Metabolic Syndrome: A Multifaceted Disease of Affluence

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Abstract

Metabolic syndrome developed in consequence of an evolutionary inadequacy: the human body was unprepared for a dietary excess of nutrients, especially lipids (largely at detriment of carbohydrate). This excess awakens metabolic signals akin to those of starvation, in which the main energy staple is the body’s own lipid reserve. Lipid dietary abundance prevents the use of glucose, which in turn limits the oxidation of amino acids. To ward against a subsequent avalanche of substrates, the immune system and hypertrophied tissues (for example, adipose) elicit a series of defence responses. This response is probably the ultimate basis of a disease that is manifested as various pathologies, which were initially defined as distinct entities but which are slowly being seen as a single pathognomonic unit in the literature. Based on their common origin of the ample availability of food in our modern society, the cluster of diseases comprising the metabolic syndrome is probably best described as a single multifaceted disease.

Keywords: Metabolic syndrome; Obesity; Hyperlipidic diet; Inflammation

Introduction

The proportion of overweight and obese people is rising unchecked, to epidemic proportions, worldwide. Diabetes, hypertension, and cardiovascular diseases account for most of the world’s metabolism-related disorders, as well as a large share of its total morbidity and mortality. Only cancer, infectious diseases, and violence/accident-related deaths combined surpass these metabolic diseases in terms of mortality, but not in terms of the extent (years) of morbidity or the social and economic aspects affecting the quality of life. Because the association between these and other diseases is not casual, many contemporary authors refer to them conjointly as the metabolic syndrome (MS).

The considerable increase in morbidity and exponential rise in health care and other social costs caused by MS is aggravated by its wide extension across ethnic, economic, and social divides, as well as by its non-responsiveness to attempted remedial measures. The increasing transcendence of MS as one of the main health problems of modern medicine has led to the generation of an enormous mass of related research. Although much of this literature includes reviews and commentary, nevertheless, the full extent of the related research information on MS cannot be fully synthesized / processed by any single investigator.

Is the metabolic syndrome a true syndrome or a multi-form disease?

As the number of diseases that may fall under the umbrella term of MS grows, researchers are finding that the pathogenic mechanisms involved in MS are much more complex than previously assumed. As a result, many related research issues have been only sparsely analyzed, whereas others have perhaps been overstudied. This imbalance is partly due to the anisotropic availability of adequate methodology, the medical and social (or commercial) interest of the public, and the availability and rigid compartmentalization of medical specialists.

The purpose of this review is to emphasize the need to include in the working concept of MS a number of associated diseases that are often considered to be related but not crucial to the core of the MS. In other words, the goal is to present MS as a multifaceted disease, rather than as a simple cluster of diseases that are only partially associated but happen to be often, coincidentally, present in patients. This view of MS is not universally shared, probably because the separate diseases (hypertension, obesity, diabetes, etc.) existed prior to the development of the concept of MS. As a result, a corpus of knowledge was developed independently for...
each disease, and the concept of MS was only defined after researchers sought to find a common relationship or shared origin for the various diseases.

Although individual pathologies obviously correlate with alterations at the molecular level, the aggregation of molecular-level changes and their eventual feedback effects depend on the overall physiological context, for example, the organism as a whole. Only by considering the molecular- and organism-level aspects together can we begin to understand the disease. In other words, both aspects must be considered to discern whether MS is comprised of numerous interconnected, albeit separate, pathologies or whether it is a single hydra-like disease with separate symptoms sharing a common pathogenic core.

Several Health-related Societies and Medical Associations have established detailed protocols for the diagnostic and characterization of the MS, with discrimination limits and algorithms derived from observational studies. However, the pathogenic relationships of the key diseases packed in the broad definition of the MS have not been yet fully established as a single pathognomonic unit other than by epidemiological association or the intuitive association of the diseases carried out by a number of experienced and insightful scientists. The MS is a widely recognized cluster of related pathological traits that affect a large proportion of adults in developed and developing societies [1, 2]. Most definitions include insulin resistance/diabetes, hyperlipidemia, arterial hypertension and obesity, often associated with hyperuricemia, small dense LDL, and endothelial inflammation (Table 1).

The Metabolic Syndrome as a Disease

Because of the generalized lack of knowledge of the pathogenic origin, and the varying degree of association of its different components, acknowledgement of the MS as a distinct pathologic entity has been slow and progressive. Metabolic syndrome was first discussed in classical times, taking form early last century (reviewed by Sarafidis and Nilsson [3]).

The MS epidemic is generally considered an unwanted consequence of social development and the access to rich, abundant and varied food, decreased physical activity and the other perks (and disadvantages) of modern-day life in most human Societies. The correlations in the incidence of the MS-related diseases have been fully established, as well as their interrelations, mainly from observational analyses; but recent research also uncovered a number of shared mechanisms: genetic, epigenetic, psychosocial, and other mechanisms [4, 5]. Because the pathologic traits share a common (although only partially uncovered) origin [6], researches have indicated that MS should be considered a multifaceted disease. However, the issue is not settled, in part because of the different views on the role of lipid/carbohydrate in the diet as the main factor eliciting MS development [7, 8].

The combination of basic metabolic regulation traits, modulated by specific allelic distributions, epigenetics, and exposures to environmental factors during early development and over one’s lifetime, may cause a wide range of symptom patterns and intensities. Accordingly, MS may be considered a multiform disease. By emphasizing pathogenesis rather than compliance with specific quantitative pathologic indicators, additional alterations are also found to be associated with MS, many of which share common pathways. These alterations can largely be defined as inflammation, and often require a considerable time-span to develop and show up.

It is difficult to determine when MS became a quantitatively significant disease, because we have only had workable definitions for MS within the last few decades. Moreover, most of the components of MS have only recently been able to be fully characterized and diagnosed. Although diabetes, gout, and ictus were described in classical times, obesity was not considered a full disease until recently, although its existence and treatment were described in very old sources [9]. Nevertheless, limited or absent food availability, infection, harsh living conditions, warfare, and exploitation drastically limited human life expectancy during most of the history of mankind, which may have prevented the slowly evolving MS-related pathologies from being manifested in a sufficient number of individuals. Information about people in affluent or privileged positions in various historical contexts showed that they lived longer, but many suffered obesity, gout, and other MS-related diseases, such as arthrosis, hydropsy, ictus, etc. [10]. Therefore, we can assume that MS has been present since historical times, although never before has it affected such huge numbers of individuals. This observation adds weight to its direct relationship with affluence, at least from a nutritional perspective.

The Pathognomic Links: Insulin Resistance

A considerable body of literature has established links between the main pathologic traits of MS with the historical precedents indicated above. As the list of related diseases grows, interrelationships continue to be found or proven by direct analysis of the pathogenic pathways or established by association through epidemiological studies.

Many researchers consider insulin resistance to be the main defining element of MS [11]. Insulin resistance is characterized by decreased sensitivity to glucose and low peripheral glucose uptake [12], which often develops into full type-2 diabetes [13]. This metabolic condition has been directly related to neurologic alterations that result in dementia [14], and Alzheimer disease [15]. The metabolic alterations induced by insulin resistance are a direct consequence of the excess availability of dietary lipid. This excess lipid is translated into hyperlipidemia/dyslipoproteinemia [16], with hy-
Table 1. Main Pathologic Traits Associated With the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Insulin resistance</th>
<th>Decreased sensitivity to glucose/Low peripheral tissue glucose uptake/Type 2 diabetes/Dementia/Alzheimer disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia/dyslipoproteinemia</td>
<td>Small, dense LDLs/Hypercholesterolemia and low HDL cholesterol/Hypertriacylglycerolemia/High ApoB/Oxidized lipoproteins</td>
</tr>
<tr>
<td>Hepatic steatosis and hepatomegaly, Altered hepatic function</td>
<td>Hyperbilirubinemia/Increased enzyme leakage/Altered antioxidant mechanisms/Altered xenobiotic metabolism</td>
</tr>
<tr>
<td>Hyperuricemia/gout</td>
<td>Inflammatory arthritis</td>
</tr>
<tr>
<td>White adipose tissue inflammation</td>
<td>Obesity/visceral or upper body obesity/Adipocyte hyperplasia and proliferation/High proportion of nonadipocyte cells/massive macrophage infiltration/Altered blood flow/Hypoxia/High leptin/leptin resistance/Low adiponectin/High resistin/Low interleukin-6/increased adipokine signaling</td>
</tr>
<tr>
<td>Altered immune response</td>
<td>Asthma, psoriasis/Other autoimmune diseases</td>
</tr>
<tr>
<td>Increased oxidative damage</td>
<td>Increased effects of free radicals, superoxide, peroxynitrite, etc./Increased synthesis and disposal of NO-/Increased nitrite and nitrate excretion</td>
</tr>
<tr>
<td>Altered composition of the microbiota</td>
<td>Altered immune system control of the biota/presence of nitrate and nitrite/Increased LPS levels/interaction with the biota</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td></td>
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<tr>
<td>Sleep apnea</td>
<td></td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>Increased peripheral blood flow resistance/Atherosclerosis/increased vascular microdamage and enhanced plaque formation/Altered rheological behavior of red blood cells/nondeformability of red blood cells</td>
</tr>
<tr>
<td>Increased cardiovascular risk</td>
<td>Atrial fibrillation/Altered blood coagulation/Pulmonary resistance/respiratory insufficiency/Heart insufficiency/Higher incidence of ictus</td>
</tr>
<tr>
<td>Altered hypothalamic-pituitary-adrenals axis function</td>
<td>Hypercortisolism/Cushing-like states/Disappearance of daily rhythms/Depression, altered thymic states/Altered gonadotropin secretion, infertility</td>
</tr>
<tr>
<td>Decreased/ altered sex hormone metabolism and function</td>
<td>Polycystic ovary syndrome (?)/Hypoandrogenism/Decreased dehydroepiandrosterone/Decreased estrogen protection</td>
</tr>
<tr>
<td>Altered nervous system functions</td>
<td>Decreased cognitive abilities/Higher incidence of psychiatric alterations/Higher autonomic nervous system activity/Peripheral nerve damage</td>
</tr>
<tr>
<td>Eating disorders:</td>
<td>Binge eating (obesity type)/Orthorexia, anorexia nervosa (secondary)</td>
</tr>
<tr>
<td>Increased incidence of some types of cancer</td>
<td>Colon, endometrial, renal cell, gallbladder, and upper digestive tracts carcinomas (largely associated with obesity, diet, and estrogen)</td>
</tr>
</tbody>
</table>
pertiacylglycerolemia [17], hypercholesterolemia with altered lipoprotein distribution of cholesterol, and small dense LDLs [18]. An obvious consequence of excess lipid energy is a decrement in the overall carbohydrate availability [8] (lipid/carbohydrate energy ratio), which also affects the handling of dietary protein and the excretion of N [19]. This picture is completed by an increased proportion of oxidized lipoproteins in the plasma [20].

Excess lipid-induced insulin resistance also leaves a large amount of glucose (largely dietary) unused, despite the lower overall carbohydrate intake. The disposal of this excess glucose falls largely on the white adipose tissue (WAT), which is already strained by the excess lipid [7], thereby favoring glycolysis and lactate production [21]. The excess lactate is used by the liver for gluconeogenesis [22] or lipid synthesis [23] (Fig. 1).

Metabolic syndrome also induces changes in the coagulation process of the blood, with altered platelet function [24], and higher reactivity with oxidized lipoproteins [25]. Hypertension enhances the response of the endothelial sheath of blood vessels [26] facilitating the deposit of atheroma plaque [27], favored by hyperlipemia and the inflammatory response of the vessels themselves. A marker of the altered peptide signaling in MS (diabetes) is acanthosis nigricans which is a cutaneous alteration of melanocyte stimulating hormone (MSH) function. In addition to depressive mood, the MS is also related to altered eating behaviors, namely binge-eating [28], and secondarily to reject mechanisms that may in the end result in eating disorders such as anorexia nervosa, bulimia or orthorexia.

Liver Steatosis

The excess of lipid availability may overwhelm the liver capacity to process it, eventually resulting in steatosis and hepatomegaly [29]. Consequently, liver functionality decreases and cannot maintain circulating glucose efficiently [30]. The liver is not able to control excess portal insulin [31], and hepatic functions are deeply altered; For example, cells tend to leak enzymes and excess bilirubin to the plasma [32]. The metabolism of xenobiotics is also affected [33] because of altered defensive ability against oxidative agents [34]. Consequences of these alterations include hyperuricemia [32], gout and arthritis, the latter of which develops because of the enhanced immune response. The circulation of excess lip-
ids favors lipid deposit throughout the tissues, including the muscles and heart [35], as well as lipid utilization from these tissues. Lipid accumulation can diminish the efficiency of the skeletal muscle and heart signal conductivity [36], inducing peripheral nerve damage [37].

**Obesity**

The excess energy availability in the adipocytes, largely driven by insulin resistance elsewhere and excesses of both lipid and glucose (and insulin) in plasma is the key element responsible for white adipose tissue enlargement. This results in obesity, mainly upper body-obesity [38], a consequence of the increase in the size and numbers of adipocytes [39]. The enlargement and continuous availability of energy provoke adipocyte bloating. The cells signal their precarious situation, eliciting an inflammatory response [40], which is largely sustained by the infiltration of immune tissue cells such as macrophages [41]. Excess substrate arrival is in part limited by hypoxic responses [42] driven by glycolysis [43] and decreased blood flow across white adipose tissue, which increases peripheral blood flow resistance and helps induce hypertension [44] (Fig. 2). The altered endocrine/paracrine function of the adipose tissue induces hyperleptinemia and leptin resistance [45], increased circulating levels of resistin and decreasing concentrations of adiponectin and interleukin 6. Increased adipokine signaling also tends to modify overall energy partition and enhance insulin resistance [46].

Despite fighting the aggression of the adipocytes by powerful means, the immune system is unable to correct the problem of excess substrate and is unprepared to counteract the tissue damages produced by the excess nutrients. This failure results in the consumption of additional immune resources and the generation of alarm signals. Thus, the inability to eliminate excess nutrients results in collateral damages that can be directly attributed to the increased immune response [47]. These damages can be observed as a higher incidence of asthma [48] or psoriasis [49] in MS patients. The increase in immune response in MS patients may also be related to the development of various autoimmune diseases [50].

**Hypercortisolism**

A consequence of the high immune-system activity is the counter regulatory action of the glucocorticoids. In particu-
lar, alterations in the hypothalamic-pituitary-adrenals axis function [51] result in hypercortisolism [52], with conditions close to those seen in Cushing disease. Daily rhythms are flattened or even lost, coincident with metabolic alterations in brain melatonin [53] and, especially, serotonin levels [54]. There is a marked relationship between mood states and the MS, with a high correlation between the syndrome and depressive states [55]. There is also a direct correlation with the duration and quality of sleep [56]. However, it is unclear whether sleep disturbances are a secondary consequence of MS or are, as is depression, a consequence of the alteration of brain function by a cocktail of hormones, cytokines, or available substrates [57]. Metabolic syndrome is also characterized by increased autonomic nervous system activity [57] which affects the response of most tissues to normal nervous regulation.

Sleep Apnea and Heart Disease

Sleep apnea is a common symptom of the MS [58]. Although it has been correlated with the main MS pathologies, including obesity, its presentation is largely independent of them [58]. The choking effect of hyperrelaxation of respiratory upper airway muscle has been related to surrounding fat control through paracrine signals. The apnea periods affect the maintenance of a structured sleep [59] and induce spikes of catecholamine secretion that restore breathing, but cause havoc elsewhere. Continued catecholamine bursts may lead to atrial fibrillation development, a common finding in the MS [60], and enhance the dangers of hypertension and overall cardiovascular risk. Respiratory insufficiency in obese individuals, compounded by sleep apnea, asthma, and heart malfunction, may result in marked cardiopulmonary dysfunctions that aggravate the metabolic damages in heart muscle contractility (accumulation of fat, diminished conductivity [35]) and signal strength (atrial fibrillation, pulmonary hypertension [61]). The overall risks of atherosclerosis, hypertension and hypercoagulability, increase considerably the probability of heart failure ictus, and cardiovascular insufficiency [62].

Nitric Oxide, Hypertension and Blood Flow

Excess available energy results in diminished protein catabolism, which promotes growth in the young, and helps
Metabolic Syndrome may precede the full appearance of MS. The presence of low,
es in the composition of the microbiota [80]. Such changes
powerful activated immune system induce functional chang-
status of the triple interaction of genetics, environment,
sequences of the cluster of diseases that are directly associated with the
large number of MS-related diseases and pathological
traits (Table 1), including some that are derived from the
“classical” components of MS, share common origins. All
of the aforementioned diseases and traits are inextricably
linked, forming a protean “disease of affluence,” the origin
of which can be traced to our nutrient-rich living conditions.

Microbiota Alterations
Excess NO• synthesis results in the production of large
amounts of nitrite and nitrate [66], which are principally
excreted though the saliva into the alimentary channel. The
presence of nitrates, higher availability of nutrients, and a
powerful activated immune system induce functional chang-
es in the composition of the microbiota [80]. Such changes
may precede the full appearance of MS. The presence of low,

Sex Hormones
In MS, hypercortisolism develops parallel to a decrease in
the levels and activity of androgens [83]. Hypoandrogen-
ism is a consistent finding in male patients with MS [84]. In
females, androgen metabolism is also altered, especially
in those affected by polycystic ovary syndrome [85]. In all
cases, the levels of dehydroepiandrosterone tend to be low
[86] because of altered adrenal function, as in advanced
age. This finding may be a consequence of alterations in the
hypothalamus-pituitary-adrenal (or -gonadal) axes by hyper-
leptinemia and/or corticosteroids. Decreased estrogen avail-
ability specially affects the health of post-menopausal wom-
en, since estrogens protect the brain [87] and low estrogen
is associated with increased oxidative damage [88]. When
compared with glucocorticoids, low sex hormone levels cannot
protect sufficiently protein and bone minerals.

The MS has been related to increased incidence of certain
cancer types (colon, endometrial, renal cell, gallbladder,
upper digestive tract) [89]. In most cases, compared to the
effects of MS, these cancers may be more directly related to the
diet and, in some cases to the local effects of increased
estrogen secretion by abundant adipose and breast tissues
[90].

Conclusions
The large number of MS-related diseases and pathological
traits (Table 1), including some that are derived from the
“classical” components of MS, share common origins. All
of the aforementioned diseases and traits are inextricably
linked, forming a protean “disease of affluence,” the origin
of which can be traced to our nutrient-rich living conditions.

The diet that our evolution-ingrained desire sought could not
be adequately processed by our actual metabolic machinery,
which is finely tuned to survive in periods of scarcity but
painfully inadequate for extended periods of plenty. Because
the cluster of diseases that are directly associated with the
MS has a common origin, we believe that it should be con-
sidered as a single disease. Like other complex metabolic
diseases, the manifestations of MS, which may include the
individual pathological traits described above, are conse-
quences of the triple interaction of genetics, environment,
and behavior. To this triad we can also include therapeutic
(or therapeutic-like) actuations which often backfire into ad-
tional iatrogenic damage.
Acknowledgement

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Competing Interests

The author has no conflicts of interest to disclose.

Abbreviations

MS: metabolic syndrome; WAT: white adipose tissue.

References


