Metabolic Syndrome

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"Structure Is an Expression of Function."

Introduction

The term "metabolic syndrome" denotes a constellation of cardiovascular risk factors related to insulin resistance and obesity with a visceral fat pattern.[1(p741),2] Definitions have varied, but the basic elements are well validated and include insulin resistance, inflammation, and immunologic dysfunction with increased oxidative stress preceding the accepted characteristics of hypertension, atherogenic dyslipidemia (high triglycerides, low HDL, high LDL), obesity (increased waist circumference, BMI, and waist-hip ratio), together with elevated fasting blood sugar level, glucose intolerance, hyperglycemia, and a prothrombotic state (see Table 1).

Although the exact criteria vary between the two key determinant projections (National Cholesterol Education Programme – Adult Treatment Panel III [NCEP ATP III] and World Health Organization [WHO]), the criteria correlate closely.

Interestingly, the WHO includes microalbuminuria (overnight urinary albumin excretion rate > 20 µg/min), which the author believes is significant in relation to the inflammation/oxidative stress element and the fact that glucotoxicity and lipotoxicity induce changes in cell signaling, protein expression, gene expression, and free radical formation. These may be relevant to associated pathophysiological factors (prothrombotic components, vascular endothelial dysfunction, and accelerated athero-embolic conditions) and are undoubtedly related to an imbalance in vascular endothelial mediators, which results in excess angiotensin II and nitric oxide deficiency. Hence, vasoconstriction, prothrombotic, proinflammatory, and pro-oxidant states ensue.[1(p741),2]

Epidemiologic key factors relating to metabolic syndrome

Here we first need to mention the genetic predisposition of an individual. Gestational diabetes is a risk factor, and so may be bottle feeding. Lifestyle factors also play a role in this context. To begin with dietary habits, the consumption of white sugar (Professor Yudkin's "pure, white, and deadly") and other high calorie foods, especially refined carbohydrates and those of high glycemic index, stand paramount. Reduced physical activity, particularly in adolescence, and an imbalanced microbial gut flora will also contribute to the development of metabolic syndrome.

Minor factors seem to be elevated homocysteine levels (> 5 µg/L), ab-

Abdominal obesity		
	• **men**	> 102 cm (40 in)
	• **women**	> 88 cm (35 in)
Triglycerides		≥ 150 mg/dL
HDL cholesterol		
	• **men**	< 40 mg/dL
	• **women**	< 50 mg/dL
Blood pressure		≥ 130/≥ 85 mm Hg
Fasting glucose		≥ 110 mg/dL
Diagnosis of metabolic syndrome is made when 3 or more of the above risk determinants are present		

Table 1: ATP III criteria for diagnosing metabolic syndrome

Table 2: Effects of adipocytokines

Promotes weight gain and inflammation	Promotes weight loss
IL-6: causes insulin resistance, proinflammatory cytokine	Adiponectin: important insulin sensitizer
IL-1: proinflammatory cytokine	Leptin: major (down-) regulator of food intake and appetite
TNF-α: increased in obesity, modulates insulin sensitivity	Resistin: modulates insulin sensitivity
Non-esterified fatty acids (NEFA): cause insulin resistance	

normalities in autonomic nervous system regulation (affecting somatostatin function in relation to beta cells in the pancreatic islets, perhaps also delta and alpha cells), and low C2 reactive protein function.[1(p742)]
To confirm the diagnosis of metabolic syndrome, 3 or more of the ATP III criteria must be present (see Table 1).

Pathophysiology

This brings us to the key player in metabolic syndrome – insulin and its receptors. Insulin (a small protein in the form of two chains with disulphide bonds, with a molecular weight around 6000 daltons) is synthesized in the pancreatic beta cells. The cytoskeletal ribosomes manufacture preproinsulin from insulin MRNA. The "pre" is enzymatically cleaved off, leaving the proinsulin to move into secretory granules in the Golgi apparatus for storage. During the secretory process, the connecting C-peptide is split off by specific endopeptidases. Equimolar quantities of insulin and C-peptide (a risk factor marker) are released into the circulation, on occasion of glucose entry via specialized glucose transporter proteins (GLUT-2). Potassium channels in the beta-cell membrane are closed (glucose metabolism ATP), the membrane thus depolarized, and calcium channels opened, leading to calcium-dependent exocytosis of insulin-rich granules.

The insulin receptor on cell surfaces is a glycoprotein that includes the insulin binding site where a cascade response is initiated, resulting in increased transport of glucose into the cell (GLUT-4). Insulin is subsequently degraded, and the receptor is recycled to the cell surface.[3]
In relation to the process above, insulin resistance is probably multifactorial, i.e., influenced by a continuum of factors including diet, exercise, body weight, toxic hypertriglyceridemia, decreased HDL cholesterol, obesity, and hypertension, together with various multi-endocrine and inflammatory factors, which will be discussed next.
It has recently been discovered that subclinical inflammatory changes are characteristic of both type 2 diabetes and obesity. Unknown abnormalities reduce the effect of insulin signaling within the cell, producing not only insulin resistance (high intracellular triglyceride is a possible factor) but also (as a result) beta-cell stress and strain due to high output failure. (The author suspects that release of NF-κB plays a role here triggered by the release of reactive oxygen species.) Proinflammatory cytokines, especially TNF-α and IL-6, are elevated in both diabetes 2 and obesity, and the raised C-reactive protein levels are associated with raised fibrinogen and PAI-1 levels (again, possibly the effect of NF-κB).

Two key endocrine organs are involved in the process: endocrine-adipose tissue and the endocrine-skeleton. Yes, the skeleton is an endocrine organ that regulates blood sugar! In higher eukaryotes, including humans, adipose tissue is the main energy reservoir – there may be evolutionary connotations here –, and its primary purpose is to store triacylglycerol in periods of energy excess and mobilize it during energy shortage. Transcriptional activation of adipocyte genes (PRARγ) is involved in directing adipocyte-specific gene expression and adipogenesis and is affected by the leptin secreted by mature adipocytes. Leptin is a recently discovered hormone that seems to regulate body fat mass by binding to its receptor in the hypothalamus (energy balance and homeostasis).[4]
Adipose tissue produces many adipocytokines, including inflammatory mediators and hormones that cause low grade chronic inflammation and other endocrine and metabolic dysregulatory effects, thus resulting in insulin resistance and cardiovascular risks (see Table 2).
The insulin resistance produces an imbalance of the mitogen-activated protein kinase (MAPK) at the level of insulin receptors and the phosphatidylinositol 3-kinase (PI3-K) pathways. The PI3-K is an anti-atherogenic pathway and the MAPK proatherogen.[1(p743),5]

Abdominal obesity, recognized by increased waist circumference, is a risk factor for developing metabolic syndrome.

Various other mediators are sourced from adipocytes,[1(p743),4] but two key ones need discussion here. First, adipose tissue-specific secretory factor (ADSF/resistin) plays a role in insulin resistance to affect adipogenesis, thereby linking obesity to diabetes. Second, the peroxisome proliferator-activated receptors (PPARα and γ) are involved not only in insulin resistance and glucose and lipid metabolisms but also in inflammation (again, through NF-κB), aging, and atherosclerosis and its complications.[4]

Surprisingly, the skeleton is also involved in this process. It is now known that the osteocalcin produced by cells in bone "increases both the secretion and sensitivity of insulin, in addition to boosting the number of insulin-producing cells and reducing stores of fat."[6]

Let us now move on to discuss antihomotoxic, integrated, naturopathic, holistic management of insulin resistance. This paper will leave aside regular exercise (aerobic and resistance) and dietary and lifestyle engineering (including cognitive behavior therapy) to concentrate on homotoxicology and nutritional engineering.

Clinical relevance

The net effect of insulin resistance on the organism is the accumulation of insulin and glucose in the tissues, which have detrimental effects through a number of pathways.

Elevated blood glucose levels lead to activation of the polyol pathway (resulting in toxic sorbitol), auto-oxidation pathway (resulting in cross-linking via advanced glycation endproducts [AGEs]), protein kinase pathway (resulting in expression of inflammatory mediators such as the transcription factor NF-κB), and oxygen radical pathway (resulting in NO reduction and tissue damage as well as the activation of NF-κB).

The end result of these pathways is chronic inflammation, tissue destruction, and an interference in cellular processes.

Antihomotoxic approach to metabolic syndrome

Where does homotoxicology fit into this picture? Hans-Heinrich Reckeweg's unique intellectual synthesis and system of medicine seems to fit metabolic syndrome like a glove, and his antihomotoxic therapy appears to have all the necessary bioregulatory and integrated holistic facets for successful management of this condition.

Dr. Alta Smit's detailed protocols, as outlined in the *Journal of Biomedical Therapy*, stand paramount.[7] This author, however, believes that because the helenalin in Arnica "douses" NF-κB, Traumeel should be added to the initial treatment protocols, which consist of the pillars of treatment for regulating the biological terrain (through detox and drainage, cellular activation, organ regeneration, immunostimulation, and immunomodulation). The above analysis of metabolic syndrome supports the use of these medications, especially in the protocols for weeks 7-12. I would add Pankreas suis (also included in Hepar compositum) and (in view of associated autonomic nervous system dysregulatory states) perhaps also Ypsiloheel and in particular Ginseng compositum as a PNETI rebalancer that simultaneously reduces gluco- and lipotoxicity. (The author is currently undertaking a practice-based study of Ginseng compositum for the annual seminar of the Society for Homotoxicology and Antihomotoxic Therapy in Great Britain.)

Elevated blood pressure is one of the components that characterize metabolic syndrome.

Adjuvant nutritional therapy

On a microbiological level, the intake of probiotics will help to overcome gut microbial dysfunction. Immunonutrition products (especially trace elements such as selenium, zinc, chromium, and manganese) and functional foods also support medicinal treatment. Last but not least, I would like to mention antioxidants (free radical scavengers) and so-called "cleansers," e.g., spirulina (an alga that provides a full range of amino acids).

Conclusion

In conclusion, now that biomedical pathophysiological research is beginning to explain conditions such as metabolic syndrome, it is becoming more important to adopt Dr. Reckeweg's integrated, holistic approaches and to incorporate concepts such as the living matrix, structural/functional interconnectedness, and bioinformational transmission into our prophylactic and therapeutic endeavours.

Recommended texts for homotoxicologists (relevant to paper)

1. Jänig W. *The Integrative Action of the Autonomic Nervous System. Neurobiology of Homeostasis.* Cambridge: Cambridge University Press; 2007.
2. Jones DS, Quinn S. *Textbook of Functional Medicine.* Gig Harbor, WA: Institute for Functional Medicine; 2005 (especially Section VII, Chapter 37, Metabolic Syndrome).
3. Oschman J. *Energy Medicine in Therapeutics and Human Performance.* Amsterdam, the Netherlands: Butterworth-Heinemann; 2003.

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1. Jones DS, Quinn S. *Textbook of Functional Medicine.* Gig Harbor, WA: Institute for Functional Medicine; 2005.
2. Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. *Am J Epidemiol* 2002;156:1070-1077.
3. Shepherd PR, Kahn BB. Glucose transporters and insulin action. *New Engl J Med* 1999;341:248-257.
4. Kim KH, Lee K, Moon YS, Sul HS. A cysteine-rich adipose tissue-specific secretory factor inhibits adipocyte differentiation. *J Biol Chem* 2001;276(14):11252-11256.
5. Xu H, Barnes GT, Yang Q, Tan G, Yang D, Chou CJ, Sole J, Nichols A, Ross JS, Tartaglia LA, Chen H. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J Clin Invest* 2003;112:1821-1830.
6. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, Confavreux C, Dacquin R, Mee PJ, McKee MD, Jung DY, Zhang Z, Kim JK, Mauvais-Jarvis F, Ducy P, Karsenty G. Endocrine regulation of energy metabolism by the skeleton. *Cell* 2007;130(3):456-469.
7. Smit A. Metabolic syndrome and diabetes type II: adjuvant treatment. *J Biomed Ther* 2004;Fall:5-6.

Physical activity and healthy, low-calorie food can help to prevent the development of metabolic syndrome.