Special Supplement on METABOLIC SYNDROME

Editorial

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Metabolic syndrome : Metabolic flexibility is the future

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Metabolic syndrome (MetS) is a well-documented clinical entity. Though the connection between various metabolic abnormalities has been known for long, MetS gained importance after Reaven propounded the concept of syndrome X.

MetS seems ubiquitous in society[1] : Its components are present not only in diabetes, but in a variety of endocrine syndromes including hypogonadism, Cushing's syndrome, NAFLD (non-alcoholic fatty liver disease) and PCOS (polycystic ovary syndrome). MetS may also be Iatrogenic, as is observed with antiretroviral therapy for HIV (human immunodeficiency virus). Though the WHO (World Health Organization) has suggested that MetS not be used as a diagnostic label, this rubric continues to enjoy clinical as well as public health importance[2].

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Metabolic Syndrome As A Secondary Target :

The components of MetS are now being used as therapeutic targets, to help decide management strategies for diabetes. Composite targets, such as weight loss, blood pressure control, lipid health and reduction in albuminuria have replaced the glucocentric approach of HbA1c (glycated hemoglobin) reduction.

Newly development glucose-lowering drugs have displayed exceptional efficacy in addressing most, if not all, components of MetS. The SGLT2 (sodium glucose co-transporter[2] inhibitors canagliflozin, dapagliflozin and empagliflozin are able to improve glucose levels, reduce blood pressure and lower body weight as well as central obesity, with near-neutral impact on lipids[3]. The GLP1RA (glucagon like peptide 1 receptor agonists) liraglutide, dulaglutide and exenatide are equally effective in this regard, and demonstrate favorable effects on lipid profile. Liraglutide has been approved for the management of both

diabetes and obesity, albeit in different doses[4]. Thus, of all currently availability drugs, liraglutide holds the greatest promise as a holistic strategy for the comprehensive management of MetS.

Metabolic Syndrome As A Primary Target :

With MetS being one of the most common, medical disorders, it is reasonable to expect, and anticipate, development of drugs which primarily target MetS. One mechanism of countering MetS components is calorie restriction[5]. Calorie restriction, or its pharmaceutical equivalent (calorie restriction mimicry) acts by working at the AMPK (adenosine monophosphate activated protein kinase) &/ or the SIRT1 (sirtuin1) pathway. This raises hopes of modulating mitochondrial biogenesis to manage metabolic dysfunction[6].

Current Research, Future Hope :

Preclinical and clinical trials have reported on the feasibility and efficacy of a novel functional thyroid hormone analogue as a MetS targeting molecule. The Indian developed iodothyronine analogue, TRC 150094 has been shown to increase energy expenditure, and improve metabolic parameters in animal models[7,8,9]. This is achieved by AMPK-independent sirtuin 1 activation. The diminished flexibility to adjust substrate oxidation to substrate supply, referred as metabolic inflexibility, is observed in diabetes[10]. TRC150094 has shown improvement in metabolic flexibility in an animal model[8]. Restoring metabolic flexibility would be helpful for MetS. Clinical trial data suggest the need to identify cohorts of patients who will respond maximally to this diodothyronine mimetic[10]. Such trials are ongoing, and if successful, will herald a new paradigm in the management of MetS.

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