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Opinion

The Metabolic Syndrome Diseases – Interventions Using Micronutrients

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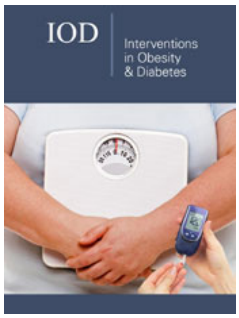

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Opinion

Metabolic Syndrome is defined as a cluster of interrelated conditions such as central obesity, dyslipidemia, impaired glucose metabolism and hypertension [1]. In addition to genetic predisposition as in South Asians, a sedentary lifestyle and a high caloric intake contribute to the development of this cluster of metabolic conditions. The worldwide increase in the incidence of this condition has made it a global epidemic. The recent Finnish study [2] attests to the decrease in incidence of Type 1 diabetes following fortification of dietary milk products with cholecalciferol. Insulin resistance and central obesity standout as the common feature of this cluster of conditions. The binding of insulin-to-insulin receptor (IR) results in the dimerization of the alpha and beta subunits and auto phosphorylation of the beta subunit leading to the activation of the Ras – MAPK and PI3K – Akt signaling cascades. The activation of PI3K associated with insulin receptors IRS1 and IRS2 results in the phosphorylation Akt-Foxo1 and is central to the control of nutrient homeostasis. The inactivation of Akt – Foxo1 pathway with the resulting activation of the forkhead/winged helix family transcription factor through suppression of IRS1 and IRS2 in organs following hyperinsulinemia, are suggested to be key mechanisms in the development of the metabolic syndrome. Hence, targeting the IRS – Akt – Foxo1 signaling cascade will provide a therapeutic approach for the treatment of the metabolic syndrome cluster of conditions. The activation of Akt affects cell survival and energy homeostasis by increasing glycogen synthetase activity, decreasing gluconeogenesis, promoting hepatic lipogenesis and cardiac cell survival. These phosphorylation-mediated cell events are the result of insulin signaling in various cells and tissues. Insulin is at the centre of adaptive metabolic transition in insulin-responsive tissues. Hyperinsulinemia inhibits the acute action of insulin on Foxo1 phosphorylation as well as transcription of IRS2 gene in insulin-responsive tissues.

Insulin resistance in adipose tissue has effects on the endocrine system in addition to its effect on metabolism. Under conditions of obesity pro-inflammatory factors – TNF alpha, interleukin and leptin – are increased and anti-inflammatory factors such as adiponectin are decreased resulting in an inflammatory condition. No single therapeutic pathway has been identified as a "therapeutic target" for treatment of the metabolic syndrome. Aggressive lifestyle changes have been shown to help in the amelioration of this condition. Where this is not adequate, pharmacotherapy including a combination of nutraceuticals affords an option. Recent studies confirm that several vitamins and their metabolites participate in various physiological processes as hormones, antioxidants and regulators of tissue growth and differentiation, lowering the risk associated with many chronic and degenerative diseases [3,4]. These protective effects are achieved at levels of the vitamin intake far higher than the "recommended dietary allowance". They have profound impact on neurological, endocrine and immune systems. Vitamins or their metabolites interact with specific protein entities

leading to their participation in cellular events. This forms part of the cellular signaling mechanism including, in many instances, the regulation of gene expression. Many vitamins participate in cellular oxidation-reduction reactions functioning as antioxidants. Type 1 Diabetes (T1D) and the adult-onset autoimmune diabetes (LADA) are autoimmune diseases in which the body's immune system attacks the Beta cells of the pancreas. Retrospective studies attest to the beneficial effect of vitamin supplementation in infancy against later risk of developing T1D [2,5]. Human and experimental data also indicate a role for vitamin D. The development of T2D with its impaired pancreatic beta cell function, insulin resistance and inflammation are responsive to vitamin D supplementation. Cross-sectional and longitudinal studies indicate an inverse relationship between serum vitamin D levels and the risk of T2D [5,6]. Conflicting results from some randomized control studies could be due to the low dose of vitamin D tested.

Vitamin A has significant effects on immune function. A deficiency of vitamin A increases proinflammatory cytokines and supplementation with vitamin A reverses the inflammatory condition [7]. Retinoic acid induces the insulin secretory response to glucose in pancreatic islet cells. Retinoic acid and insulin synergistically induce the glucokinase gene. The effects of vitamin A are similar to the effects of the vitamin biotin. Investigations since the 1960s have shown that hepatic glucokinase was depressed in biotin-deficient rats and insulin or biotin restored the enzyme levels to normal [1]. Pharmacological doses of biotin increased glucokinase activity in biotin-replete animals. This role of biotin has been established in run-on transcription assays using isolated liver nuclei. In both fasted and diabetic rats, hepatic PEPCK, a rate-limiting enzyme of the gluconeogenic pathway, was markedly increased in the fasting or diabetic condition and markedly decreased following treatment with biotin. There are many similarities between biotin and insulin in their actions on the enzymes of glucose metabolism. Both induce certain glycolytic enzymes and repress gluconeogenic enzymes. Foxo1 proteins promote hepatic glucose production and the expression of Foxo1 was decreased by biotin. This concept is emphasized by the similarities in the action between biotin and insulin across eukaryotic species whose phylogenetic lines diverged over a billion years ago, pointing to a strongly selected role of biotin in the control of carbon metabolism [1]. Pharmacologic dose of biotin has specific effects on the pancreas. It maintains the differentiated state of the pancreatic beta cells, beta cell mass and its glucose-stimulated insulin secretion. Biotin repletion activates numerous repair and anti-inflammatory pathways, reduces fibrotic gene expression and induces multiple genes involved in pancreatic endocrine and exocrine functions [8]. Biotin also has a triacyl glycerol- and VLDL- lowering effect in Type 2 diabetic patients and in non-diabetic subjects with hypertriglyceridemia [9]. In a study of the effect of biotin on glycemic control and plasma lipid concentrations in type 1 diabetes patients biotin administration as an adjuvant in addition to insulin, improved glycemic management and decreased plasma lipid concentrations in poorly controlled type 1 diabetic patients [10].

The diabetic condition results in micro- and macrovascular dysfunction leading to cardiovascular complications. The involvement of Advanced Glycation (AGE) and Advanced Lipoxidation (ALE) end products in the pathogenesis of diabetes-mediated uremic complications is well recognized. Chemicals which have an inhibitory effect on any of the individual steps leading to the vascular pathologies would have a role in the therapy of micro- and macro- vascular defects associated with the diabetic condition. Pyridoxamine (a vitamin B6 vitamer) and benfotiamine (a lipid-soluble form of thiamine) have a significant place in the therapy of the microvascular defects associated with diabetes [1]. Diabetes mellitus (T2D) is the most common endocrine disease in the world. Although genetically, South Asians are prone to this metabolic disease, it is increasingly becoming world-wide in its occurrence. The costs associated with the treatment of patients with the diabetic condition are very high both on the society and on the individuals affected with this condition. The nutrient-base supplements to traditional therapies holds much promise in the amelioration of the diabetic condition and its complications. Experimental and clinical studies indicate that several vitamins and their derivatives are useful adjuvants in the treatment of chronic conditions. These protective effects are achieved at the vitamin intake much higher (pharmacological dose) than the "recommended dietary allowance" [3]. Nitric oxide (NO) has been recognized as a signaling molecule and the effects extend beyond cardiovascular regulation. Impairment of this system in experimental animals results in hypertension and metabolic dysfunction as indicated by increase in abdominal fat, dyslipidemia and impaired glucose tolerance. Treatment of these animals with nitrate attenuated the biochemical abnormalities. The nitrate-nitrite-NO signaling pathway acts not only on mitochondrial oxidative systems but also on metabolic regulatory systems including AMPK and GLUT4 translocations, similar to the action of biguanide antidiabetic drugs. Nitrate might be added as a cost-effective adjuvant to drugs used to treat diabetes [11]. The earlier scare regarding the carcinogenic effect of nitrate has been replaced by the understanding that nitrate has robust NO-like bioactivity in the cardiovascular system. For assessment of any treatment benefit, the Randomized Control Trial (RCT) is considered to be the gold standard and provides average treatment efficacy for the study population. Modest benefits seen in some clinical trials can be misleading as they might reflect a mixture of substantial benefits for some with little or no benefit for others. The single patient (n-of-1) trial has been developed to increase the scientific rigor of individual patient assessment and can be used to select the optimal treatment based on the point-of-use data [4].

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