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UNIVERZITA KARLOVA PRAHA

LÉKAŘSKÁ FAKULTA V PLZNI

HORMONES AS PREDICTIVE FACTORS FOR ONCOLOGY COMPLICATION OF METABOLIC SYNDROME

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INTRODUCTION

Metabolic syndrome is a major atherogenic syndrome in our population. Its prevalence has been significantly increasing during the last decades. It is currently estimated to be approximately 25% - 43% in developed western countries. [1] The lower prevalence is found when NCEP ATP III criteria were used, the higher prevalence is seen when IDF criteria were used as the incidence rate may vary according to the criteria for metabolic syndrome definition used. The latest definition is based on the consensus among several medical societies from 2009. [2]

It has been known for many years that this syndrome is very closely related to the accelerated atherosclerosis that leads to the increased cardiovascular morbidity and mortality. Patients with metabolic syndrome survive longer these days due to the successful treatment of the individual components of the metabolic syndrome. But due to the longer life expectancy these patients are in higher risk for other diseases, particularly cancer development. The association between diabetes mellitus and cancer was reported more than one hundred years ago.[3] Population studies have shown increased evidence of this association. One of the largest epidemiology prospective studies was conducted by L. Garfinkel for 12 years. Mortality ratios were computed in relation to overweight, cancer, and other diseases. The study included 750 000 persons. Each person was given a weight index. Death rates for overweight and underweight persons were compared with rates for persons of average weight. Men who were 40% or more overweight had a mortality ratio for cancer of 1.33. Women under similar conditions had the mortality ratio for cancer of 1.55. Overweight men had significantly higher mortality ratios for colorectal and prostate cancer; overweight women had much higher rates for cancer of the endometrium, gall bladder, and cervix; and also significantly higher rates for ovary and breast cancer.[4] Later, prospectively studied population of more than 900,000 U.S. adults (404,576 men and 495,477 women) who were free of cancer at enrollment in 1982, there were 57,145 deaths from cancer during 16 years of follow-up. We examined the relation in men and women between the body-mass index in 1982 and the risk of death from all cancers and from cancers at individual sites, while controlling for other risk factors in multivariate proportional-hazards models. [5]

TABLE 1:
CANCER RISK IN RELATIONSHIP TO OVERWEIGHT (GARFINKEL L 1985)

	Overweight			
	10 – 19 %	20 – 29 %	30 – 39 %	> 40 %
Male				
Colorectal ca	-	-	1.53	1.73
Prostate ca	-	1.37	1.33	1.29
Female				
Endometrial ca	1.36	1.85	2.30	5.42
Cervical ca	-	1.51	1.42	2.39
Ovarian ca	-	-	-	1.63
Gall bladder ca	1.59	1.74	1.80	3.58
Breast ca	-	-	-	1.53

It is certain that a crucial role played is by interactions between genetic factors and risk factors of external environment. Undoubtedly, insulin resistance, central obesity and impaired metabolism of adipose tissue play an important role in the pathogenesis of metabolic syndrome, and there are other pathogenetic theories. Obesity and its associated parameters that are related to the metabolic syndrome are considered as a risk factor for different cancer types development based on its molecular and metabolic effects of some biomarkers: insulin, insulin like growth factor 1 (IGF1), leptin and adiponectin. However the clear relationship between metabolic syndrome and its consequent metabolic derangements and cancer development still remains unexplained [6]

THE ROLE OF INDIVIDUAL BIOMARKERS IN CANCER DEVELOPMENT

Insulin

Basic characteristic

The human insulin protein is composed of 51 amino acids with molecular weight of 5.8 kDa. It is a dimer of an A-chain and a B chain, which are linked together by disulfide bonds. It is produced by beta cells of the pancreas. Insulin is generated by proteolytic cleavage from its precursor – proinsulin. Proinsulin splits into equimolar

amounts of insulin and C-peptide. Cleavage into insulin and C-peptide takes place in Golgi bodies and in immature secretory granules of beta cells. In response to stimulation, beta cells release insulin and C-peptide in equimolar quantity into the blood with small amounts of proinsulin. Insulin is secreted primarily in response to elevated blood concentrations of glucose. Insulin is secreted in two phases. In the early phase is released endogenous stock of ready insulin stored in beta cells secretory granules. This phase takes 10 minutes from the time of the stimulus. The late phase characterized by new insulin synthesis comes after 10 minutes and lasts for at least 60 minutes. Its main function is to regulate energy metabolism, stimulate cell proliferation and anabolic processes as a function of available energy. Effect of insulin on cells goes through a specific insulin receptor (IR). Insulin has also afinity, but lower, to the IGF1 receptor (IGF1R) and hybrid receptor composed of the IR and IGF1R subunit. IR is member of tyrosine kinase family. This type of the receptor phosphorylates tyrosine residues on the C-terminus of the receptor as well as tyrosine residues in the insulin receptor substrate 1 (IRS1) protein. [7] Two types of tissues are most strongly influenced by insulin, as far as the stimulation of glucose uptake is concerned: muscle cells (myocytes) and fat cells (adipocytes). Hypoglycemic effect of insulin is opposed by counter-regulatory hormones mainly glucagone, catecholamines, cortisol and growth hormone.

Insulin - mechanism on carcinogenesis

Several studies implicated hyperinsulinism, a condition that prevails prior to the onset of diabetes, part of metabolic syndrome, as candidate mediator in carcinogenesis. High levels of insulin decrease the production of IGF1 binding proteins and hence increase levels of free IGF1. Plasma insulin levels are elevated in the obese compared with the non-obese due to a need for higher insulin concentrations to carry out metabolic processes, regardless of the diabetic status.[8]

Insulin then can stimulate production of IGF1. Insulin and IGF1 may activate several signaling pathways that may result in risk of cancer development. Insulin may downregulate the production of insulin growth factor binding proteins, which bind IGF1 and inactivate it. Finally, there is a significant link between insulin/IGF1 and the ras activation pathway. The activation of ras, which is promoted by insulin, caused ras transforming effects to the plasma membrane. [9]

Further investigation of insulin's relationship with IGF1 system and insulin's role in carcinogenesis has been very challenging in order to reveal clearly the mechanism of carcinogenesis. The role of insulin and insulin resistance would be also an interesting subject in cancer prevention and treatment use. The signaling pathways influenced by IGF1 play the most important role in relationship insulin - IGF1 - cancer.

Insulin and cancer

Insulin and breast cancer.

One study suggests that type 2 diabetes might be associated with up to 10 – 20% excess risk for breast cancer.[10] In next study was tested the group of 1600 women with breast cancer. Breast cancer women had a higher BMI and had significantly higher plasma levels of IGF1 and C-peptide than controls. In one US study breast carcinoma risk was found to be statistically significantly increased when higher serum levels of C-peptide and IGF1 were observed. The results of this study confirm the fact that insulin resistance with elevated insulin and IGF1 levels may synergistically increase the risk of breast carcinoma. [11]

Insulin and endometrial cancer

Insulin resistance and hyperinsulinaemia represent a very significant risk factor for endometrial cancer development due to the high serum levels. Insulin acts directly within the endometrial tissue as mitogennic and anti-apoptotic growth factor. A large cohort study concluded that diabetes is associated with a modestly increased risk for endometrial cancer among women. In one prospective cohort of 93 676 postmenopausal women, insulin levels were positively associated with endometrial adenocarcinoma. [12] Obesity is also associated with high levels of insulin, a known mitogen. However, no prospective studies have directly assessed whether insulin is associated with endometrial cancer.

Insulin and ovarian cancer

Supporting the theory confirmed on other cancer types it is possible to claim, that elevated serum level of insulin will trigger the pathway cascade resulting in overproduction of IGF1. This factor together with elevated serum level of insulin may cause the higher risk for ovarian cancer development. Results from larger systematic

clinical studies investigating the impact of elevated serum levels of insulin on ovarian cancer have not been available yet.

Insulin and prostate cancer

The association between high glucose and reduced risk of prostate cancer has been already discussed for many years. Some authors reported a protective effect of diabetes on prostate cancer. However, the clinical implications of the protective effect are very controversial.

In one multiethnic study with the group of 86 000 men, diabetics had significantly lower risk of prostate cancer and significantly lower levels of PSA serum levels compared to the healthy individual. [13] Another study observed time since diabetes diagnosis significantly affected prostate cancer risk in a cohort of 72 000 men, with a positive association between cancer risk and being diagnosed with diabetes longer than 4 years prior to prostate cancer and an inverse association for men with diabetes less than 4 years. [14] This fits with the natural development of type 2 diabetes. Elevated glucose levels leads to an initial insulin rise and then eventually to insulin resistance. Diabetes mellitus develops consequently as the second step followed by lowering of insulin levels due to damaged beta-cells in pancreas. Since elevated insulin can be involved in growth of tumors, including prostate tumors, low insulin levels, may be protective for prostate cancer. [15] The prediction of protective effect of diabetes on prostate cancer remains unclear. Diabetic men have lower PSA levels than healthy men. However, a detection bias may exist in prostate cancer diagnostics and it may explain the decreased risk. Diabetic men may not reach the PSA threshold for biopsy and thus have delayed diagnosis. A nested case-control study from the Prostate Cancer Prevention Trial (PCPT) examined men who underwent biopsy determined prostate cancer presence or absence regardless of PSA and found decreased prostate cancer risk in diabetics. Additionally, the same study showed a 28% reduced high-grade prostate cancer risk in diabetics versus non-diabetics, which is unexpected if diabetic men truly suffered from delayed diagnosis. Thus, the meaningfulness of lower PSA in diabetic men remains unclear. [16]

Insulin and colorectal cancer

Insulin acts experimentally as growth/mitogenic factor for many cancer types. The closest relation was epidemiologically found for colorectal cancer. Elevated serum levels of insulin result in IGF1 increase. Recent studies support the theory that the synergic effect of elevated insulin and IGF1 play a crucial role in colorectal carcinogenesis. [17, 18]

Insulin and pancreatic cancer

Glucose metabolism disorders are described in 70% of patients with pancreatic cancer and significantly higher insulin resistance indexes are found compared to the healthy population. Pancreas is the insulin producer. Based on the currently performed clinical studies it is not clear whether elevated serum levels of insulin are the potential risk factors of pancreatic cancer development or if hyperinsulinemia followed by the diabetes mellitus development appears secondary as a result of pancreas destruction caused by tumor progression. [19]

Insulin and thyroid gland cancer

Patients with insulin resistance and elevated serum levels of insulin have a higher prevalence rate of thyroid gland nodules. 50% patients with well differentiated thyroid cancer were found to have insulin resistance. It was higher when compared with healthy population. When assuming obesity as an additional risk factor, insulin resistance was found in 75% cases in a thyroid cancer group with BMI over 25 kg.m-2. It is assumed that elevated serum levels and obesity are significant risk factors for thyroid cancer development. [20, 21]

Clinical use of insulin for routine practice

Insulin or C-peptide (more stable fragment of proinsulin) assessment has been currently used for routine diagnosis and monitoring of several diseases. Insulin and C-peptide are very important tests for diagnosis of diabetes mellitus - insulin deficiency state defined as a group of disorders characterized by hyperglycemia. Other disorders using this laboratory assessment include metabolic syndrome, polycystic ovary syndrome, thyrotoxicosis, Cushing syndrome and acromegaly.

IGF1

Basic characteristic

Insulin-like growth factor 1 (IGF1) is a peptide having a low molecular weight 7649 Da. It consists of a single chain of 70 amino acids. IGF1 participates on growth regulation, metabolism regulation, surviving and differentiation of the cells. They are regulated by growth hormone (GH). IGF1 is synthesized in the liver by the endothelial and Kupffer cells and the levels of IGF1 occur in other body fluids. Up to 95% of IGF circulates in the blood bound to specific binding proteins. [22] The function of the binding protein is to prolong the half-life of growth factors in the circulation. Half life of free IGF1 in the blood is about 10 minutes. The half life of IGF1 in complex with Insuline-like growth factor binding protein 3 (IGFBP3), which is the main bounding protein in serum, is about 12 hours. IGF1 levels are age dependent. The highest concentrations are found in children during puberty. In later years, their levels decline by approximately 10 percent every 10 years. The lowest levels are found in elderly. Their extrahepatic production and autocrine and paracrine mechanism has been already described. IGF1 is produced locally in many other tissues such as kidney, heart, lung, fat tissue and the tissues of various glands. IGF1 is also produced by chondroblasts, fibroblasts, and osteoclasts. [23] Effect of IGF1 on cell goes through a specific IGF1 receptor (IGF1R). IGF1 also binds to the insulin receptor (IR). IGF1 as the heterologous ligand has a lower affinity to the IR than to the IGF1R (approx.100 times less). Further, IGF1 can bind to a hybrid receptor composed of the IR and IGF1R subunit. IGF1R belongs to the group of tyrosine kinases receptors which phosphorylate the substrate on tyrosine residues. Intact and functional IGF1R is essential for cell surviving. [24]

IGF1 - mechanism on carcinogenesis

A connection between metabolic syndrome, elevated IGF1 levels and increased risk for cancer diseases has be explained bellow.

Some authors reported that increased levels of IGF1 are related to the Type 2 diabetes mellitus [25] and insulin resistance and hyperinsulinemia, and there is a positive correlation between insulin levels and IGF1 levels. [26] But some authors claim that increased risk for cancer diseases is found only when insulin levels are

elevated independently from IGF1 levels, as it has been already mentioned in a part dedicated to the insulin.

The higher levels of IGF1 are also demonstrated in the obese individuals compared with the non-obese population. This occurs via the upregulation of growth hormone receptors in the liver, which then bind with secreted growth hormone, the main stimulus for IGF1 production. [27]

Both symptoms, diabetes mellitus type 2 and obesity belong to the parameters of metabolic syndrome.

Based on knowledge of IGF1 effect on cells it is assumed that high IGF serum levels increase the risk for cancer development. They also stimulate proliferation and risk of malignant transformation. But high serum levels of IGFBP, particularly dominant serum binding protein IGFBP3, should decrease the risk and inhibit the cellular growth.

It is assumed that malignant transformation of the cells can occur independently from serum levels of IGF1 in case of presence of functional IGF1R. It is interesting that the potency of oncogenes to cause the malignant transformation is dependent on their ability of IGF1R phosphorylation. Intact tyrosine kinase domain is necessary for IGF1R functions – i.e. intensive anti-apoptotic and transformation effect.[28]

Summarization above mentioned data provides three fundamental conditions for signal transduction of IGF1 system into the cells: presence of functional receptors, intact tyrosine kinase (TK) domain and phosphorylation of TK domain. If the ability to receive signals remains, three extracellular risk factors start to play their role: local extrahepatal IGF1 production, autocrine and paracrine IGF1 function and increased IGF1 serum levels. Other two factors are intracellular and seem to be the most risky: signal pathway mutations and gene mutations. With more sophisticated knowledge about IGF1 system function, some hypotheses were evaluated in order to confirm the theory of the relationship between IGF1 and some malignant diseases development. First pilot prospective epidemiology studies did not confirm any relationship between elevated IGF1serum levels and cancers. But some recent extent clinical studies confirmed that high circulating IGF1 concentrations and low IGFBP3 serum levels are related to increase risk for cancer diseases. Negative correlation between IGFBP3 levels and risk of cancer diseases corresponds to protective role of IGFBP3 (i. e. high IGFBP3 concentration results in low free IGF1 levels). Some extent studies did not

clearly confirm relationship between IGF1, its binding proteins and tumors. Autocrine and paracrine role of IGF1 seems to be also important. Increased local production of IGF1 were found at different cancer diseases and there was usually the positive correlation with tumor progression. [29, 30] Regarding to the IGF1R expression, some theories appear that increased expression suggest a worse prognosis of cancer disease. But the prognostic role of IGF1R must be interpreted very carefully, due to the inconsistent clinical studies results. [31]

IGF1 and cancer

IGF1 and breast cancer

If we compare components of signaling pthway IGF1 in breast cancer patients and healthy women, we can see that many parts of the IGF1 axis shows changes in the circulation of patients with cancer and in the tumor tissue itself. Recently, many studies have been done, however, conclusions are somewhat controversial.

Some authors found a positive correlation between elevated levels of IGF1 and risk of breast cancer in premenopausal women. [32, 33] Cohort study conducted in Australia, which included 423 cases of breast cancer and 1901 controls showed that increased levels of IGF1 and IGFBP3 were positively associated with risk of breast cancer in patients older than 50 years but not in younger women [34] . The study The European Prospective Investigation into Cancer and Nutrition (EPIC), which analyzed data from 1081 patients with breast cancer and 2,098 healthy women, concluded that high levels of IGF1 and IGFBP3 are associated with a 40% increased risk of breast cancer in older women than 50 years but not in younger women [35].

Cohort study of people in different areas of Japan showed insignificant role IGF1 in the risk of breast cancer. Higher levels of IGFBP3 decreased risk in premenopausal women, postmenopausal women with no relation to the diagnosis was not confirmed [36]).

Chinese authors conducted a review of data from more than hundreds of studies. Based on this assessment concluded that elevated serum levels of IGF1 positively correlated with an increased risk of breast cancer [37].

American study with the group of women till 45 years of age examined the dependency levels of IGF1, IGFBP1, IGFBP3, GH and risk of breast cancer, but no statistically significant correlation were found [38].

Besides epidemiological data experimental evidence also affect the role of IGF1 system in the etiology of breast cancer. Activation IGF1R protects breast cancer cells from apoptosis. IGF1R gene is highly expressed in breast cancer cells. The exact biological significance is not clear yet. Low incidence IGFIR was found in benign lesions, and normal breast tissue compared to malignant tissue. However, high expression of IGF1R were found in the well and moderately differentiated breast carcinoma tissues, but much lower expression was found in poorly differentiated carcinomas. Some authors believe that high expression of IGF1R shows worse prognosis.

IGFIR expression was significantly higher in tumors with a genetic mutation suppressor gene BRCA1 (breast cancer 1) compared with tumors without the mutation [39, 40]. Levels of some components of the IGF1 signaling pathway, including IGF1R, were more frequently elevated in normal and tumor tissue in women with a strong family history of breast cancer than women without such history.

Expression of IGF1 induced genes significantly correlates with tumor aggressiveness. Tumor cells can be divided into two groups. In the group with higher expression of IGF1-induced genes, survival was significantly shorter than that in the group with lower expression [41]. ER (estrogen receptor) positive clones of cells had increased levels of IGF1R, ER negative clones had a reduced level. High levels of IGF1R lead to recurrence of breast cancer after radiation and can also contribute to the development of resistance to treatment with Herceptin (trastuzumab - monoclonal antibody against HER2 receptor) [42].

Blocking IGF1R leads to a reduction in tumor cell proliferation in breast cancer. Although early results from clinical studies that targeted the IGF1R showed some evidence of response, larger randomized studies have not shown clear clinical benefit of targeting this pathway in combination with conventional strategies. Despite of the long time of investigation is still necessary to develop biomarkers to clearer understanding of insulin receptor function. [43]

IGF1 and endometrial cancer

In endometrial cancer, a number of studies in which were measured circulating levels of IGF1. Unfortunately, results are contradictory.

Earlier studies have described higher levels of IGF1 in women with endometrial cancer after menopause. In a study with a relatively large set of 288 patients with endometrial cancer and 392 control women's ensemble was no correlation between cancer risk and concentrations of IGF1. [44] In some studies even found an inverse relationship IGF1 and the risk of endometrial cancer, which means that patients with the highest levels of IGF1 have the lowest risk and vice versa [45]. In accordance with a central role in IGF1R endometrial cancer were found significantly increased expression of IGF1R and IGF1R mRNA in endometrial carcinoma biopsies. [46]

IGF1 and ovarian cancer

Results of the studies of IGF1 serum levels and risk of ovarian cancer are not completely clear. Some authors claim that elevated levels of IGF1 increase the risk of ovarian cancer [47, 48], whereas higher levels of IGFBP3 slightly reduce this risk. A turning point seems to be the age of about 55 years. Rating IGF1 levels in women older than 55 years brought no change in risk depending on the levels of IGF1 and IGFBP3. On the other hand, several retrospective studies, concentrations of IGF1 levels in women with malignant ovarian cancer is lower than in the control group.

In in vitro experiments, the clones of tumor cell lines of ovarian cancer was demonstrated autocrine production of IGF1 and creation IGF1R. It was founded by the autocrine growth loop. RNA analysis revealed the presence of the IGF1 and IGF1R mRNA in 100% of freshly isolated tumor specimens. Blocking IGF1R leads to reduced cell proliferation of ovarian cancer. [49]

IGF1 and prostate cancer

Data suggest that IGF1 signaling system plays an important role in the set and progression of prostate cancer. High levels of circulating IGF1 increased risk of prostate cancer [50, 51], while higher concentrations reduce the risk of IGFBP3 (Chen B., 2009). Another study showed that circulating levels of IGF1 were significantly higher in patients with prostate cancer than in healthy men. [52] An interesting finding is that the ratio IGF1/PSA had better predictive value regarding the

prediction of risk of prostate cancer than the actual measurement of PSA or IGF1. [53]

It should also be noted that IGF1 levels were predictors of advanced stage prostate cancer, but not the early phase. [54]

On the other hand, some studies have failed to find a correlation between the concentration of IGF1 levels and cancer risk. Even studies on a large cohort of patients (727 cases of prostate cancer and 887 healthy controls) concluded that there is no clear link between the level of IGF1 and prostate cancer. [55]

Studies on the mechanism of prostate cancer point to an important role of autocrine production of IGF1. Prostate cancer induced by high doses of testosterone in rats was supported by increased autocrine production of IGF1. Study 54 biopsies of prostate found significant upregulation IGF1R protein levels and mRNA in primary prostate cancer compared to benign prostatic tumor. The study focused on the search for IGF1R in frozen tissue sections of prostate cancer found an increased incidence of IGF1R in normal prostate tissue, the tissue of prostate cancer and metastases, but did not find almost no IGF1R in prostate tissue, benign tumors. [56]

IGF1 and colorectal cancer

A number of studies is devoted to the relationship of circulating IGF and colorectal adenomas.

Interesting results were achieved in monitoring levels of IGF1, depending on the recurrence of colorectal adenomas. Serum levels of IGF1 were measured at the first detection of adenomas in 299 men. IGF1 levels were significantly positively associated with the presence of adenomas. In contrast to this finding, the concentrations of IGF1 indirectly associated with repeated findings of colorectal adenoma. The authors theorized that when the adenoma is removed, higher concentrations of IGF1 reduces the likelihood of new lesions in the rectum [57]. Other authors have shown that the increased risk of primary adenoma with high IGF1, risk reduction at high IGFBP3. The recurrence of adenoma, however, the authors found the longest recurrence intervals with high levels of IGF1 and IGFBP3 [58].

The authors of studies concerning the relationship of the risk of adenomas and serum IGFBP3 and risk of adenomas and tissue expese IGFBP3 mRNA found no significant relationship between serum levels of IGFBP3 and risk of adenoma, but

found a negative correlation between lower tissue mRNA expression of IGFBP3 and risk of adenomas. [59]

Studies on the expression of IGF1R as a basic element for the functioning of signaling pathways IGFs yielded interesting findings. Earlier study reported increased IGF1R expression during progression of colorectal adenoma and adenocarcinoma metastasis through. IGF1R expression correlated with stage of disease. More recent studies on this topic indicates that IGF1R is expressed at high levels in the early stages of tumor aberrations. In advanced tumors with low differentiation were found in low exrese IGF1R. [60] Other authors found no correlation between the expression of IGF1R and long-term prognosis in a study of 86 metastatic colorectal cancer. [61]

Patients diagnosed with colorectal cancer, the same theoretical assumptions about the risks in the development and subsequently the growth as adenomas. Findings from available studies, however, showed no relationship between elevated serum levels of IGF1 and the incidence of colorectal cancer. [62].

A separate chapter is patients with acromegaly. Increased GH production in these patients also causes an increase in serum IGF1. Patients with acromegaly occur increasingly adenomatous polyps of the colon. Patients with acromegaly are two-fold increased risk of developing colon cancer. [63]

In patients treated with GH due to the mechanism of action of IGF1 considered a possible increased risk of cancer intestinal mucosa. An increased risk for the development of colon tumors in patients treated with GH was not significant. [64]

IGF1 and pancreatic cancer

In four american prospective cohort study was to evaluate 144 cases of pancreatic cancer. Were evaluated serum levels of IGF1, but no relationship between IGF1 increased risk of pancreatic cancer was found. [65] In the Finnish study, the authors evaluated the relationship IGF1 for pancreatic cancer in male smokers [66]. Were evaluated 93 cases of adenocarcinoma in Finnish men - smokers aged 50-69 years. Serum levels of IGF1 were compared with levels in 400 randomly selected controls. Serum levels of IGF1 or IGF1/IGFBP3 ratio was not significantly associated with adenocarcinoma of the pancreas.

When studying IGF1R and its signaling pathway in relation to pancreatic cancer were included in tissue culture cells, pancreatic cancer specific added IGF1R

inhibitors. There was thus blocking signal transduction cascade PI3K/PKB. Both inhibitors cause apoptosis in cancer cells. [67]

IGF1 and thyroid gland cancer

IGF1 levels were examined in connection with thyroid disorders. High serum concentrations of IGF1 are associated with goiter, with nodes in the thyroid visible on ultrasound and reduced TSH. The thyroid adenomas are described lower serum IGF1 levels compared to healthy controls. [68]

Increased expression of IGF1R correlated with thyroid tumors with poor prognosis. For IGF1R find obvious correlation between their expression and differentiation of tumor cells. For good and moderately differentiated carcinomas found significant expression of these receptors while anaplastic carcinomas have expression is lacking. This phenomenon the authors explain that the anaplastic cells is activated by a sufficient amount of growth-signaling pathways mediated IGF1R and distance are no longer needed. [69]

Clinical use of IGF1 for routine practice

From a diagnostic point of view, IGF1 beneficial examination especially during growth disorders. Unlike GH secretion which is pulse, its level in the serum at a constant.

Leptin and adiponectin

Leptin and adiponectin are next two important players in the mechanism of the development of cancer.

High serum leptin levels might be associated with cancer. Leptin stimulates cell proliferation and reduce apoptosis via the same pathways like insulin and IGF1. However, local leptin production and autocrine and paracrine effect is a better predictor of carcinogenesis than circulating leptin levels. The next effect of leptin is the mediation of cytokines in specific cells and up-regulating VEGF pathway for a number of tumors. [70]

The mechanism of anti-carcinogenic effects of adiponectin has been unclear. However, in vitro, recombinant adiponectin potently inhibited endothelial cell proliferation and migration and induced caspase-mediated endothelial cell apoptosis

Reduced adiponectin levels lead to the development of insulin resistance and compensatory, chronic hyperinsulinaemia. Increased insulin levels lead to reduced liver and tissue synthesis of insulin-like growth factor binding proteins. This results in increased levels of bioavailable IGF1. Insulin and IGF1 signal through the insulin and IGF1 receptors promote cellular proliferation and inhibit apoptosis in many tissue types. [71]

The detailed description of cancer development mechanism would exceed limitations of this article. Role of leptin and adiponectin in the selected tumors will be described in details in the subsequent publication. But the schema presented bellow is provided the complete relationship between all the mentioned biomarkers - insulin, IGF1, leptin and adiponectin.

Relationship between individual biomarkers related to the cancer development

Biological effect of leptin, IGF1, insulin and adiponectin is mediated by the receptors. Leptin, IGF1 and insulin activate two main prosurvival signal cascades. Signal pathway PI3K (phosphatidylinositol-3-kinase)/PKB (proteinkinase B) and signal pathway ERK (extracellular signal regulated kinases), which represents one of the several MAP kinase pathways (MAPK mitogen activated protein kinases). [72]

IGF1 is a main activator of these pathways. Signal pathway PI3K/PKB is integrated into many normal cellular processes related to the proliferation, metabolism, growth and survival of cells. Abnormality of this pathway can result in different forms of cancer diseases. Central component of this pathway is formed by PI3K. Activation of PI3K changes immediately membranous fosfatidylinositol-3,5-biphosphate (PIP2) into triphosphate form (PIP3). PIP3 further induces phosphorylation of PKB (Akt in other words) via PDK1 protein. Complex PI3K is under the normal condition negatively regulated by specific phosphatase PTEN. Loss of PTEN function stimulates PIP3 accumulation, which results in deregulation of signal transduction via PI3K/PKB cascade. PKB is involved in other signal cascades and it interferes with many cellular processes (proteosynthesis, survival, proliferation, glucose metabolism, etc.). Activation of deregulated signal pathway PI3K/PKB provides signals to the cells for unlimited growth and survival. Second signal pathway is represented by the ERK cascade (extracellular signal regulated kinases). Signal is transmitted after IRS1 activation via Ras GTPase and Raf and MEK kinase. This process finally results in MAP kinase activation, particularly ERK. ERK belongs

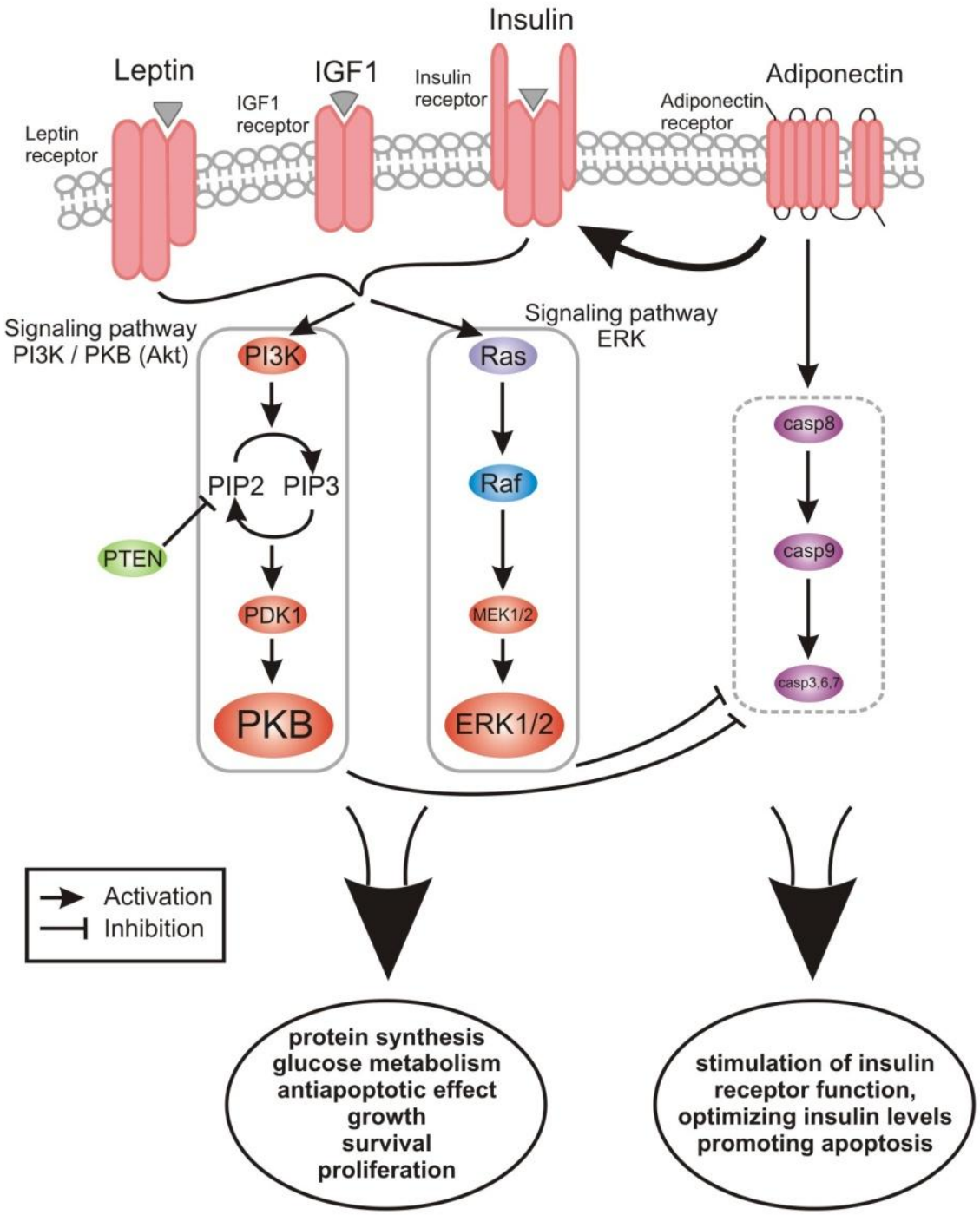
among the first well explored MAP kinases of the mammalian cells. Group of enzymes called MAP kinases regulates gene expression and eventually cellular proliferation and differentiation.

High insulin serum levels can stimulate production of IGF1. Insulin alone (or together with IGF1) may activate both survival pathways. Insulin can acts via IGF1 receptor and conversely. The affinity of insulin to the IGF1 receptor is ten times lower than to insulin receptor. This relationship is valid also for IGF1 and insulin receptor.

Leptin binds to leptin receptors located throughout the central nervous system and peripheral tissues. Leptin stimulates PI3K pathway and also ERK pathway. Leptin stimulate cell proliferation and reduce apoptosis by mediating cytokines and also up-regulates VEGF pathway. [73]

Adiponectin has an anticancerogenic efect. Adiponectin stimulates the sensitivity of peripheral tissue to insulin but the mechanism is unknown. Reduced adiponectin levels lead to the development of insulin resistance and compensatory, chronic hyperinsulinaemia. This results in increased levels of insulin and also IGF1 and stronger stimulation of survival pathways. Adiponectin decreases the expression of leptin and its receptors in the neoplastic cells. Adiponectin inhibits endothelial cell proliferation and migration and induces caspase enzyme mediated cell apoptosis. Conversely, PI3K/PKB and ERK pathways inhibit caspase enzymes and block the apoptosis. [74]

FIGURE 1: SIGNAL PATHWAYS FOR INDIVIDUAL BIOMARKERS (INSULIN, IGF1, LEPTIN AND ADIPONECTIN)



Shortcut description: ERK - extracellular signal regulated kinases, **casp** – caspase, **IGF1** – insulin like growth factor 1, **MEK** - serine/threonine-specific protein kinase **PDK1** - pyruvate dehydrogenase kinase isozyme 1, **PI3K** - phosphatidylinositol-3-kinase, **PIP2** - fosfatidylinositol-3,5-biphosphate, **PIP3** - fosfatidylinositol-3,5-triphosphate, **PKB (Akt)** - proteinkinase B , **PTEN** - phosphatase and tensin homolog, **Raf** - proto-oncogene serine/threonine-protein kinase, **Ras** - small GTPase

CONCLUSIONS

Metabolic syndrome, a growing health problem worldwide, has been associated with the obesity, diabetes, cardiovascular disease, hypertension, and other chronic diseases. Recently, the metabolic syndrome has been reported to be associated with increased risk of several cancer types and can also lead to poorer treatment and increased cancer-related mortality. Biological mechanisms explaining the relationship between metabolic syndrome and cancer have not been fully explained so far. Multiple hormones, growth factors, cytokines, and other mediators associated with the metabolic syndrome may play their role in cancer development, but better understanding of their mechanisms by which metabolic syndrome may influence cancer development and progression is important to develop strategies for prevention and prediction cancer incidence and to improve outcomes for the patients. We detailed focused on the role of insulin and IGF1. Therefore an intensive multicenter long-term research will verify the individual parameters of biological activity – as risk factors for cancer development and progression, particularly in high risk population with metabolic syndrome. This issue has been a challenging topic for further prospective clinical studies.

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