

A systems analysis of metabolic syndrome in human and the role of gene polymorphisms AGTR1/A1166C, ACE/ID and FGA/T312A in its development.

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The metabolic syndrome is a complex disease which is characterized by insulin resistance, obesity, high level of lipids in blood samples and high blood pressure. Starting with just observable overweight, the disease progresses and in several years to the scale of a systemic syndrome when multiple organ systems are affected. Understanding metabolic syndrome is one of the goals of systems biology, since understanding and explaining the mechanisms of systemic diseases serves as a crucial test for the applicability and correctness of theories [1]. Increasing the understanding of metabolic syndrome as systems phenomenon was the main aim of our research. Our particular goals were:

- a) To find the criteria which would allow us to associate the measured parameters with the primary causes and the consequences of the syndrome.
- b) To study the role in the syndrome of the genotype of 3 naturally polymorphic loci which are associated with the regulation of blood pressure and coagulation, the parameters affected in the patients with the syndrome.

We carried out the analysis of a set of more than 30 biochemical parameters and physiological characteristics of 83 patients diagnosed with metabolic syndrome and 32 people considered as healthy.

The genotypes of the following genes were studied: angiotensin converting enzyme (ACE) – insertion/deletion intron polymorphism, type 1 angiotensin receptor (AGTR1) – single nucleotide substitution (SNP) in the 3'-UTR and fibrinogen chain alpha (FGA) – an SNP leading to a single aminoacid substitution.

Using a combination of basic statistics with methods of metabolic control analysis (MCA) [2] and the analysis of partial derivatives, we demonstrated the separation of all of the parameters into two major classes. The first class contain physical and physiological parameters connected to a single functional unit (Figure 1) [2]. All other parameters were observed to act as individual factors in the development of metabolic syndrome. The observed intensity of coagulation, the concentrations of fibrinogen, the level of low density lipoproteins and cholesterol were demonstrated not only to induce the shifts between the mean and median normal and the mean and median pathological values of the parameters belonging to the first class, but also destabilize the values by increasing their observed dispersion among the patients. The measured binding activity of plasminogen in whole blood samples and the level of high density lipids (HDL) – the parameters of the third class - could be described as strong and the only stabilizers of all the mentioned destabilizing parameters (Figure 2). At the same time, the level of HDL was associated with the reduction of the shifts from normal to pathological mean values of the parameters-destabilizers, while plasminogen binding activity was associated with the increase of the shifts. In previous studies both HDL and plasminogen activity in the blood were associated

with early stages of chronic inflammation which later leads to the development of type 2 diabetes, obesity and hypertension. This conclusion was further confirmed in the current study by the results of our analysis of the structure of metabolism among patients of different genotypes in the locus ACE.

References:

1. Kitano et. al. (2004). Diabetes 53(3) P:S6-S15
2. Rohwer et al. (1996) J Theor Biol. 179(3) P: 213-228

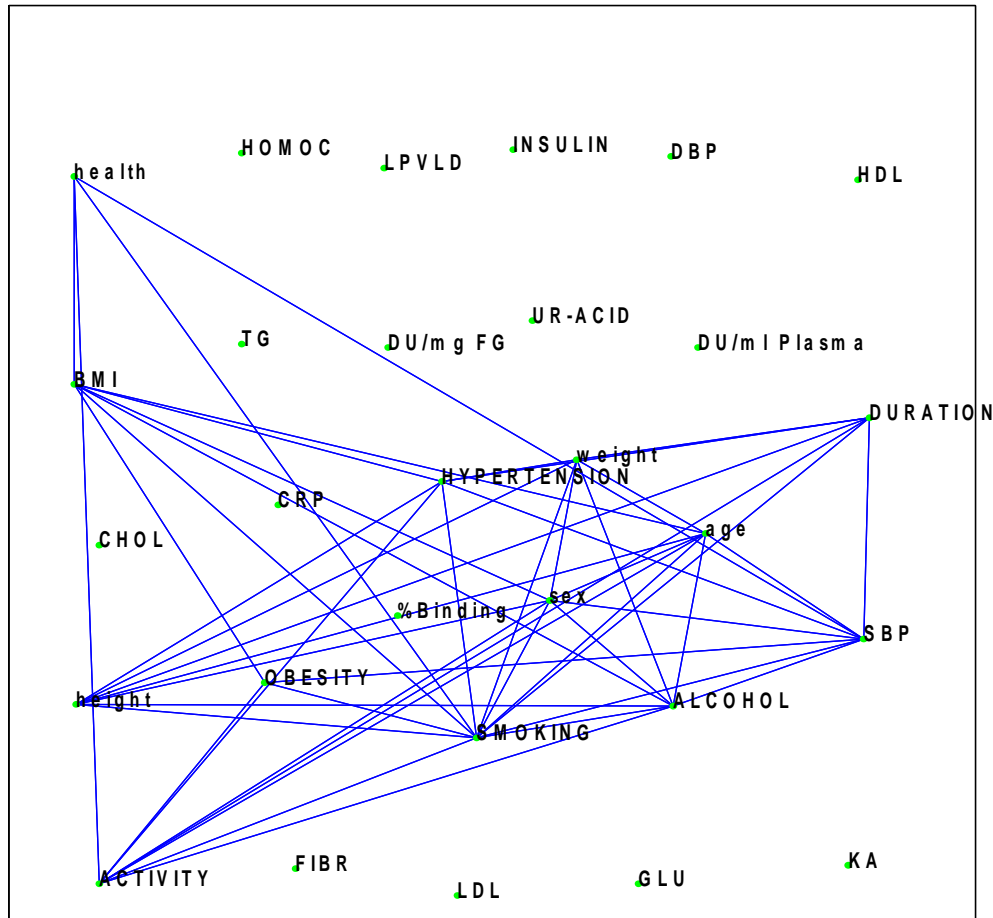


Figure 1. The main functional unit consisting of physiological parameters: diagnosed metabolic syndrome (“health”), body mass index (“BMI”), height, level of regular physical activity (“ACTIVITY”), diagnosed obesity (“OBESITY”), diagnosed hypertension (“HYPERTENSION”), smoking, gender (“sex”), age, level of alcohol consumption (“ALCOHOL”), duration of the diagnosed hypertension (“DURATION”), systolic blood pressure (“SBP”). The lines represent the connectivities between the parameters, calculated with a method derived from co-response analysis and are represented with values between 0 and 1 (not shown).

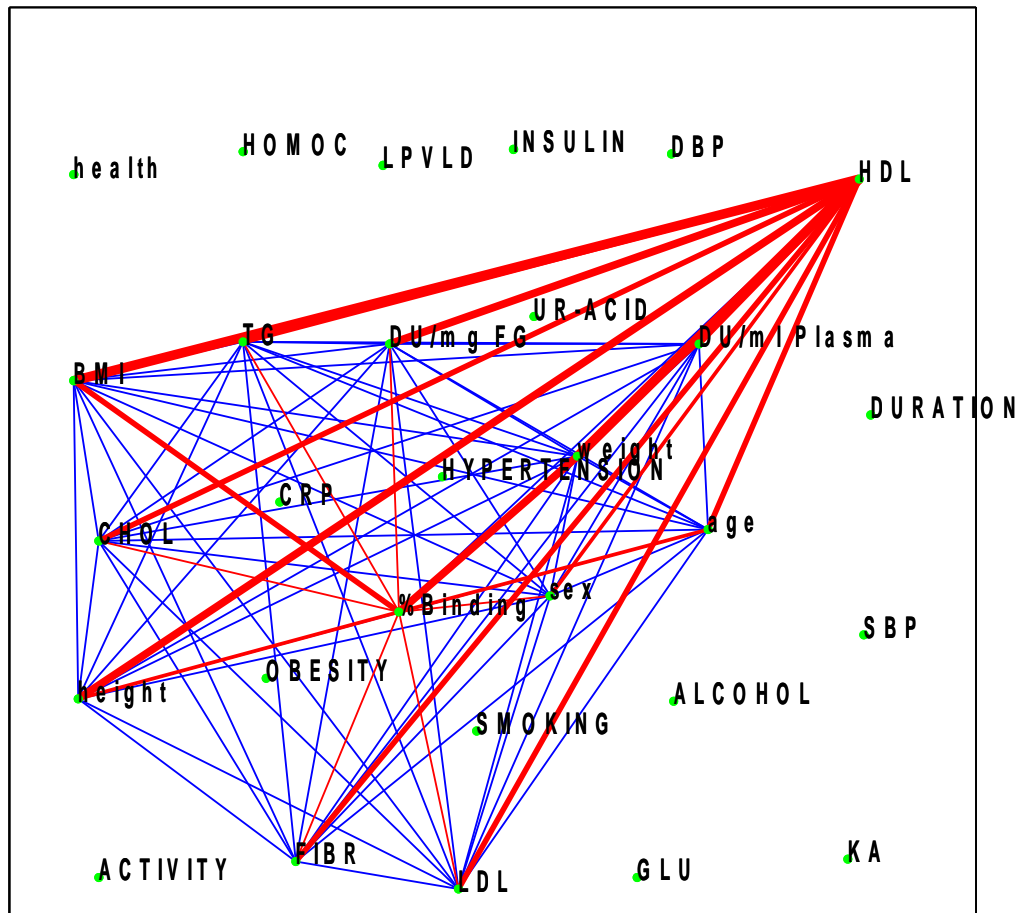


Figure 2. The stabilizing action of high density lipid blood concentration (“HDL”) and plasminogen binding activity measured in the whole blood sample (“Binding”) on the parameters body mass index (“BMI”), total cholesterol concentration (“CHOL”), patients’ height (“height”), triglyceride concentration (“TG”), fibrinogen concentration (“FIBR”), enzymatic activity of plasminogen per mg of fibrinogen (“DU/mg FG”), low density lipids concentration (“LDL”), weight, gender (“sex”), enzymatic activity of plasminogen per ml of blood plasma sample (“DU/ml Plasma”), the age of patients (“age”). The lines represent the values of partial derivatives between the standard deviation values of the parameters differentiated along the scale of diagnosed pathology depth. Red lines correspond to the negative values of the partial derivatives, blue lines correspond to the positive ones. The thickness of the lines reflects the magnitudes of the absolute values of the derivatives.