



## You are what you eat: food ingredients and the metabolic syndrome.

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Editorial

**KEY WORDS:** Food ingredients, metabolic syndrome, thrifty gene, epigenetic, DNA methyl transferase, histone deacetylase, calorie restriction, fetal programming, processed foods

### INTRODUCTION

*Our food should be our medicine. Our medicine should be our food (Hippocrates).*

The clinical disorders collectively known as the 'metabolic syndrome' comprise hypertension, obesity, dyslipidaemia and insulin resistance. The proliferation of the metabolic syndrome in recent times has been attributed to many factors. The Mendelian explanation, termed the 'thrifty gene' hypothesis, although not irrefutable, provides a possible explanation for the relatively greater prevalence of obesity and diabetes in recent static (non-migrant) populations and/or in those populations recently exposed to western diets. In its simplest form, it states that the genes that were positively selected to withstand 'feast or famine' cycles of the past are now detrimental because they accumulate fat in a futile anticipation of famines that never materialize. This causes an imbalance between energy storage and energy expenditure, at the expense of the latter. There is evidence indicating that the incidence of diabetes and obesity among indigenous popu-

lations, such as the Pima Indians, Australian aborigines, the inhabitants of the central Pacific island of Nauru, and select migrant populations in the 'New World' have increased significantly in direct chronological proportion to their exposure to western diets.

The Lamarckian explanation, generally termed the 'fetal programming' or the 'thrifty phenotype' hypothesis, derives from observations that suboptimal nutrition during pregnancy can have marked consequences for the offspring that can manifest itself over several generations. The best documented example is that of the Dutch famine of 1944 in the German occupied part of the Netherlands. The children of the women who were pregnant during the famine were smaller. When these children grew up and had children, those children were also smaller than average. It is suggested that maternal undernutrition causes epigenetic changes in the promoter regions of the 'thrifty genes' leading to their relatively greater expression. This encourages efficient (thrifty) utilization of scarce energy substrates in the post natal period such that a metabolic advantage is conferred. If, however, the post natal environment has a relative excess of energy and nutrients, the individual is maladapted under these

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mismatched conditions. A stark example of such a mechanism is the silencing of the *agouti* gene by feeding the *agouti*<sup>+/+</sup> pregnant mother rats a diet rich in methyl donors. The progeny do not display their parents susceptibility to cancer, diabetes or shortened life spans.

The 'genetic drift' theory, suggests that obesity was selected against in early hominids because of the risk of predation. Upon removal of this risk due to development of fire and weapons, this trait ceased to be actively selected against, allowing for its random 'drift'. This hypothesis of 'predation release' provides an explanation for the ability of a large proportion of the sedentary population to resist obesity, even when exposed to high fat processed western diets. Because the genes that predispose to obesity, upon predation release, the hypothesis is that it is due to drift, rather than positively selected for, and they would not be subject to negative selection in times of prolonged abundant food supply.

The 'genetically unknown foods' hypothesis posits that the range of diets, as well as, the ratios of the nutritional components existing in such diets, for which human beings are genetically programmed, has undergone a significant change with the introduction of 'processed foods'. These foods, commonly available in western diets, are genetically unknown, and hence may be responsible for chronic degenerative diseases such as diabetes, hypertension, and atherosclerosis. As an example, it is argued that sucrose is a genetically known food only below a certain concentration and in the presence of potassium, in which form it occurs in fruits and sugarcane. Diabetes was absent in cane cutters who ate large amounts of sucrose, in its genetically known form, by chewing cane, but common in their employers, who ate large amounts of refined sucrose, a form not known genetically.

A common motif that emerges from these, at times disparate hypotheses, is that when changes in the environment, specifically in

energy availability or energy expenditure, occur at a greater rate than the ability of the genome or the epigenome to keep pace, the result may manifest as a metabolic disorder. The obvious solutions are, to either recreate the ancestral environment with regard to energy consumption/expenditure and/or, to intervene epigenetically or pharmacologically, in terms of food supplementation or medicines in order to modulate and closely align the genome/epigenome to energy consumption/expenditure in the current environment.

In the light of the evidence, it has been argued that folate (or indeed any) fortification of food may actually be harmful to populations that are recently urbanized or those that have not been exposed to such fortification less than a generation ago. Although an inverse correlation exists between folate intake and neural tube defects, the wisdom of supplementation to treat relatively low incidences of what is admittedly a multifactorial disorder needs to be weighed against the dangers of such supplementation causing a significantly larger intragenerational susceptibility to the metabolic syndrome. It has also been suggested that 'processed foods' should contain the same ratio of nutrients and/or electrolytes that occur in fruits and vegetables so that exposure to 'genetically unknown' foods is minimized. At first glance, suitable amounts of potassium could be added to refined sucrose, high fructose corn syrup or high sugar beverages in order to mimic its genetically known form found in fruits. It would also be valuable to document the ratios of food components found in 'naturally' existing fruits, vegetables, meats and dairy products akin to the Svalbard global seed vault repository. This is especially important because the increasing trend of genetically modifying these foods could very well render their ancestral nutritional ratios extinct, along the lines of extinct languages. A documented chronological record will enable a reversion to such ancestral ratios, if required in the future.

Although it is unethical to suggest that populations starve themselves periodically to simulate ancestral 'feast or famine' environments, it is eminently sensible to disseminate information about the irrefutable beneficial effects of calorie restriction. A plethora of research suggests that calorie restriction is unequivocally associated with the modulation of signaling pathways that increase longevity and decrease the risk of age related diseases such as cancer, diabetes and obesity.

Preclinical or clinical trials of medicines that target enzymes responsible for methylating/demethylating DNA and of those responsible for acetylating/deacetylating histones are underway. DNA methyl transferases (DNMTs), histone methylases (HMTs), histone acetylases (HATs), histone deacetylases (HDACs) are the pharmacological targets of such epigenome modulating drugs that hope to alleviate the metabolic syndrome.

The genome and the epigenome appear to play an important role in the predisposition to, and to the development and persistence of the metabolic syndrome in recent times. The epigenomic component of this puzzle appears to be capable of significant modulation by dietary habits and food components.