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Course notes

Biomarkers in Obesity

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Background

Obesity is one of the most important "epidemics" of our times and one of the major factors contributing to mortality together with arterial hypertension. Prevalence doubled or even tripled in developed countries from the 1970s to the 1990s. The tendency is similar worldwide, based on an analysis of 450 surveys in 144 countries. In Romania, the tendency of increase is not so abrupt, and the global prevalence of obesity and overweight in children seemed to be a little lower than the in Europe (28.3 % versus 38%) (1-5). A recent Statement of the Endocrine Society mentioned the main consequences: increased global mortality, increased cardiovascular mortality, increased appearance of type 2 diabetes mellitus (T2DM), hypertension, myocardial infarction, stroke, some types of solid cancer, sleep apnea, some hepatobiliary diseases, gout, and osteoarthritis (6).

The "equation" of obesity seems simple: calories intake exceeds consumption by much and for a long-term. The therapeutic solution seems as well simple: reducing intake on the one hand and increasing consumption by physical activity on the other hand.

In reality, life is much more complicated. Rudolf Virchow, in the 19th century, (cited by 1) stated that *"epidemics appear, and often disappear without traces when a new culture period has started" and that mass diseases are "due to … disturbances of human culture."* What are the cultural elements of obesity? On the one hand, the huge offer of calories intake: solid aliments like fast foods with a great density of calories on volume unit, which are eaten in excess before hunger disappears, sugar beverages and easy access to foods near schools or the working place. On the other hand, little physical activity in the era of computers at work and home, television instead of sports, and car displacement instead of bicycle or jogging.

But looking otherwise, obesity is an illness and medicine should have its role in therapy. Beyond lifestyle advice, including diet, drugs or

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other interventions could act by themselves at different points of the obesity equation. At that moment it was seen that obesity also has general endocrine involvement, like glucagon or insulin influence (not speaking about direct endocrine diseases with obesity), that hunger may be influenced by drugs, that burning of calories may also be influenced differently than by thyroid hormones.

Mechanisms and biomarkers involved in obesity

The equation of obesity is not as simple as described before. In reality, more factors than intake and consumption of calories have to be analyzed (7): genetic factors, fetal programming, environment, socio-economic status, lifestyle, nutrition, microbiota. The effects of obesity also have to be detailed regarding the status of (7): insulin resistance, inflammation and oxidative stress.

Different mechanisms of obesity may be produced or monitored by biochemical substances. Even the intimate molecular mechanism of obesity may be analyzed by studying the associated biomarkers. These biomarkers may give information on the mechanism of obesity and by which obesity acts negatively in the body, potential of non-drug or drug interventions, monitoring of therapy effect. Unfortunately, there are no biomarkers for all mechanisms and some of the therapies do act without having a proper biomarker for monitoring.

The biomarkers described in obesity have a definite role in the mechanism of producing this disease, in the persistence of obesity status, in the mechanisms of action of obesity on insulin resistance, cardiovascular system, hepatobiliary system, etc. However, most of the analyses of obesity biomarkers do not put them in a definite category, but describe their presence and potential mechanism of intervention (6-11).

Genetic determinants of obesity may play a role beyond the main mechanism between intake and consumption of calories. A very recent large analysis of such factors was done by Zhu ZL et al (8). Some genetic markers, such as the "thrifty gene" hypothesis, were discussed more than a decade before (9), presuming that some individuals have a greater capacity to store fat, to be used in the time of famine. Levy et al. (7) consider that 40-70% of obesity status in adulthood could be linked to a genetic marker. This domain is far from being elucidated.

Socha et al. (10) consider that obesity could be a consequence of **programming in early childhood**. Breastfed children are definitely less frequently obese than those formula fed. The hypothesis is that the dense artificial feed and some definite amino-acids could program the newborn organism to develop more fat tissue (10). So, there could be a **metabolic programming** in the first 2 years of life for a late outcome. Which nutrients (probably different than those in the maternal milk) and which hormones and other biochemical products could contribute to this programming are questions under investigation (10).

The **environment** and **the socio-economic** status constitute those elements of culture described above by Virchow. At a moment of the culture evolution, obesity was considered a sign of beauty (see Rubens paintings). Later on, individuals belonging to a high social and economic status, dominant adult members of high societies, rarely were lean persons.

Lifestyle and **nutrition** also evolved in the direction of favoring obesity. It is true that exercise has been advocated for a long time, but this was rarely performed after youth– and obesity and T2DM develop exactly after the young age. Regarding nutrition, the accelerated lifestyle of the last half century has favored fast food, which is dense and with a lot of calories.

Microbiota of the gut probably plays a more important role in pathology than we believe (7).

The whole DNA composition of the microbiota in any moment is 100 times or greater than the whole DNA heritage of our body (11). Gut microbiota is implied in mechanisms of illness in neurology, rheumatology, obesity, T2DM or atherosclerosis (11). In the case of obesity and T2DM, some bacteria of the gut produce elements which increase insulin resistance (7). The hypothesis was raised that we could contribute to treat T2DM by manipulating this microbiota and its products or actions. For instance, bariatric surgery, among other actions, consistently modifies gut microbiota (7). Unfortunately, gut microbiota varies along different diets and, probably, different metabolic or endocrine conditions along the year and we cannot be sure what action a special microbiota has and for which period (11). However, it is certain that the microbiota of obese persons, as a population, is much less various than in the general population (7).

The discovery of **leptin** in 1994 was considered a cornerstone in the mechanism of obesity. Leptin is released by adipocytes and acts in the hypothalamus, drastically reducing appetite (9,12). The leptin level is much higher in breast-fed children than those formula fed. Leptin is influenced by catecholamine, reproductive hormones, glucocorticoids, cytokines, agonists of peroxisome proliferator-activated receptor-gamma and seems to be produced not only by adipose tissue but also by the brain, muscles and the stomach (9). Thus, its role seems to be much more complex than previously believed. No drug acting on appetite is based on a linkage with leptin action.

Adiponectin has strong anti-inflammatory and anti-atherosclerotic effects. The higher the concentration of adiponectin, the fewer complications of obesity seem to be produced. The correlation between adiponectin activity and the cardiovascular effects of obesity are under intense investigation (9, 10). As for leptin, no drug action today used in obese therapy is identified.

The **Free Fatty Acids** (FFA) theory of producing the increased resistance to insulin may be considered one of the milestones of the mechanisms contributing to the development of T2DM (9). For the T2DM associated with obesity, some cytokines released by the abdominal adipose tissue are involved. However, the "lean" T2DM also increases in prevalence and this condition does not have abdominal obesity. As an alternate mechanism, the increase in FFA, present almost always in T2DM could be responsible for increased insulin resistance. The uptake of FFA by the inactive skeletal muscles and also by the adipose tissue is decreased in obese patients. On the other hand, the increased concentration of FFA found in obesity drastically increases the insulin resistance of the liver and also of the skeletal muscle (7, 9 ,10). The decrease in FFA by drugs is used in the therapy of T2DM, but this is not a cornerstone of the treatment of this disease.

Cytokines produced by the adipose tissue are thought to play a major role in the mechanisms contributing to the development of T2DM (6, 7, 9). They also do harm to the cardiovascular system. Their action is so varied and complex that the abdominal fatty tissue, which produces them, was considered an endocrine organ.

One of the most studied is **TNF-alpha**. Neutralizing it in experimental models clearly reduced insulin resistance (9). The mechanism of its action is at the level of tyrosine kinase activity at the insulin receptor level. Another important action of TNF-alpha is to stimulate **interleukin 6 (IL-6)**, which, in turn, increases the inflammatory marker **C Reactive Protein (CRP**). Inflammation is another common and constant feature of obesity and T2DM and its magnitude correlates with cardiovascular damage and prognosis. Some consider that monitoring the high sensitivity CRP (**hs-CRP**) is as important as monitoring LDL-cholesterol for treatment efficacy. Among drugs which decrease hs-CRP are cited Angiotensin Converting Enzyme Inhibitors

(ACEI) and statins. These are important therapies for cardiovascular primary and secondary prevention in the ambient of T2DM and/or obesity.

Other substances such as **Plasminogen Activator Inhibitor (PAI-1), Resistin, Adipsin** or **Fibronectin** are increased in obesity (9). Each plays a particular role in the mechanisms involved in cardiovascular harm produced by obesity and, later on, by T2DM. Some of them, like PAI-1, have therapeutic consequences for antithrombotic therapy. The magnitude of the cytokines and other substances released by abdominal fat define the abdominal adipose tissue as an endocrine organ.

The **Oxidative Stress** status in obesity is another demonstrated condition which influences the impact of obesity on the cardiovascular system and insulin resistance (7, 13). To date, no validated biomarkers to measure this status are used in clinical practice, although clinical research is developed in this field (7, 14).

Measurement of **Insulin Resistance** may be accomplished by simpler or more sophisticated methods. All of them are based on the correlation between insulin concentration and glucose level. One of these methods is the **Homeostatic Model Assessment (HOMA)**, which may be configured to measure homeostatic resistance (HOMA-R) or homeostatic sensitivity (HOMA-S) (7, 9). This test gives values for a basal state, assuming that this is stable for a particular patient in a given interval. More advanced methods, like **Quantitative Insulin Sensitivity Check Index (QUICKI),** give values in a dynamic manner. Both categories of tests are dependent on the accuracy of measure insulin concentration itself. The value of each method of measurement of insulin is still under evaluation and discussion (9). The methods of measuring insulin resistance may be used for epidemiologic and even clinical studies, but to date, they have not had a great impact on practice.

Most of the biomarkers described are used for research of the mechanisms of obesity and type 2 diabetes mellitus. Few of them are used for monitoring the therapy. However, in recent years, pharmacological therapy in both illnesses (obesity and T2DM) has been developing remarkably (6, 15-17). Therefore, we will briefly describe drugs used in therapy and, when appropriate, biochemical markers of monitoring will be mentioned.

Drugs in Obesity

Orlistat is one of the oldest drugs used for treating obesity. It is a pancreatic lipase inhibitor and acts by decreasing the intestinal absorption of triglycerides.

Lorcaserin targets the serotonin-2 receptors in the brain. It reduces the sensation of hunger and decreases food intake.

Liraglutide is a strong and quick reducing weight drug. It is a glucagon-like peptide-1 receptor (GPL-1) agonist and acts mainly as a glucose lowering agent. However, it also consistently lowers weight. It is one of the first glucose-lowering drugs (except metformin) which reduced cardiovascular major events and cardiovascular mortality acting mainly on glucose levels (6, 15-17).

Lixisenatide is also a GPL-1 receptor agonist recently introduced in the therapy of obesity and T2DM as well (17). It has a good action on weight reduction and, at the same time, it is a potent reducer of glycemia in comparison even with rapid acting insulin.

Phentermine and topiramide extended-release (PHEN/TPM ER) is a powerful combination of drugs either reducing body weight r glycemia (6, 18). These drugs decrease appetite, the first acting on epinephrine in the hypothalamus, the latter acting on the gamma-aminobutyric acid (GABA) receptors - the chief inhibitory compound in the mature vertebrate central

nervous system. The combination also improves glycemic control, lowers blood pressure, and acts favorably on dyslipidemia, possibly in part by the action on obesity.

Naltrexone/ bupropion combination reduces appetite by complex central nervous system actions. Besides weight loss, which is important, the combination also consistently reduces HbA1C and acts favorably on dyslipidemia (6).

Various **surgical interventions** for weight loss may act not only by reducing absorption of food but also acting on some hormonal mechanisms in the duodenum and first part of the jejunum which are not totally understood and are under important investigation (6, 15, 17).

Perspectives

Obesity is an epidemic of recent decades, as it is the illness most linked to obesity: Type 2 Diabetes Mellitus. Obesity is an endocrine disorder. Biomarkers released by abdominal obesity are numerous and their action undoubtedly plays a role in the cardiovascular risk linked to this disease. However, their exact role is not always well-identified, neither is their evolution in respect with various therapies of obesity. Under these circumstances, the determination of the biomarkers present in obesity are a good way to understand the mechanisms of the disease, of its cardiovascular complications, and of the mechanisms of therapy.

Conflict of interest

None to declare.

Abbreviations

ACEI = Angiotensin Converting Enzyme Inhibitors
CRP = C reactive protein
DPP-4 inhibitors = Inhibitors of dipeptidyl peptidase 4
FFA = Free Fatty Acids
GABA = gamma-aminobutyric acid
GPL-1 = glucagon-like peptide-1 receptor
HbA1C = hemoglobin A1 C
HOMA = Homeostatic Model Assessment
HOMA-R = Homeostatic Model Assessment Resistance
HOMA-S = Homeostatic Model Assessment Sensitivity
hsCRP = high sensitivity C reactive protein
IL 6 = interleukin 6
LDL = low density lipoprotein
QUICKI = Quantitative Insulin Sensitivity Check Index
PAI-1 = Plasminogen Activator Inhibitor 1
PHEN/TPM ER = Phentermine and topiramide extended-release
T2DM = type 2 diabetes mellitus
TNF-alpha = tumor necrosis factor alpha

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