Pathol. Oncol. Res. (2012) 18:123–133
DOI 10.1007/s12253-011-9466-8

REVIEW

Interplay Between Insulin Resistance and Estrogen Deficiency as co- Activators in Carcinogenesis

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Received: 6 January 2011 / Accepted: 29 September 2011 / Published online: 9 October 2011

Abstract Both insulin resistance and estrogen deficiency result in complex metabolic disorder based mainly on defective cellular glucose uptake and on an atherogenic serum lipid profile. These alterations may be regarded as high risks for several life-threatening human diseases, such as type-2 diabetes, cardiovascular lesions and malignancies. Insulin resistance and estrogen deficiency are concomitant disorders with mutual interrelationship. Insulin resistance and the compensatory hyperinsulinemia provoke increased androgen synthesis at the expense of decreased estrogen production. Similarly, a moderate or severe decrease in serum estrogen levels enhances the prevalence of insulin resistant states both in men and women. Healthy premenopausal women enjoy the defensive effect of estrogens against metabolic and hormonal disorders. However, even a slight decrease in their circulatory estrogen levels associated with insulin resistance may increase the risk for cancers, particularly in the organs having high estrogen demand (breast, endometrium and ovary). On the other hand, postmenopausal state with profound estrogen deficiency confers high risk for cancers in different organs with either high or moderate estrogen demand. After menopause, hormone replacement therapy improves insulin sensitivity and decreases the enhanced inclination to malignancies in postmenopausal women. Recognition of the thorough interplay between insulin resistance and estrogen deficiency may illuminate many apparently controversial experimental and clinical findings concerning cancer development and therapeutic possibilities. Moreover, their interactions in the initiation and progression of human malignancies may supply new strategies in primary cancer prevention and cancer cure.

Keywords Insulin resistance · Estrogen deficiency · Carcinogenesis · Obesity · Type-2 diabetes · Growth factor, menopause, sexual steroid · Cardiovascular disease

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Introduction

Insulin has pivotal roles in the facilitation of anabolic processes and in the activation of transport systems being associated with the metabolism of carbohydrates proteins and lipids [1]. It is also a potent regulator of human sexual steroid hormone synthesis and interferes with their signal transduction at cellular level. Insulin resistance is a disorder of cellular glucose uptake and results in a complex metabolic and hormonal disturbance [2]. It may be regarded as high risk for several life-threatening human diseases, such as type-2 diabetes, cardiovascular lesions and malignancies [3].

Actions of female sexual steroids are much wider than having crucial roles in female physiology and reproduction. Estrogen receptor signals are fairly involved in the beneficial regulation of metabolic processes and in the gene regulation of cell growth, differentiation and proliferation both in men and women [4]. Physiological estrogen levels in healthy premenopausal women supply a favor against hypertension and cardiovascular diseases as compared with men in the same age. However, after menopause a decreased ovarian estrogen synthesis will be associated with a rapidly increasing prevalence of ischemic stroke, myocardial infarction and pulmonary emboli among women [5].

Both insulin and estrogens transfer potent mitogenic stimuli and share important functions in the control of cell proliferation. This suggests that equilibrium of their signal transduction pathways have crucial role in cancer prevention.

Insulin resistance and estrogen deficiency are concordant disorders and they have mutual interrelationship [6]. Moderate or severe estrogen deficiency proved to be a high risk factor for insulin resistance both in premenopausal and postmenopausal women as well as in male cases [7–10]. On the other hand insulin resistance and hyperinsulinemia provoke a severe imbalance in sexual steroid synthesis resulting in excessive androgen and low estrogen levels and interferes with estrogen effect even at receptor level [11].

Our knowledge concerning the consequences of insulin resistance is relatively young; its multifaceted metabolic and vascular complications were revealed near the end of the 20th century [12]. Recognition of correlations between insulin resistance and malignancies suffered several years' delay, but recently the role of insulin resistance in the initiation and progression of cancer has been undoubtedly justified [13]. On the contrary, estrogen deficiency had been a traditional etiologic factor for postmenopausal cardiovascular diseases and stroke for a long time, however, its correlation with cancer risk remained obscure till now.

The currently prevailing concept is the carcinogen capacity of estrogen, especially for the highly estrogen responsive organs of women. The Women's Health Initiative (WHI) hormone replacement therapy trial included more than 161000 women and worked on strategies for the prevention of heart disease, bone fracture and breast cancer in postmenopausal women. Results of this study as originally interpreted established that estrogen treatment was associated with a high incidence of breast cancer [14].

Estrogen deficiency as a cancer risk factor emerged first in a study on Hungarian oral cancer cases in 2007 [15]. Accumulation of non-smoker, non-drinker elderly postmenopausal female cases among oral cancer patients suggested a heretical idea: carcinogenic capacity of estrogen deficiency. This newly revealed correlation means a contradiction to the traditional concept of estrogen-induced breast cancer. Critical reevaluation of the contradictory results of hormone replacement therapy yielded a complete conversion: no estrogen but rather its deficiency may cause cancer initiation [16].

Recently a sensational review and reanalysis reversed the earlier results of WHI hormone replacement therapy trial. The authors established that estrogen is not carcinogenic rather a protective agent for breast cancer risk, as well as for many other aspects of women's health [17]. This shocking result may help after a long delay to focus on estrogen deficiency as cancer risk factor.

The present study gives a short review on the proven carcinogenic capacity of insulin resistance and a balanced analysis of the controversial epidemiologic and experimental associations between estradiol and cancer risk. As a further step, this work summarizes the mutual correlations between insulin resistance and estrogen deficiency as players in cancer development.

Correlations Between Insulin Resistance and Cancer Risk

Insulin resistance (IR) is a defect of insulin-mediated cellular glucose uptake, which may elicit many disorders in the gene regulation of cellular metabolism, growth, differentiation and mitotic activity [13].

Discovery of IR as a complex metabolic disturbance was a milestone in understanding the base of human illnesses [2]. Nowadays, IR is regarded as a worldwide risk factor for the two most dangerous human disease groups; namely for arteriosclerotic cardiovascular lesions and malignancies [13]. Insulin resistance syndrome has five basic criteria: hyperglycemia, visceral obesity, elevated serum triglyceride and low HDL-cholesterol level (dyslipidemia) and hypertension. Each of these criteria alone is cancer risk factor and they mean together a multiple risk [3].

The first compensated phase of insulin resistance in the liver, skeletal muscles and fatty tissue leads to a reactive hyperinsulinemia by the increased secretory capacity of the insular β-cells and the serum glucose level remains within the normal range. Insulin has diverse metabolic effects and at the same time functions as a growth factor and the elevation of insulin level in itself is a high cancer risk [18]. Hyperinsulinemia increases the production and mitogenic activity of other, insulin-like growth factors, such as IGF-I and IGF-II, which have important role in cell proliferation and tumor induction at several sites [19].

In the second uncompensated phase of insulin resistance the secretor capacity of insular β-cells is exhausted and with elevation of fasting glucose (EFG) type-2 diabetes develops. Hyperglycemia promotes the increased DNA-synthesis of tumor cells by several pathways [20]. It provokes deliberation of free radicals, which will cause the derangement of both DNA and enzymes having role in the repair mechanisms and leads to harmful non-enzymatic glycation of protein structures.

All phases of IR are proven risk factors for pancreas, liver, colon, urinary bladder, prostate, salivary gland and oral cavity cancers and even for malignancies of the highly estrogen responsive breast, ovary and endometrium [15, 20–29]. Nowadays we are on the route to regard malignan-

cies as complications of IR. Tumor progression is promoted by IR as well. In cancer patients with EFG or type-2 diabetes the rate of tumor recurrence, metastatic spread and fatal outcome is higher as compared with patients without metabolic disease [3].

Recognition of correlations between IR and tumor development reveals new possibilities in primary and secondary cancer prevention. Healthy diet, physical activity and weight loss increase insulin sensitivity and decrease the risk for both cardiovascular diseases and malignancies.

Historical Review of Associations Between Estrogen and Cancer Development

Epidemiological Data Suggesting the Carcinogenic Capacity of Estrogen

Idea of correlation between female sexual steroids and breast cancer risk had emerged more than 100 years ago [30]. From the early 1980s epidemiological and clinical studies have increasingly pointed to an elevated breast, endometrial and ovarian cancer risk associated with estrogens [31–36].

Even a slightly elevated serum level of endogenous estrogen was regarded as risk for breast cancer [27, 33, 37]. Exogenous estrogens alone or in combination with progestin were found also to be risk factors for breast cancer [34, 36, 38, 39]. Pike et al. summarized the results of population based epidemiological studies that had been published supporting the relative breast cancer risk from the use of postmenopausal hormone replacement therapy (HRT) [40]. Available literary data suggested that the use of HRT for more than 5–10 years means an increased relative risk for breast cancer [41].

Hyperestrogenism is regarded as a causal factor for endometrial hyperplasia and later to epithelial atypia, which may be the predecessor of endometrial adenocarcinoma. Epidemiologists accepted exogenous estrogen administration as a risk factor for human endometrial carcinoma [42].

In the USA an increased risk of ovarian cancer mortality was associated with postmenopausal estrogen use based on a large prospective study [43]. A collaborative reanalysis of European studies found a relative risk of ovarian cancer for ever use of HRT [44]. Recently, in a cohort study a strong relationship was established between duration of estrogen therapy and risk of ovarian cancer [45].

Carcinogenic activity of steroidal estrogens has been summarized in 2000 by the International Agency for Research on Cancer (IARC), which classified the evidences for these effects in humans [46].

Controversies of Experimental Results Concerning the Carcinogenic Capacity of Estrogen

Though earlier epidemiological studies have long been suspected that estrogens play a central role in breast cancer development, the mechanism of their carcinogenic capacity on human breast epithelial cells has not yet been clearly demonstrated [47].

Hormonal contribution of estrogen to carcinogenesis is based on its physiological functions in gene regulation [48]. Estrogen-induced proliferation of human tumor cell line and renal carcinogenesis induced by excessive estrogen doses in Syrian hamsters were inhibited by hormone antagonists [49]. These results were evaluated as crucial role of estrogen receptors in tumor growth either by fixation of spontaneous mutations or by induction of DNA damages. However, in these models only the excessive overdosage of estrogen could induce tumors, which has no predicting value in carcinogen testing [50]. Bacterial and mammalian gene mutation assays failed to justify any *mutagenic activity of estrogen* [51, 52].

Epigenetic, estrogen-induced carcinogenesis was also proposed via estrogen receptor-mediated proliferation of mammary epithelial cells carrying spontaneous replication errors [33]. However, the absence of ERs in proliferating human mammary epithelial cells provided evidence against this assumed carcinogenic pathway [53].

Carcinogenesis by covalent modification of estrogen receptors was also a proposed mechanism and through this route a permanent stimulation of receptors was suggested to induce uncontrolled cell proliferation [54]. However, further studies could not justify the estrogen-induced carcinogenesis by covalent receptor modification [55]. *Catechol metabolites of estrogen* were demonstrated to induce neoplastic transformation in human endometrial cells [56]. However, the rate of catecholestrogen production proved to be too low to result in significant amounts of genotoxic metabolites [51].

Estrogen-induced chromosomal abnormalities emerged also as explanation for carcinogenic capacity. Chromosomal changes or genome mutations might be provoked by estrogen in cell cultures and in laboratory animals [57, 58]. However, the estrogen induced neoplastic transformation of Syrian hamster embryo cells was reported without detectable concomitant gene mutations [59]. These results suggested that in addition to spontaneous chromosomal abnormalities other mutations are necessary for cells to acquire carcinogenic capacity.

Free radical mediated DNA-damage also emerged as an indirect mechanism of estrogen-induced carcinogenesis. Concentrations of 8-hydroxyguanine DNA bases, formed by hydroxy radical reaction, were increased in DNA incubated by catecholestrogens [60]. However, literary data

has established that estrogens have definite antioxidant activity and protective effect against oxidative stress especially in premenopausal women [61].

In vitro experiments, which tried to clarify the carcinogenic mechanism of estrogen effect, were fairly simplified models disregarding the cross talks and feedback mechanisms of mediators under biological circumstances.

Recent Results Supporting the Anticancer Capacity of Estrogen

Differences in exposure to known exogenous risk factors in men and women don't seem to explain the sex differences in cancer incidence rates. Recently, the justified associations of healthy reproductive and menstrual factors with decreased cancer risk in women helped to explain their lower tumor incidence rate as compared with men [15, 62].

Later menopause and longer duration of fertile life in women seemed to be inversely associated with the risk for cancers of urinary bladder, stomach, oral cavity and upper gastrointestinal tract [15, 62–64]. Vast majority of authors supposed that female sexual steroids help to maintain the local integrity of epithelial surfaces, which may counteract exogenous carcinogenic agents. Nevertheless, estrogen may also exert a systemic anticancer capacity by its advantageous effects on hormonal, metabolic and immunologic processes [16].

Many studies have found an inverse relationship between parity and cancer risk; such as for breast, endometrial, urinary bladder, pancreas and oral cancers [65–68]. It remained unclear how parity may decrease cancer risk, however, a healthy equilibrium of female sexual steroid production associated with good fertility may have tumor protective impact at several sites [69].

Hormone replacement therapy (HRT) in postmenopausal women supplies excellent possibilities to study the associations between female sexual steroid hormones and tumor incidence. Till now, the prevailing concept is that HRT is associated with an increased prevalence of gynecological and breast cancers [32, 35].

By contrast, recent clinical studies on HRT user women yielded beneficial anticancer effects against oral, esophageal, gastric, colorectal, cervical, liver and lung cancers [32, 64, 70–74]. Moreover, a decreased risk for endometrial cancer could also be observed among postmenopausal women with HRT use [75]. Doubts concerning associations between estrogen treatment and ovarian cancer risk have also emerged [76]. These results suggest a systemic protective effect of estrogen for cancers at several sites.

Nowadays, breast cancer remained as a last fortress to support the principle of the carcinogenic capacity of estrogen. However, in 2004, in the WHI Randomized Controlled Trial, the estrogen treatment of women with prior hysterectomy over 6–8 years reduced significantly the breast cancer risk [77]. The authors suggested further investigations to justify this unexpected result. Recently, in 2011, a continued follow up study of the same trial on hysterectomized cases strengthened a significantly lower risk for breast cancer in estrogen-treated survivor women [78]. Considering the principle of estrogen deficiency induced cancer, the breast cancer risk of women with hysterectomy may be near uniformly high. Their abrupt, shocking hormone deprivation may be more dangerous for the health as compared with those undergoing natural menopause. HRT studies on these homogenously selected cases seem to be much more reliable [16].

The next sensational study was published in 2010, which re-evaluated the earlier results of WHI Hormone Replacement Therapy Trial suggesting a strong carcinogenic capacity of estrogen for female breast [14]. After a proper selection of the same cases HRT use proved to be not only safe but rather protective for breast cancer risk [17]. This conversion is not surprising if we take into consideration that breast cancer is a multicausal disease and the previous WHI study examined the involved women in two pooled groups; cases with and without hormone treatment. WHI authors disregarded the individual reproductive and menstrual differences and other known or suspected risk factors for breast cancer and the obtained results were misleading [16].

These recent, methodologically correct examinations yielded excellent proofs for the protective effect of estrogen even for breast cancer risk. The walls of the last fortress seem to be crumbling.

Ambiguous Functions of Estrogen in the Regulation of Cell Proliferation

Estrogen receptors (ERs) belong to the steroid-thyroid hormone nuclear receptor superfamily [79]. The classic, genomic mechanism of ER action is that estrogen binding activates ERs in the nucleus and they act as transcriptional modulators by binding to specific sequences in the promoter region of target genes [4, 80]. ERs can also regulate gene expression without direct binding to DNA by interaction with transcription factor proteins, which may result in either stimulation or inhibition in gene transcription processes [79]. Moreover, ERs may regulate the expression of genes that do not contain estrogen responsive elements (EREs).

Estrogen have also non-genomic actions by membrane-associated ER signaling cascades, which may influence both the functions of cytoplasmic protein network and the regulation of gene expression in the nucleus [81]. Finally, genomic and non-genomic pathways of ER signaling converge on the target genes [4]. This complex signaling

system provides an exquisitely safety control and plasticity of tissue responses to estrogen modified by the nature of temporary intra- and extracellular stimuli.

There are two receptor isoforms; ER-α and ER-β, which are widely expressed throughout the body with a predominance of one or the other [79]. Both ER isoforms are markedly expressed in the mammary glands, uterus, brain, bone and cardiovascular system. All these sites are especially endangered in postmenopausal women by the decreased hormone production of ovaries. Ischemic attacks in the central nervous system, osteoporosis and cardiovascular diseases show conspicuously increased prevalence in women after menopause. Cancer risk of moderate estrogen loss in young women, especially in the highly estrogen responsive organs; such as breast, endometrium and ovary seems to be a newly recognized danger [16].

Estrogen receptor isoforms (ER-α and ER-β) differently regulate cell proliferation and apoptotic cell death. In a mammary gland epithelial cell line, deriving from pregnant mouse, selective agonists for ER-α provoked cell proliferation, whereas agonists for ER-β induced inhibitory effect [82]. Mouse mammary cell line could exhibit physiological resistance to estradiol induced cell proliferation as concomitant activation of ER isoforms may equalize the opposing cellular responses.

Embryonic development well demonstrates the physiologic role of all the ambiguous actions of estrogen [83]. High estrogen levels in pregnant women might ensure explosion-like cell proliferation in the developing embryonic tissues and organs due to the predominance of ERα signaling pathways. By contrast, when the growth should be stopped, cessation of high mitotic activity results in a dynamic equilibrium of cell number conducted by a concomitant activation of both receptor isoforms. Moreover, by the predominance of ER-β activity, a stimulation of apoptotic cell death may induce an involution of embryonic structures, which have lost their function.

Crosstalk between ER and GFR (growth factor receptor) signaling pathways are well-known both in healthy tissues and malignancies. Estradiol liganded ERs in the plasma membrane can rapidly transactivate the epidermal growth factor receptor (EGFR) or insulin-like growth factor-I receptor (IGF-IR) by feedback mechanism [84]. Estradiol may induce both growth stimulation and growth inhibition depending on the ratio and activity of ERs and GFRs [85]. On the other hand, the mitogen associated protein kinase (MAPK) system of GFR signaling is capable to modulate the aminoterminal activity of ERs by phosphorylation [86].

In human breast cancer cells, expressions of ERs and EGFRs are often inversely correlated [87]. Inhibition of growth factor signaling in apparently ER-negative breast cancer cells successfully restored ER expression suggesting a dynamic, inverse relationship between the two receptor systems [88]. Estrogen treatment could inhibit lung carcinogenesis by the reduction of IGF-I level, which is a potent mitogenic agent for malignancies [89]. These results suggest rather an alternative role of estrogen and growth factor actions in tumor cell proliferation. Nevertheless, the presumed synergistic contribution of ERs and GFRs to cancer development and progression would be a permanent danger without contraregulatory impact.

In emergency situation of estrogen deficiency, GF initiated activities may induce estradiol specific ER responses by a physiological coupling of the two signaling pathways when intact nuclear ERs are available [90, 91]. However, a permanent absence of estrogen may induce overwhelming GF signals. Unopposed GF signaling may modulate the functions of exposed, non-liganded ERs through the phosphorylation of certain receptor residues [85]. Predominance of GF activities and an alteration of non-liganded ERs may provoke a breakdown in the gene regulation of cell proliferation beyond retrieval [16, 69].

Molecular Mechanism of Interplay Between the Actions of Estrogen and Insulin

Effects of Estrogen on Glucose Metabolism

Estrogen has beneficial effects on the energy metabolism and glucose homeostasis by means of several possible pathways [92]. It regulates the insulin production capacity of the pancreatic islet cells [93]. In the liver, estrogen regulates insulin sensitivity by the activation of glycogen synthetase and glycolytic enzymes and advantageously modulates the glucose uptake of peripheral target tissues as well [94, 95]. Experimental and clinical studies justify that estrogen deficiency or alterations in ER signal transduction result in insulin resistance.

Increased insulin secretion of pancreatic β-cells controls elevated plasma glucose level during the post-prandial phase. In animal experiments ovarectomy is associated with an increased risk of diabetes, whereas estrogen treatment improves the insulin response to glucose load [96]. Estrogen administration enhanced the glucose-induced insulin secretion in rat pancreas and in mouse islet cells [93]. These data might explain the suppression of glucose induced insulin secretion in estrogen deficiency.

In aromatase knockout (ArKO) mice the enzyme for estrogen biosynthesis is inactivated, and these estrogen deficient animals are insulin resistant; they have reduced glucose oxidation, increased adiposity and high insulin levels. Glucose intolerance of ArKO mice can be reversed by estrogen treatment both in females and males! [97]

After menopause, type-2 diabetes and obesity may be only partially reversed by restricted diet because it cannot

improve pancreatic β-cell mass and function. However, in postmenopausal women regular physical activity or estrogen replacement alone has more beneficial antidiabetogenic effect suggesting their direct improving impact on the insulin secretion capacity of β-cells [93].

In the liver, insulin regulates the glucose uptake and glucose output and ensures glucose homeostasis in case of normal insulin sensitivity [92]. Estrogen receptors (ERs) have crucial roles in the glucose metabolism of the liver. In ER-α receptor knockout (ERKO) animal, hepatic insulin resistance is associated with decreased glucose uptake in skeletal muscles [94]. These findings reveal that estrogen receptor-alpha plays an important role in the regulation of glucose homeostasis and of insulin sensitivity in mice.

Estrogen receptors are newly recognized important players in glucose metabolism [92]. They advantageously modulate insulin stimulated cellular glucose uptake through regulation of the tyrosine phosphorylation of insulin receptor protein [98].

ERs have crucial roles in cellular glucose uptake by the regulation of glucose transporter (GLUT) containing cytoplasmic vesicles. They participate both in GLUT4 expression and translocation. In ovarectomized rats, estradiol substitution increased the amount of GLUT1 protein in the blood–brain barrier [99]. In immature rat uterus estradiol treatment caused a fourfold increase in GLUT1 protein content and also increased glucose uptake [95]. In polycystic ovarium syndrome (PCOS) cases, in which an ovarian overproduction of testosterone is characteristic, insulin stimulated glucose uptake was reduced due to decreased amounts of GLUT4 on adipocyte membrane [100].

ER-α and ER-β seem to have opposite actions on glucose homeostasis and modulation of GLUT4 activities. Mice that lack ER-α are insulin resistant; exhibit impaired glucose tolerance and obesity, affecting both males and females. By contrast, ER-β activation might have a diabetogenic effect and opposes the action of ER-α [92]. Presumably, a continuously adjusted balance between ER-α and ER-β maintains the ideal GLUT4 expression and glucose homeostasis.

Higher concentrations of estradiol can inhibit insulin signaling by modulation of insulin receptor substrate-1 (IRS-l) phosphorylation in adipocytes [101]. As insulin has not only metabolic but also mitogenic effects, an inhibition of excessive insulin receptor signal by estrogen may be a safety impact both against pathological glucose uptake and cell proliferation.

Estrogens have pivotal role in growth hormone (GH) activity by means of inhibitory effects on its secretion and on cellular GH receptor functions. These observations suggest that estrogens play a major and positive role in the regulation of GH-IGF-I axis in both genders [102], which may be in close correlation with their antidiabetogenic and anticancer capacities.

Effects of Estrogen on Lipid Metabolism and Fat Deposition

Estrogen has positive regulatory effects on the maintenance of serum lipid levels, on the insulin sensitivity of adipocytes and on advantageous body fat distribution. Postmenopausal women exhibit more atherogenic serum lipid profile as compared with premenopausal cases and estrogen treatment may reduce the risk of cardiovascular disease by favorable changes in plasma lipid levels [103].

In aged rats, estradiol administration lowered the level of lipid peroxidation and improved the dysfunction parameters of the liver [104]. Moreover, an androgen receptor-mediated antagonism of estrogen-dependent low-density lipoprotein receptor (LDLR) transcription was observed in cultured hepatocytes [105]. This observation may reveal the antagonistic associations of sexual steroids with lipid metabolism and vascular diseases.

Estrogen regulates the total mass, regional body distribution and metabolism of adipose tissue, which plays a pivotal role in energy homeostasis, insulin sensitivity and immune responses [106].

In healthy premenopausal women central, abdominal adipocytes show higher insulin sensitivity than in male cases [107], which means lower risk for insulin resistance in the generative period of women. However, menopause results in increased central adiposity and higher fasting insulin levels suggesting higher risk for metabolic and cardiovascular diseases [93, 108] and for malignancies [109].

Obesity is an excessive deposition of adipose tissue and predisposes patients to a variety of diseases such as; cardiovascular lesions, type-2 diabetes and malignancies [110]. Obesity and overweight are important concomitants of insulin resistance and disturbed equilibrium of male to female sexual hormone concentrations in women [111]. There are controversial correlations between increased body weight and estrogen action. Some authors could find linear correlation between high body mass index (BMI) and elevated serum estrogen level [110]. Others observed associations between androgen excess and central adiposity both in pre- and postmenopausal cases [112].

There are major sex differences in insulin sensitivity and deposition of adipose tissue. Estrogens induce predominantly gluteofemoral adipose tissue deposition, whereas in case of androgen excess rather intraabdominal fat accumulation is typical [108]. “Android women” with excessive circulatory androgen levels exhibit central obesity, which is strongly associated with insulin resistance and its complications [111, 112].

Effects of Insulin on Sexual Steroid Hormone Production and on Their Signals at Receptor Level

Insulin is a potent effector of human sexual steroid hormone production in the endocrine organs and modulates estrogen signals at receptor level as well.

In women insulin resistance may contribute to hyperandrogenism and anovulatory dysfunction through several pathways [113]. Hyperinsulinemia in the first, compensated phase of insulin resistance stimulates the testosterone biosynthesis of human ovarian theca cells from women with polycystic ovarium syndrome (PCOS) [114]. This results in excessive androgen and deficient estrogen production. Treatment by insulin sensitizing Metformin reduced the hyperinsulinemia and inhibited directly the androgen overproduction in human ovarian theca cells [115].

Insulin may affect the pituitary to favor the secretion of luteinizing hormone (LH) and increases adrenal androgen production by means of an increased adrenal sensitivity to adrenocorticotropin [116]. Insulin and insulin-like growth factor-I receptors may synergize with LH to promote androgen production by ovarian theca cells [114].

There are contradictions concerning the hormonal and metabolic disturbances in PCOS cases and the interpretation of complications in such patients. High risk for endometrial cancer in women with PCOS was presumed to justify the "unopposed estrogen hypothesis" supposing normal or elevated bioavailable estrogen, but low level of progesterone [36]. Nevertheless, both obesity and hyperinsulinemia in these cases are associated with defective ovarian estrogen and excessive androgen synthesis [11], thus unopposed high estrogen level cannot be blamed for endometrial cancer risk. Moreover, high estrogen level would be contradictory to anovulatory infertility as ovulation may be provoked by excessive estrogen administration. Recently, androgen-excess and the associated metabolic alterations are regarded as common sources of cardiovascular risk and other complications in PCOS cases [117]. Hyperandrogenism explains both anovulation and hirsutism, which are characteristic disorders in women with PCOS.

Clinical Correlations Between Estrogen Deficiency, Insulin Resistance and Cancer Risk

A moderate or severe decrease in female sexual steroid hormone levels enhances the prevalence of insulin resistant states both in premenopausal and postmenopausal cases. On the other hand, elevated fasting glucose, type-2 diabetes and obesity are closely associated with anovulation and altered reproductive functions in young women and with postmenopausal changes in the elderly [9, 10].

In premenopausal women long or highly irregular menstrual cycles suggesting defective ovarian function are predictors for risk of type-2 diabetes [118]. In young women endometrial cancer risk shows close correlation with nulliparity, irregular menstrual cycles, diabetes and hypertension [28]. In conclusion, the hormonal treatment of menstrual disorders helps to lower the risk for both diabetes and endometrial cancer.

Polycystic ovarium syndrome (PCOS) in young women is an important pathologic example of correlations between the disturbed equilibrium of sexual steroids and insulin resistance [13]. The cardinal symptoms are anovulation, infertility, hirsutism and obesity. In PCOS cases insulin resistance and hyperinsulinemia overregulate ovarian androgen synthesis at the expense of decreased estrogen production. Use of insulin sensitizing drugs in PCOS cases lowered serum insulin level and improved menstrual abnormalities, ovulatory dysfunction, infertility and hirsutism [11].

Insulin resistance in PCOS cases means general health risk for the affected women. Metabolic syndrome and type-2 diabetes has been shown to be consistently frequent among women with PCOS diagnosis [9, 119]. Moreover, an increased prevalence of premature cardiovascular diseases and malignancies, preferentially in breast, endometrium and ovaries were observed in PCOS cases [117, 120]. In a mortality study on patients with PCOS breast cancer proved to be the leading cause of death [121].

In "android women" the excessive androgen level may be due to the decreased conversion of testosterone to estrogen by aromatase cytochrome P450 resulting in decreased estrogen level [111]. Hyperandrogenism in women is closely associated with insulin resistance and disorders of fertility. These patients have male characteristics of muscle mass, visceral adiposity, increased risk of hypertension, type-2 diabetes and cardiovascular disease [112, 117, 122]. Visceral obesity and type-2 diabetes are in close correlation with tumor development.

In the *climacteric and postmenopausal period*, increased body weight and central obesity are often observed in women and the prevalence of metabolic syndrome and type-2 diabetes increase dramatically with age [123, 127]. Theories emerged that estrogen deficiency and increased androgen activity are responsible for the worsening of glucose homeostasis in postmenopausal women [128].

Cancer risk shows strong correlations with elevated fasting glucose level, hyperinsulinemia, increased IGF level, hypertriglyceridemia, type-2 diabetes and excessive body weight [20, 110, 124, 125]. These alterations are more frequent among postmenopausal women as compared with younger cases. In postmenopausal women a progressive increase was observed in insulin resistance and in serum insulin levels that relate to time since menopause rather

than to the chronological age of patients [126, 127]. After menopause, a close correlation between insulin resistance and the decreasing ovarian estrogen production has been consistently reported as risk factor for cardiovascular diseases and for malignancies [16, 128].

Elevated fasting glucose (EFG) level is an easily accessible mirror reflecting the insulin resistance of patients. EFG was a strong predictor of breast cancer among estrogen deficient perimenopausal and postmenopausal cases but it was not similarly dangerous for young premenopausal women [20]. In postmenopausal women, after age of 65 years, newly diagnosed breast cancer incidence showed strong positive association with their highly elevated blood glucose levels [129].

Central adiposity is associated to increased risk of breast, endometrial and colorectal cancers, particularly after menopause [110]. In obese postmenopausal women weight loss, regular physical activity or estrogen replacement alone has beneficial antidiabetogenic effect by improving the insulin sensitivity [93]. HRT use in women attenuates the obesity associated cancer risk, especially for the malignancies of breast and endometrium [130, 131]. Recently, beneficial systemic changes; such as increased insulin sensitivity and elevated estrogen levels were found to decrease the oral cancer risk in women with moderate alcohol consumption [132].

In men the metabolic significance of estrogen environment has newly been recognized and today its role in male physiology seems also to be essential [8]. Sporadic male cases with complete estrogen deficiency exhibit severe type-2 diabetes being resistant to usual therapy but they may be treated by estrogen substitution. Based on the findings found in women, a disturbed equilibrium of sexual steroids associated with insulin resistance may also be important cancer risk in men.

Conclusion

Thorough interplay between two systemic alterations; insulin resistance and estrogen deficiency may illuminate many apparently controversial experimental and clinical findings in oncology. Equilibrium of sexual steroid levels may be crucial for the health both in women and men. Correction of altered androgen to estrogen levels increases the insulin sensitivity, whereas treatment of insulin resistance may help to improve the sexual steroid equilibrium.

Interactions between insulin resistance and estrogen deficiency and their role in the initiation and progression of human malignancies may supply completely new strategies in primary cancer prevention and tumor therapy.

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