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INFLUENCE OF SIGNALING FACTORS AND CYTOKINES ON THE DEVELOPMENT OF ADIPOSE TISSUE, OBESITY AND DIABETES

Abstract: The process of energy consumption is ongoing, while energy recovery through food intake occurs only occasionally. Therefore, during evolution, it was necessary to form a system that would create energy reserves, and preserve them for periods between food intake–adipose tissue. The development of adipose tissue is affected by numerous signaling and hormonal factors, which in turn determine the distribution of adipose tissue into subcutaneous and visceral fat. Besides its indisputable role in energy homeostasis, adipose tissue is an important endocrine and paracrine organ that releases many hormones and cytokines, and crucially affectsall metabolic and immunological processes in the body. As such, primarily visceral adipose tissue synthesizes significant amounts of adipocytokines: leptin, adiponectin, tumor necrosis factor-α, interleukin-6 and many others. Fat can actually be a crucial alarm system that triggers innate immunity and acute phase inflammation. Chronic inflammation is the hallmark of the metabolic syndrome, and inflammatory signals originate mainly from visceral adipose tissue. Therefore, excess adipose tissue can easily be linked to the emergence of numerous metabolic disorders and the development of diabetes, type 2 as well as type 1.

Key words: adipose tissue development, visceral adipose tissue, adipocytokines, metabolic syndrome, hybrid diabetes

WHITE ADIPOSE TISSUE

White adipose tissue serves as the main source of energyfollowing theperiod of infancy, and into lateryears (1). It is distributed throughout the body as visceral (VAT)

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and subcutaneous (SAT). Visceral ("abdominal" or "central") adipose tissue is localized around internal organs, the mesenterium and omentum, and accounts for about 20% of total body fat. Subcutaneous adipose tissue accounts for about 80% and is predominantly distributed in two main regions, the abdominal and gluteofemoral (2). Between these two forms of adipose tissue exist significant differences in histological structure,adipocyte endocrine profile, lipolytic activity, as well as responsiveness to insulin and other hormones. SAT is the physiological sitefor deposition of excess fat, where an excess of glycerol and free fatty acids are easily deposited in the form of triglycerides in otherwise inert adipocytes. VAT is the metabolically very active part of the adipose tissue, which in surplus is crucial in establishing a number of metabolic disorders, including diabetes. There are two basic types of adipocytes in the adipose tissue: small - newly synthesized,and large- mature cells. The composition of adipose tissue depends on the balance between de novo synthesis of small adipocytes and apoptosis of large cells. Small adipocytes secrete insulin sensitizing moleculessuch as adiponectin, they are much more sensitive to insulin and have a greaert ability to take on free fatty acids and triglycerides, thus preventing their deposition in nonadipocyte tissues(3). Large adipocytes are dysfunctional, resistant to the antilipolytic effects of insulin and actively secrete numerous adipocytokines that cause a variety of pathological conditions, notably the metabolic syndrome. Insulin resistance of large adipocytes prevents deposition of triglycerides while favouring lipid oxidation, thereby creating highly toxic products such as lipid peroxides.

Unlike SAT, which is mostly composed of small adipocytes, VAT contains predominantly large adipocytes, macrophages and other inflammatory cells. Visceral adipose tissue is much better innervated and vascularized. Unlike SAT, which secretes into the systemic circulation, VMT due to its anatomical position drains directly into the portal circulation. This allows direct impact of the released free fatty acids (FFA) and adipocytokines on the liver, this being the way interleukin-6 (IL-6) plays a stimulating role in the production of C-reactive protein (CRP) in the liver (4).

The largest energy reserves in the body are in the form of triglycerides deposited in adipose tissue. Under the action of lipoprotein lipase (LPL) in the endothelium of capillaries triglyceridesfrom chylomicrons and very low density lipoproteins (VLDL) are hydrolyzed to FFA and glycerol, which are then deposited in fatty cells, where they will be reesterified into triglycerides. When there is a need for energy, the triglycerides deposited in adipocytes, under the influence of hormone sensitive lipase (HSL),are broken down again to glycerol and FFA. HSL is activated by means of AMP-activated protein kinases (AMPK). AMPK are activated by catecholamines, while glucocorticoids, thyroid hormones and growth hormone have an inhibitory role. Conversely, AMPK inhibit insulin and, indirectly, IGF-1, adenosine and prostaglandins. The increased release of FFA into the circulation is consequently followed by an increase insugar and triglyceride synthesis in the liver, as well as a decrease in insulin clearance, which favors the development of insulin resistance.

DEVELOPMENT OF ADIPOSE TISSUE

Adipose tissue is composed of three groups of cells: stem cells, preadipocytes, and mature unilocular adipocytes with deposited triglycerides. Preadipocytes are morphologically and biochemically almost indistinguishable from fibroblasts, but their differentiation toward adipocytes occurs under certain physiological conditions during life. Preadipocytes can be unlimited in number,however, this depends on the number and activity of stem cells, from which osteoblasts, hondroblastsand mioblasts can also develop. In which direction will differentiation of stem cells turn - towards adipocytes or nonadipocytic lines, will depend on a range of hormonal, cytokine and signal influences.

Adipocytes normally develop from precursor mesenchymal cells under the influence of various hormonal and signaling mechanisms (5). What path will differentiation of mesenchymal stem cells take will depend on many hormones: testosterone will inhibit the development of adipose tissue and favor the emergence of muscle tissue. Differentiation of stem cells will also depend on different signaling, transformational factors such as Notch1c (shifts osteoblast differentiation toward adipocytes) or RhoGTPase (potentiates differentiation towards miogenesis).

In the formation of adipose tissue, angiogenesis plays an important role - adipogenesis and neovascularization are intrinsically linked processes. Without angiogenesis, differentiation of preadipocytes will not take place. Therefore preadipocytes strongly secrete VEGF (vascular endothelial growth factor) and TGF-β (transforming growth factor beta) and directly stimulate angiogenesis. This fact explains the link between cancer and obesity: since tumor growth is deeply dependent on angiogenesis, it is possible that obesity through excessive synthesis of VEGF and TGF-β affects tumor formation and progression.

Once created, preadipocytes undergo proliferation and differentiation.

Stimulation of inert adipocytes takes place under the influence of insulin, glucocorticoids and factors that increase cAMP levels, thus becoming powerful adipogenic stimuli. After clonal expansion of preadipocytes, their terminal differentiation is influenced by a nuclear receptor which functions as a transformational factor and is referred to as PPARγ (peroxisome gamma proliferation activating receptor). The activity of PPARγ is infuenced by natural (SMK) and synthetic ligands (thiazolidinediones) causing its activation and allowing terminal differentiation of adipocytes. Theglucocorticoid receptors could also serve as a differentiating factor.

Undeniable phenotypic similarity of Cushing's syndrome and patients with simple central obesity explains the essential connection between an excess in glucocorticoids and the occurrence of obesity. Glucocorticoid receptors play a central role in the clonal expansion and terminal differentiation of adipocytes, but also in the distribution of adipose tissue and its metabolic activity. The largest number of glucocorticoid receptors is revealed in VAT (6). Decisive influence on the activity of glucocorticoids in adipose tissue belongs to the enzyme 11β-hydroxy steroid dehydrogenase (11β-HSD),

which regulates the translation of the active form of glucocorticoids (cortisol) into the inactive form (cortisone) and vice versa (7). While type 2 of this enzyme is predominantly expressed in the kidney where it has a role in the homeostasis of sodium and regulation of blood pressure, type 1 is active in adipose tissue and the liver. Although this is a "two-way" enzyme (transforms active into inactive forms and vice versa) in adipocytes and the liver it predominantly activates cortisone to cortisol! This has important metabolic consequences - stimulates gluconeogenesis in the liver, while promoting adipocyte expansion and differentiation. It seemsrational to conclude that central obesity is a possible consequence of increased subcutaneous expression of type 1 11β-HSD in adipocytes.

The first adipocytes are formed around the 15th week of gestation, followed by an increase in number and volume, predominantly under the influence of fetal insulin and placental lactogen (8). In the term infant,body fat makes up about 12% of total body weight –maturation of adipose tissue depends more onthe duration of pregnancy and much less on the mothers nutrition. Further increase in adipose tissue does not ideally follow body growth - there is a sudden increase in adipose tissue with a peak in the sixth month of life –at this point in time fat makes up 25% of body weight. Furthermore there is a tendency to reduce the amount of fatty tissue until puberty (9). Then there is a second round of fat tissue growth - much more intense in females (due to a lesser growth of muscle tissue) than in boys. In late adolescence, fat reserves make up 15-18% of the body mass of males and 25-28% of females. In the same period, total body weight increases only 10-15%, suggesting that the increase in weight during female puberty is a result of increase in quantity of adipose tissue and reduction in "lean body mass".

In the first cycle (sixth month of life) an increasein fat is mainly due to the increasing volume of adipocytes - *hypertrophy*. "Obesity" in this period is almost a physiological occurrence (as much as 60% of all children) and prepares the infant for the risk of insufficient or inadequate diet after stopping breastfeeding. Average size of adipocytesin children at the end of the first year of life does not differ significantly from the size of adipocytes in non-obese adults - adipocyte size, therefore, remains unchanged during childhood. The growth of adipose tissue in puberty is characterised by an increase in the number of adipocytes - *hyperplasia*. Thus, childhood obesity is initially the result of an increase in the volume of adipocytes ("hypertrophic obesity"), later, when adipocytes reach a critical volume (maximum capacity of deposit) adipocytes tend to multiply - "hyperplastic obesity" (10).

ENDOCRINE ACTIVITY OF ADIPOSE TISSUE

Adipose tissue is not simply an organ meant for fat storage - it is actually an active endocrine organ and part of the innate immune system that affects many physiological and pathological mechanisms, such as glucose homeostasis, inflammation,

angiogenesis, cell proliferation and differentiation (11). This endocrine role primarily belongs to adipocytes, but also to activated macrophages which infiltrate adipose tissue - a significant source of proinflammatory cytokines. Adipocytes express low levels of monocyte chemotactic protein 1 (MCP-1). With the occurrence of obesity and the accumulation of MCP-1, macrophage attraction and accumulation occur, they usually surround dead adipocytes forming a “crown-like structure”. At the beginning of the phylogenetic process, it was believed that the presence of macrophages in adipose tissue was necessary for defense against infection or injury, however, it is known today that macrophages actually have a role in removing necrotic adipocytes (12). If adipocyte necrosis is the initial event leading to the macrophage infiltration, it is likely that hypoxia is the leading cause of adipocyte necrosis. With obesity and progressive enlargement of adipocytes, their blood supply becomes reduced, hypoxia and necrosis ensue, followed by macrophage infiltration and onset of inflammation.

Enlargement of adipocytes and accumulation of triglycerides can be benign phenomena as they will prevent the accumulation of fat in the liver, muscles and other ectopic tissues. Inflammation will occur when the expansion of adipocytes is limited, either due to defective development of adipose tissue (PPAR-γ disorder), or any disturbance in the synthesis of fat, where free fatty acids will accumulate in the liver and muscles, which will be accompanied by insulin resistance. PPAR-γ agonists (thiazolidinediones) promote adipogenesis, increase the production of adiponectin and have a clear antinflamatory effect on adipose tissue resident macrophages, thus reducing insulin resistance.

Tumor necrosis factor- α

The pricipal cytokine of adipose tissue is tumor necrosis factor-α (TNF-α). Although TNF-α is secreted mainly by macrophages which infiltrate adipose tissue, a certain amount of mRNA for this cytokine is detected also in adipocytes - the more so if obesity is more pronounced (11). Circulating levels of TNF-α increase with obesity and correlate with the degree of insulin resistance.

TNF-α primarily reduces the activity of insulin receptors: by activatingits TNF-R2 receptors it reduces phosphorilation of tyrosine and induces insulin resistance. By stimulating its TNF-R1 receptor via nuclear factor kappa B (NF-kB), the activity of PPAR-γ is inhibited, which not only stops the differentiation of preadipocytes to adipocytes, but also causes reversal of mature adipocytes to less differentiated forms. The larger the adipocyte, the more TNF-α it produces, which in turn limits the size of adipocytes and induces apoptosis.

In this way - by inducing apoptosis of preadipocytes, blocking their differentiation and promoting regression of mature adipocytes to less differentiated forms, TNF-α actually allows deposition of fat in tissues other than the adipose tissue, thus promot-

ing insulin resistance and occurrence of the metabolic syndrome. Moreover, TNF-α induces lipolysis and increases circulating levels of FFA, in which way it encourages hepatic lipogenesis and further exacerbates insulin resistance.

Finally –the final constitution ofmarked insulin resistance in obesity in the presence of increased concentrations of TNF-α is a consequence of inflammation resulting from a decrease inproduction of antiinflammatory adiponectin and increased activation of NF-kB.

Interleukin-6

Interleukin-6 (IL-6), the second most important adipose tissue cytokine, monitors the behavior of TNF-α and leptin, thus in obesity its secretion is also increased. Unlike TNF-α which is mostly secreted by macrophages, IL-6 is synthesized predominantly by mature adipocytes. About 30% of the total serum IL-6 originates from adipose tissue. Circulating IL-6 is the most important factor that controls the synthesis of acute phase reactants. In addition to the synthesis of CRP, IL-6 controls the production of fibrinogen, causes a rise in the number and activity of platelets, as well as the expression of adhesion molecules on endothelial cells thereby increasing the overall risk for thrombus formation. In addition to effects on insulin resistance similar to TNF-α-, IL-6 also induces lipid abnormalities - by increasing the activity of HSL it mobilizes lipids from adipocytes and increases concentrations of FFA, which in conjunction with increased blood coagulability leads to the develoment of atherosclerosis. In the CNS it acts almost identically to leptin binding to the same anorexigenic neurons.

Insulin and glucocorticoids, as well as TNF-α increase the production of IL-6. Therefore, in the setting of obesity and pronounced hyperinsulinemia, an increase in circulating concentrations of these cytokines will occur. The development of inflammation and insulin resistance is aided by the inhibitory effect of TNF-α on the expression of adiponectin genes (13). Elevated triglycerides and FFA are potent inducers of TNF-αsynthesis.

Leptin

Leptin (from the Greek “Leptos”, thin) is a peptide of subcutaneous adipose tissue with 167 amino acids encoded by “OB” genes on the long arm of the seventh chromosome. Its secretion is proportional to the size of adipose tissue. The main role of this lipostatic hormone is to reduce appetite and increase energy consumption, thus by means of the negative feedback mechanism “communicate” with higher nerve centers and maintain body weight unaltered. Leptin, therefore, informs the hypothalamus about the size of energy depotsin peripheral tissues, binding to its receptors, class 1 cytokine receptors, at the level of the hematoencephalic barrier, and later in the nucleus

arcuatus. OBR genes, which encode theactivity of leptin receptors are located on the short arm of the 1stchromosome. Leptin secretion is pulsative, stimulating anorexigenic and inhibiting orexigenic neurons (14). In peripheral tissues, leptin shows a strong inhibitory effect on ghrelin orexigenic molecule - a decrease in ghrelin is not a result of direct action of leptin, but represents a physiological adaptation to conditions of positive energy balance associated with obesity.

The quantity of leptin is strongly dependent on the amount of white adipose tissue and triglyceride content, as well as acute changes in caloric intake (starvation or overeating). During starvationthe "level of adiposity" is reduced, as well as the concentration of leptin in the blood, which stimulates appetite and reduces energy consumption by preventing further loss of weight - within a couple of hours of fasting leptin concentrations decline rapidly in the blood. Conversely, increased food intake by means of "increasing adiposity" increases leptin concentrations in the blood which reduces appetite and increases energy consumption, thereby preventing further obesity (negative feedback). The longer the period that elapses from the last meal, the greater the speed and intensity of the drop in serum leptin concentrations -this reduction actually plays a role in the transition from a state of satiety to the feeling of hunger (15). In other words, low leptin is the signal for hunger,while high leptin is a sign for satiety .

At physiological concentrations, leptin easily transverses the hematoencephalic barrier and binds to anorexigenic receptors in the hypothalamus, above all those in proopiomelanocortine and cocaine-amphetamine neurons while inhibiting centers that stimulate appetite - one in neuropeptide Y and Agouti related peptide. Leptin also increases energy consumption in the periphery: through activation of corticotropin-ereleasing hormone (CRH) and via sympathetic nervous system-induced lipolysis, but also through up regulation of uncoupling protein 3 (UCP3) in charge of regulating the level of energy consumption in the mitochondria of peripheral tissues. Leptin, therefore, effectively reduces both appetite and body weight.

However, in obesity these effects of leptin are absent and resistance to leptin develops. Such resistance can be caused by a defect in the leptin receptor as well as disrupted transport of leptin through the hematoencephalic barrier. With constant food intake, due to reduced sensitivity of hypothalamic satiety receptors ("down" regulation), there is a constant and progressive increasein the production of leptin, that is resistance to leptin develops (16). In addition, leptin concentrations in cerebrospinal fluid compared to serum are much lower in the obese than in the lean. This is due to the fact that in obesity exists an overproduction of CRP by adipocytes, this CRP binds to leptin thereby inhibiting its transport across the hematoencephalic barrier to the satiety center. In obesity of anyetiology, existing leptin resistance prevents stimulation of proopiomelanocortine and cocaine-amphetamine neurons (and hence the secretion of those peptides that reduce appetite such as proopiomelanocortin, CRF and α-MSH) permitting dominance of the orexigenic hypothalamic influences, primarily neuropeptide Y (17).

A very special relationship exists between the two main "obesity hormones" leptin and insulin, in peripheral tissues, and at the level of the CNS. Insulin stimulates leptin production, probably via its trophic effect on adipocytes. In physiological conditions, leptin inhibits insulin secretion (and insulin mediated peripheral uptake of glucose, glycogen synthesis and lipogenesis), however, it can mediate an independent increasein uptake of glucose by skeletal muscle, brown adipose tissue, brain and heart (18). These effects are absent in cases of leptin resistance - functionally inactive hyperleptinemia that exists in obesity. Unlike insulin, leptin in skeletal muscle, increases the degree of oxidation of FFA. It is estimated that here leptin can attenuate 50% of the antioxidant and lipogenetic effect of insulin. In summary, insulin is an anabolic and attempts to mobilize energy (glucose, free fatty acid) in muscles – leptin is a catabolic, mobilizes triglycerides and oxidizes free fatty acids increasing energy consumption.

Leptin also shows dominanat effects on the processes of angiogenesis, proliferation and migration of vascular smooth muscle cells, platelet agregation and arterial thrombosis.

TNF-α and IL-6 increase expression of leptin genes and levels of circulating leptin.

Adiponectin

Adiponectin is a cytokine produced also by adipocytes by means of unique regulatory principle: circulating adiponectin levels are inversely correlated with body fat and proportional to the degree of insulin sensitivity. In contrast to leptin, in obesity production of adiponectin declines due to a reduction in adiponectin gene expression, but also due to hyperinsulinemia, given the fact that insulin inhibits the release of adiponectin.

Its receptors are located in muscles and the liver. In the liver, by potentiating the inhibitory effects of insulin on gluconeogenesis, it improves insulin sensitivity, and thus the peripheral uptake of glucose. In muscles it has lipolytic actions - through AMP-activated protein kinases it stimulates β-oxidation of fatty acids which reduces the amount of triglycerides primarily in skeletal muscles thereby reducing insulin resistance (19). By Increasing the expression of PPAR-γ, adiponectin improves insulin sensitivity by increasing energy consumption. Similar to PPAR-γ agonists, adiponectin improves metabolic profile allowing expansion of adipose tissue,thus reducing the distinct infiltration of adipose tissue by macrophages. The influence of the thiazolidinediones on insulin sensitivity is significantly reduced in the absence of adiponectin suggesting a key role of adiponectin in reducing lipotoxicity and inflammation associated with obesity (20). Its decreased activity is a possible etiologic factor of the metabolic syndrome.

This important adipocyte hormone has a clear antiinflammatory role, since it is a powerful inhibitor of TNF-α production and stimulates IL-10 synthesis. Adiponectin also inhibits the activity of NF-kB and IL-2 stimulated NK cells. It is therefore logical that levels of adiponectin in diabetes and coronary artery disease are low - that is, in syndromes where inflammation may play a role in pathogenesis. Statistically proven peak incidence of diabetes in puberty can be explained by the fact that sexual maturation is accompanied by a reduction in adiponectin synthesis, being more common in boys due to the dominant inhibitory effect of testosterone (21). Low levels of adiponectin in prediabetes have a high predictive value, allowing the maintenance of inflammation of "low degree" and hint the onset of overt disease. The antidiabetic effect of adiponectin is represented by its effects on increasing insulin sensitivity, increasing FFA oxidation and reducting gluconeogenesis.

Apart for an antiinflammatory, adiponectin also possesses a vasoprotective and antiatherogenic effect via inhibition of expression of adhesion molecules, proliferation of blood vessel smooth muscle cells and transformation of macrophages into foam cells (22).

An increase in activity of transcription factor PPARγ, increasesserum levels of adiponectin. Oxidative stress, sympathetic nervous system, TNF-α and IL-6 suppress adiponectin expression.

Plasminogen activator inhibitor-1

Global fibrinolytic activity in obesity is often reduced. Plasminogen activator inhibitor-1 (PAI-1) is increased which reduces translation of plasminogen to plasmin. Although increased synthesis of PAI-1 in the liver may be due to permanent hyperinsulinemia, the largest amounts of PAI-1 are secreted by adipocytes under TNF-α stimulation. Additionally, there exists endothelial dysfunction – characterized by increased activity of endothelin-1, a marker of endothelial dysfunction and injury. Since endothelin-1 is a potent vasoconstrictive peptide, its increase is an early sign of abnormal vascular reactivity, which with subsequent dysfunction and dyslipidemia forms the basis for development of atherosclerosis. Thus, in obesity there is increased production of PAI-1 (23), this increase in production can serve as an excellent predictor of the development of type 2 diabetes.

Renin-angiotensin system

Mature adipocytes express all components of the renin-angiotensin system, including renin, angiotensinogen, converting enzyme - even the type 1 angiotensin receptor! Transformation of preadipocytes to mature adipocytesis accompanied by a rise in angiotensinogen expression and can be considered a late marker of adipocyte differ-

entiation. Angiotensinogen gene expression increases with obesity which is important in the regulation of blood flow through adipose tissue as well as for normal growth and adipocyte differentiation (24).

IMPACT OF OBESITY ON DIABETES ONSET

When adipocytes are filled with triglycerides, leptin secretion increases in an attempt to prevent the deposition of lipids in unprepared nonadiposetissues: skeletal muscle, liver, myocardium or beta cells. In obesity, when there is either leptin deficiency or resistance, functional lack of leptin will lead to generalized steatosis, lipotoxicity and lipoapoptosis. Lipotoxicity of beta cells, skeletal muscle or myocardium leads to type 2 diabetes, cardiomyopathy and insulin resistance, that is,to the greatest global problem of modern civilization - the metabolic syndrome (25)! After excessive accumulation of fat in nonadipose tissues, free fatty acids via increased production of nitric oxide cause apoptosis of myocardial or beta cells- hence an important role in the prevention of this syndrome belongs to restrictive diet and certain medications (thiazolidinediones).

Leptin leads to the reduction of expression of CD4+CD25+ cells - the so-called "regulatory T cells", which develop under the influence of IL-2 and transformational growth factor β (TGFβ), which are known to inhibit the immune response (26). In obesity due to overproduction of leptin and fall in activity of T regulatory cells, activation of Th1 response ensues, accompanied by the accumulation of macrophages in adipose tissue and increased production of interferon-γ (IFN-γ), IL-6 and TNF-α. The accumulation of these Th1 cytokines through a mechanism of oxidative stress and apoptosis may directly damage beta cells (TNF-ά) or modulate beta cell proliferation (IFN-γ). It has been proven that dieting and loss of body weight lowers leptin levels, which in turn reduces levels of IFN-γ. Inversely, obesity is accompanied not only by an increase in the level of IFN-γ but also an increase in the titer of antibodies to glutaminic acid decarboxylase (GAD) specific for type 1 diabetes.

There is no doubt that an increase in body fat is followed by mobilisation of macrophages and activation of Th1cytokine path and constitution of inflammation - inflammation of the "low degree" is hallmark of overnutrition and obesity (27)! It is likely that the two main types of diabetes occur according to the pathogenetic model of inflammation. In type 1,there exists a chronic inflammation within the pancreatic islets accompanied by autoimmune antibodies detectable in the periphery, whereas in type 2 diabetes we have a true model of systemic inflammation with acute phase reactants of inflammation in the circulation. Reliable markers of disease onset will include an increase in CRP, however determination of fibrinogen, plasminogen, PAI-1 and ceruloplasmin also has predictive significance. There is a strict correlation between CRP and BMI - body mass index is actually the best predictor of CRP levels in children. The

fact that there is also a high correlation between CRP levels and insulinemia during starvationsuggests not only a predictive, but also a causal relationship between CRP and insulin resistance.

The first evidence that systemic inflammation is the basis of diabetes datesfrom more than 130 years ago- Professor Ebsteins attempts to reduce glycosuria with high doses of aspirin were successful! Salicylates inhibit the activity of molecules that play a key role in the regulation of inflammation, immune response and apoptosis –transcription factor NF-kappaB. This factor is activated by diverse stimuli –from the "toll like" receptors (important in the pathogenesis of diabetes type 1) to free radicals and cytokines (important in the pathogenesis of both type 2 diabetes and type 1). Belongs to the group of ''fast acting" transcription factors which for their actions do not require the synthesis of new proteins, but in an effort to protect cells from harmful stimuli can directly activate several genes - a cytokine, chemokine, apoptotic, adhesion. Aberrant expression and activation of NF-kappaB may be responsible for the generation of systemic inflammation and the development of a range of autoimmune diseases - including diabetes type 1 (27). Also, by increasing the activity of serum-kinase, this pathological expression of NF-kB leads to increased phosphorilaion of serin and reduced phosphorilation of tyrosine which in turn inhibits the enzyme tyrosine-kinase which further reduces activity of insulin receptors and promotes insulin resistance-which forms the basis for development of type 2 diabetes.

In other words, obesity through pathological activation of NF-κB can be responsible for both the destruction of beta cells and development of insulin resistance, which confirms the link between the epidemiology of obesity in children and the youth and development of a new type of diabetes: both types 1 and 2 – ''double'' or ''hybrid'' (28).

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