IMS Digest 2011;1:2-5.
4. Gohike - Barhroff C. Coronary artery disease is menopause a risk factor? Basic Res Cardiol 2000;95:177-83.
5. Yajnik CS, Lubree HG, Rege SS, Naik SS, Deshpande JA, Deshpande SS, et al. Adiposity and hyperinsulinemia in Indians are present at birth. J. Clin Endocrinol Metab 2002;87:5575-80.
6. Mercer JR, Cheng KK, Figg N, Gorenne I, Mahmoudi M, Griffin J, et al. DNA damage links mitochondrial dysfunction to atherosclerosis and metabolic syndrome. Circ Res 2010;107:1021-31.
7. Park HK, Jin CJ, Cho YM, Park DJ, Shin CS, Park KS, et al. Changes of Mitochondrial DNA Content in the Male Offspring of Protein-Malnourished rats, Mitochondrial Pathogenesis from Genes and Apoptosis to Aging and Disease. Ann N Y Acad Sci 2004;1011:205-46.
8. Jeemon P, Neogi S, Bhatnagar D, Kennedy J. Cruickshank, Prabhakaran D. The impact of migration on cardiovascular disease and its risk factors among people of Indian origin. Current Science 2009;97:378-384.
9. Vaidya AD, Vaidya RA, Joshi BA, Nabar NS. Obesity (medoroga) in Ayurveda. In: Mishra L, editor. Scientific basis of Ayurvedic therapies. United States: CRC Press; 2004. p. 149-68.