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Adiponectin as novel key player in tumors of adrenal glands – what do we know? A review

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Abstract

Introduction: Adrenal incidentalomas without clinically apparent hormonal activities have becoming a huge socio-economic problem due to recent advances in radiological techniques. Patients with incidentalomas are considered to be at high risk of developing metabolic disorders and cardiovascular diseases. That is why, the two-way relationship between adipose tissue activity and adrenal glands is in high interest and an object of extensively studies.

Aim of the study: This article summarizes the current knowledge about adiponectin and its receptors in the tumorigenesis of adrenal neoplasia as well as their role in the developing obesity-related diseases.

Description of knowledge: Adiponectin, an adipose tissue-derived pleiotropic hormone, with anti-inflammatory, anti-atherogenic, anti-diabetic, and insulin-sensitizing properties is engaged in developing diabetes mellitus type 2, hypertension or ischemic heart disease, but the latest researches also revealed its role in tumor cells proliferation and angiogenesis. The possible effects of adiponectin and its two receptors in both physiological processes and pathophysiology of adrenal glands is not fully understood. Recent studies suggested that adiponectin receptors expression is significantly higher in hormonally active adrenal tumors as compared to normal tissues of adrenal glands, which may prove the involving of adipose tissue and periadrenal fat depot in regulating the function of adrenal cortex or medulla.

Conclusions: Adiponectin may be predictive factor of developing metabolic disorders in the group of patients with accidentally detected adrenal lesions. The discovering of its exact mechanism may result in modifying novel screening options as well as diagnostic process and treatment scheme. Therefore, further research is required to determine the effect of adiponectin and its role in the pathogenesis of obesity-related diseases in the course of adrenal tumors.

Key words: adiponectin, incidentaloma, adrenal glands, metabolic disorders

Introduction

Adrenal tumors, generally called incidentalomas are defined as adrenal lesions with a diameter ≥1 cm, discovered incidentally during radiological examinations performed for many different reasons [1]. According to different data, they are detected in about 3-10% of patients in general population with still increasing prevalence from 0.2% in third decade to 7% in elderly people [2-5]. What is more, the latest epidemiological reports suggest that incidentalomas have becoming an endocrine epidemic and at the same time a huge economic and social problem since their discovery in 1941 [6].

Among them the most common pathologies are non-functioning benign lesions (82.5%), predominantly adenomas (61%), followed by cortisol-secreting adenomas (5.3%), pheochromocytomas (5.1%), adrenocortical carcinomas (4.7%), metastatic lesions (2.5%), and aldosteronomas (1%) [3-4]. So far, it was considered that hormonally inactive adrenal incidentalomas do not present any hyperfunction, notwithstanding the studies of recent years revealed chronic subclinical hormonal activity of the cortex or medulla, which may lead to many different complications [7-9]. The association of obesity and related metabolic disorders like insulin resistance, prediabetes (impaired fasting glucose, impaired glucose tolerance), diabetes mellitus type 2, dyslipidaemia, hypertension, and other cardiovascular diseases in the course of Cushing's syndrome, subclinical Cushing's syndrome or pheochromocytoma is established quite well, whereas there are limited data on developing such disturbances in patients with non-functioning adrenal incidentalomas [5, 10-14]. Moreover, according to the current statistical analysis the leading causes of mortality among patients with tumors of adrenal glands are usually not strictly connected with the adrenal masses, but they rather died from cardiovascular events or obesity-associated complications [15-16]. That is why, the relationship between adipose tissue is in high interest and an object of many studies in the context of adrenal glands' homeostasis regulation.

Adipose tissue, treated as a hormonally inactive fat storage for many years, in the last decades was recognized as a unique endocrine organ, exerting pleiotropic effects on many functions and processes in human organism by secreting multiple pro-inflammatory and anti-inflammatory hormones and cytokines [17-18]. Adipocytes produce adipocytokines, a group of variety hormonal proteins, including leptin, resistin, apelin, visfatin, omentin, newly discovered adiponectin, and adipolin as well as cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), monocyte chemoattractant protein 1 (MCP-1), pigment

epithelium-derived factor (PEDF), and progranulin (PGRN), which acts at autocrine, paracrine, endocrine levels. The results of recent years' studies have revealed the possible cross-talk between adipokines and endocrine function of adrenal glands as well as have demonstrated the novel pathophysiological pathways involved in the pathogenesis of adrenal tumors and their comorbidities, especially obesity-related diseases [19]. A better understanding of above-mentioned correlations will likely result in innovative approach to diagnostic process and rationalizing treatment methods of these highly prevalent disorders in the future.

Aim of the study

The aim of this review was to present the association of adiponectin with metabolic disturbances and cardiovascular diseases in patients with incidentalomas. Moreover, we also discussed the current and future perspectives of the usefulness of this adipocytokine as diagnostic as well as prognostic factor in functioning and non-functioning adrenal glands' tumors.

Materials and methods

The available literature was subjectively selected due to its usefulness in showing clinical approach to the role of cytokines, especially adipocytokines as markers of metabolic disorders in the course of adrenal glands' tumors. Furthermore, data which reveals inconsistency in results was shown as well. Articles in English in the EBSCO and the PubMed database have been analyzed using key words in various combinations: adiponectin, adipokine, incidentaloma, pheochromocytoma, subclinical Cushing's syndrome, tumor of adrenal gland, metabolic disorders, diagnostic and prognostic marker.

Cross-talk between the hormonal activity of adrenal glands and adipose tissue

The two-way relationship between adipose tissue-derived hormones, participating not only in the developing metabolic diseases, but also in tumorigenesis, and adrenal glands, has lately been a subject of extensively in vivo and in vitro studies. Adiponectin, primarly known as adipocyte complement-related protein of 30 kDa, Acrp30, AdipoQ, apM1, and BGP28, is a regulatory peptide mainly produced by adipose tissue and secreted into the bloodstream in the concentration ranging from 3 to 30 μg/ml (100 nM-1μM) in three multimeric fractions: low molecular weight (LMW) trimers, middle molecular weight (MMW) hexamers, and high molecular weight (HMW) multimers, which is the most active form [18, 20]. This newly discovered in 1990s and at the same time one of the best known pleiotropic hormone, with

anti-inflammatory, anti-atherogenic, anti-diabetic, and insulin-sensitizing properties, is suggested to play a pivotal role in the regulation of glucose homeostasis, lipid metabolism and insulin sensitivity. Most its metabolic functions and processes in human organism are mediated by AMPK (AMP-dependent protein kinase) and PPAR-α (peroxisome proliferator-activated receptor alpha) signaling pathways. Adiponectin exerts its effects via two transmembrane adiponectin receptors (AdipoR1 and AdipoR2) localized mainly through skeletal muscles (AdipoR1) and liver (AdipoR2), and in smaller extent expressed in pancreatic β-cells, brain, heart, kidneys, placenta, testis, ovaries, macrophages. What is interesting, but not widely known, both adiponectin receptors were also found in cortex and medulla of histologically normal adrenal as well as adrenal tumor tissues [21-27]. Therefore, in table 1 we attempt to summarize the association between the expression of adiponectin receptors in particular tumors of adrenal glands and the risk of developing obesity-related diseases as well the correlation with hormonal status and body mass index (BMI) [Table 1].

So far it was considered that adrenal glands are involved in the etiopathogenesis of carbohydrate disorders and cardiovascular diseases by secreting hormones, such as glucocorticoids, mineralocorticoids or catecholamines. Nowadays, since Rossi GP et al. for the first time in 2006 discovered the expression of AdipoR1 and AdipoR2 genes at mRNA level, as well as the following studies revealed the presence of adiponectin protein both in normal and pathological human adrenal glands, their regulatory role in adrenal functions and adrenal tumors' growth is widely discussed [21]. Recent reports proved significantly higher expression of adiponectin receptors in hormonally active adrenal neoplasia as compared to normal tissues of adrenal glands [25]. Moreover, in vitro study demonstrated the functionality of adiponectin receptors and possible modulating impact of adiponectin on steroidogenesis for the first time in 2009 [22-23]. However, confusing date coming from in vitro study did not reveal stimulatory effects of adiponectin on steroidogenesis in human adrenocortical cell line that is NCI-H295R cells [28-29].

AdipoR2 and mainly AdipoR1 were expressed both at mRNA and protein level in the cortex of mouse adrenal glands and Y-1 cell line, which may proved its predominant role in adipocyte-adrenal gland interaction, whereas both AdipoR1 and AdipoR2 were weakly expressed in the adrenal medulla [22]. On the other hand, the study on pheochromocytoma tissues from 49 patients showed expression of AdipoR1 and AdipoR2 at mRNA level, which indicated their presence not only in pathological, but also through normal adrenal medulla

tissue [27]. The correlation between AdipoR1 mRNA expression and catecholamine secretion, especially its higher presence in adrenaline-type tumors both in diabetic and non-diabetic individuals than in noradrenaline ones, may also suggest that adrenaline is involved in adiponectin signaling pathway.

What is more, in vitro research conducted by Paschke et al. revealed a significant increase in adiponectin expression during developing and regenerating processes of adrenal cortex in rat model [23]. It is noteworthy that expression of adiponectin and its receptors in response to experimental malfunctions in hypothalamus-pituitary-adrenal (HPA) axis depends on the origin of fat depots. The study confirmed increased expression of adiponectin and AdipoR2 in subcutaneous adipose tissue while ACTH administration or ether stress, whereas adiponectin and AdipoR1 were suppressed at mRNA levels after dexamethason treatment. However, adiponectin sytem was not changed in visceral adipose tissue [23]. This can be explained by morphological and functional differences between subcutaneous and visceral adipose tissue. The researchers also proved the presence of two adiponectin receptors at mRNA level in all zones of rat adrenal cortex and medulla, whereas adiponectin expression at mRNA and protein level was detected only in zona glomerulosa [23]. What is more, ACTH role as the suppressive factor of proliferation in primary adrenocortical cell culture and at the same time down-regulated of adiponectin mRNA expression, suggested higher proliferative potential of zona glomerulosa as compared to other layers of adrenal glands [23]

The recent study showed that BMI is the most significant factor related to the expression of AdipoR1 and AdipoR2, while there were no correlation with hormonal status of adrenal tumors [25]. Then, Babińska et al. tried to assess the relationship between serum adiponectin concentration and the expression of its two receptors in 12 cases of human adrenal tumors. They revealed the statistically significant positive correlation only in case of AdipoR1 expression. Therefore, the study group was too small to achieve significance and further researches are needed [25]. In the light of the above reports, it is of high interest if overweight and obesity are causes or consequences of hormonal oversecretion of adrenal glands [19]. It is well established that excessive secretion of glucocorticoids, mineralocorticoids and catecholamines by adrenal tumors is connected with increased risk of carbohydrate disorders and cardiovascular diseases [25]. However, there are only a few studies, which assessed the impact of sublinical activity of adrenal cortex or medulla on the development of obesity-related disturbances [7,10,12,25,30]. It is worth mentioning that

overweight and obesity lead to decreased expression of AdipoR1 and AdipoR2, and in this way they reduce adiponectin sensitivity. What is more, it is believed that plasma or serum adiponectin concentration is lowered in patients with obesity both in healthy ones and these with diabetes mellitus type 2 as well as diseases of cardiovascular system [25]. Besides, Ermetici et al. hypothesized that patients with adrenal incidentalomas, who were not affected by hypertension, diabetes mellitus, obesity, and other relevant diseases, had a tendency to increased plasma adiponectin levels [30].

Furthermore, adrenal glands as well as adrenal tumors are not only subjected to adiponectin circulating in the blood, but also are surrounded by adipose tissue, which may suggest its paracrine and endocrine influence. It is even believed that there is a new hormonal network between adipocytes and adrenal cortex with the proposed name adrenal-adipose tissue axis [19,21]. Adiponectin mRNA expression was proved in fat depots surrounding the adrenal neoplasia and was significantly correlated with adiponectin plasma levels [31]. It was also noticed that adiponectin expression derived from adrenal tumors was significantly decreased than that from both peri-renal and subcutaneous adipose tissue.

The hormonal activity of adipose tissue in the cell proliferation of adrenal tumors, especially not associated with obesity, still remains unclear. Therefore, Babińska et al. in the clinical study assessed the immunohistochemical expression of adiponectin receptors as diagnostic and prognostic markers of adrenal tumors as well as their significance in histopathological differentiating between benign and malignant adrenal neoplasia [26]. The date proved the role of AdipoR1 and AdipoR2 as useful factors in diagnostic process of patients with uncertain adrenal cortical carcinoma, which is a neoplasm associated with poor prognosis [26]. Some authors hypothesized that serum hypoadiponectinemia, usually favoring carcinogenesis, may lead to increased adiponectin receptors expression at the same time. Such results were also observed in adrenal cortical carcinoma. Moreover, a statistically significant correlation was determined for steroidogenic factor 1 (SF1), insulin growth factor 2 (IGF2), AdipoR1 and AdipoR2 according to multivariate analysis with respectively 14%, 22%, 23%, 36% higher odds ratio of an adrenal cortical carcinoma diagnosis adjusted for hormonal activity, age, gender, and tumor size [26].

According to current knowledge, the role of adiponectin and its impact on adrenal tumors' hormonal activity is not completely clarify. In the following part of the review, we focus on its possible effects in adrenal tumors of particular relevance, that is non-functioning

adrenal incidentalomas, cortisol-secreting adenomas, pheochromocytomas, and aldosteronomas.

Adiponectin and non-functioning adrenal incidentalomas

There are increasing date indicating the correlation of clinically silent adrenal incidentalomas with metabolic syndrome and diseases of cardiovascular system [12,32]. Nevertheless, these pathomechanisms are still not completely understood. One of them is hyperinsulinemia, which is suspected of exerting chronic proliferative action on adrenal neoplasia [33]. What is more, it should be emphasized, that tumors treated as hormonally inactive, may demonstrate subclinical hormonal activity, such as subclinical Cushing's syndrome, subclinical pheochromocytoma, and even low-symptomatic adrenocortical cancer [7,14].

A few clinical studies suggest that higher risk of cardiovascular disorders and metabolic diseases in the group of patients with non-functioning adrenal incidentalomas is associated with cytokines, especially adipocytokines secreted by adipose tissue [14]. However, the latest reports notify no consistent effect of adiponectin system in non-functioning adrenal incidentalomas. Some authors presented increased adiponectin at mRNA levels in non-functioning adrenal incidentalomas as compared to functioning incidentalomas with statistically significant difference observed only in case of peri-renal adipose tissue of aldosterone-producing adenoma [31], whereas the others noted significantly decreased adiponectin plasma concentration in non-functioning adrenal tumors independently from glucocorticoid and catecholamine secretion and BMI [14,34]. Moreover, the concentration of adiponectin increased six months after surgery, which was performed in 5 individuals [14]. Although, the studied group was too small to assess the obtained results with statistical analysis [14]. Lazúrová I et al. also proved significantly lower serum adiponectin concentration in individuals with adrenal adenomas than in controls with at the same time significantly higher BMI, HOMA, and triacylglicerols levels, but they did not revealed significant differences in these parameters among patients with or without subclinical Cushing's syndrome [32]. On the other hand, Tuna MM et al. noted the similar adiponectin plasma levels in patients with non-functioning adrenal incidentalomas and in controls [12].

Adiponectin and subclinical Cushing's syndrome in the course of cortisol-secreting adenomas

The incidence of subclinical Cushing's syndrome associated with adrenal incidentalomas ranges between 5 to 47% and it is the most common subclinical state encountered in clinical practice [5]. Body weight disturbances resulting in various metabolic complications are relatively common both in patients with Cushing's syndrome and subclinical Cushing's syndrome with the prevalence, respectively 79 to 95% and 43 to 67% according to different date [14]. It is not completely obvious if increased risk of hypertension, atherosclerosis or carbohydrate disorders is a consequence of the higher frequency of overweight or obesity in subclinical hypercortisolemic individuals, which may lead to decreased serum adiponectin levels. It is suggested that subclinical hypercortisolemia itself do not change the adiponectin system homeostatis [25]. What is more, the diagnosis of subclinical hypercortisolemia is difficult due to no generally accepted hormonal criteria, that can cause the inconsistency in obtained results of different studies [14,32].

Furthermore, obesity connected with reduced serum adiponectin levels and HPA axis malfunctions, lead to disorder of inhibitory effect of adiponectin on ACTH-stimulated steroid secretion [22]. The interaction between glucocorticoids-mediated effects and adiponectin system are established quite well [23]. The latest studies discussed their role in the suppression of adiponectin expression at mRNA level in adipocyte, and at the same time decreasing plasma adiponectin concentration, which can be mediated by glucocorticoid response element in adiponectin promoter region [23].

According to some authors, patients with subclinical Cushing's syndrome related to slight chronic oversecretion of cortisol had lower adiponectin levels than individuals with non-functioning adrenal incidentalomas or controls [13-14]. What is interesting, Dogruk Unal A et al. revealed decreased adiponectin concentration in subclinical Cushing's syndrome for the first time. Besides, they proposed adiponectin as useful marker in predicting the presence of subclinical hypercortisolemia in adrenal tumors with the 87.5% sensitivity and 77.4% specificity for an adiponectin level of ≤13 ng/mL [13]. Also, the case study of 46-year-old female patient with Cushing's syndrome in the course of a left adrenal adenoma proved the possible modulating effect of glucocorticoids on adiponectin as its concentration increased after adrenalectomy with concomitant decrease in body weight and normalization of serum cortisol concentration [35]. Similar observations in adiponectin levels was made in *ob/ob* mice model after performing removal of adrenal tumor [36].

Adiponectin and pheochromocytoma

Carbohydrate disorders in the form of glucose intolerance occurs in 25% to 75%, and diabetes mellitus is reported in about one third of pheochromocytoma patients [10,27]. Overproduction of catecholamines by adrenal medulla exerts suppressive effect on insulin secretion, which results in developing insulin resistance, and then diabetes mellitus [10]. Catecholamines also induce adipose tissue lypolysis, that is why the individuals with pheochromocytomas are lean in most cases, but on the other hand modern lifestyle results in an increased incidence of obesity or overweight among them [37].

There are several reports that revealed both increased and decreased adiponectin levels in patients with pheochromocytoma [10,27,37]. The study conducted on 26 serum samples from pheochromocytomas' individuals showed significantly increased of adiponectin levels after surgical removing of tumors as compared to preoperative period despite increased their BMIs [10]. Moreover, the levels of adiponectin were decreased to normal concentration after adrenalectomy of pheochromocytoma in 10 cases [27]. Okauchi Y et al. presented a rare case of an obese 37-year-old man with catecholamine crisis in the course of pheochromocytoma. What is worth mentioning, the serum adiponectin level was decreased during this life-threatening condition and increased after adrenalectomy, but its concentration decreased again during the follow-up in 2-years period with concomitant increased body weight, which suggests the interaction between adipose tissue and hormonal activity of adrenal tumors [37]. On the contrary to above-mentioned studies, Bosanska L et al. demonstrated no difference in serum adiponectin levels before and six months after successful adrenalectomy in 18 patients diagnosed with pheochromocytoma, despite significantly increased body weight after surgical treatment [38]. However, the limitation of this study is lack of control group involving healthy volunteers. Therefore, further studies and extension of examined groups of patients are needed.

Adiponectin and aldosteronoma

Aldosteron-producing adenoma is one of the main causes of primary hyperaldosteronism (PA) diagnosed in about 27%-30% of hypertensive patients with PA, which constitutes 1.6% of general population suffering from hypertension [39-40]. It is well known that excess secretion of aldosterone is associated with metabolic syndrome and higher rate of cardiovascular events [40-41]. The recent reports about serum or plasma

hypoadiponectinemia in developing arterial hypertension are conflicting [21,42]. There are also lacking date linking the adiponectin concentration to aldosterone secretion [21]. The discovering of both adiponectin receptors (AdipoR1 and AdipoR2) in human adrenal cortex of aldosteronoma demonstrated for the first time the possible relationship between adipose tissue hormonal activity, blood pressure level and the function of adrenal glands [21]. On the other hand, some authors failed to prove the adiponectin role in stimulating adrenocortical aldosterone secrertion, so further studies are necessary [28-29].

Conclusions

To conclude, it is worth to emphasize that adiponectin may be a predictive factor of developing metabolic disorders, such as diabetes mellitus, hypertension in the group of patients with incidentally detected adrenal lesions. The discovering of its exact mechanism may result in modifying novel screening options as well as diagnostic process and treatment scheme. Therefore, further research is required to determine the effect of adiponectin and its role in the pathogenesis of obesity-related diseases in the course of adrenal tumors.

Table 1. Expression of adiponectin receptors (AdipoR1 and AdipoR2) in cortex and medulla of adrenal tumors' tissues and their correlation with body mass index (BMI), hormonal status.

Study (Reference)	Type of study	Type of adrenal tumor	AdipoR1	AdipoR2	Level of expression (mRNA/protein)	Correlation with BMI	Correlation with hormonal status	Comments
Rossi GP et al., 2006 [21]	in vitro (human)	histologically normal human adrenal cortex tissue (n=10)	+	+	mRNA	not examined	not examined	both receptors were expressed at a significantly higher level in APAs than in the normal adrenal cortex, for the first time at mRNA level
	in vitro (human)	adrenocortical zona glomerulosa cell-derived aldosterone-producing adenomas (APAs) tissue (n=10)	+	+	mRNA	not examined	not examined	
Li P et al., 2009 [22]	in vitro (animal)	normal mouse adrenal glands tissue (male C57 mice)	+	+	mRNA and protein	not examined	adiponectin acutely reduced basal levels of corticosterone and aldosterone secretion and inhibited ACTH-induced steroid secretion	for the first time both at mRNA and protein level, adiponectin itself was not expressed, the predominant expression of AdipoR1 in mouse adrenal cortex and Y-1 cell line
	in vitro (cell line)	adrenocortical Y-1 cell line	+	+	mRNA and protein	not examined		
Isobe K et al., 2009 [27]	in vitro (human)	pheochromocytoma tissue (n=49) (divided into 4 groups according to the tissue content of adrenaline and noradrenaline: adrenaline-type diabetics, noradrenaline-type diabetics, adrenaline-type non-diabetics, noradrenaline-type non-diabetics	+	+	mRNA	AdipoR1 expression significantly correlated with tissue adrenaline content even when adjusted for inter alia BMI	AdipoR1 expression correlated with catecholamine oversecretion and it was higher in adrenaline-type tumors than in noradrenaline-type tumors both in diabetics and non-diabetics	AdipoR1 expression correlated with an increased risk of diabetes mellitus, AdipoR1 and AdipoR2 expression were decreased in adrenaline-type diabetics compared to adrenaline-type non-diabetics, for the first time the expression of AdipoR1 and AdipoR2 receptors in pheochromocytoma tissues was proved
Paschke L et al., 2010 [23]	in vitro (animals)	tissue sample from rat adrenal gland	+	+/–	mRNA and protein	not examined	acute (ACTH or ether stress) and prolonged	AdipoR2 was only detected at mRNA level in rat adrenal

	in vivo (animals)	5 experimental groups: rats administered with ACTH at hours 0,12, 24 and decapitated 12 h after the last injection, with dexamethasone at hours 0, 12, 24 and decapitated 12 h after the last injection, with a bolus injection of ACTH 1 h before decapitation, submitted to acute ether stress 1 h after decapitation , control group	not examined	not examined	not examined	not examined	(ACTH) adrenal stimulation resulted in lowered adiponectin levels, acute treatment upregulated the expression of AdipoR1 and AdipoR2, while chronic ACTH administration remained them unchanged, prolonged dexamethasone administration only decreased AdipoR2 expression	cortex, adiponectin expression at mRNA level was increased during adrenocortical cells proliferation, FIAC used to assess the response to ACTH, PACC used to assess the proliferative activity
	in vitro (cell line)	freshly isolated adrenocortical cells (FIAC)	+	+	mRNA	not examined		
	in vitro (cell line)	primary adrenocortical cell culture (PACC)	+	+	mRNA	not examined		
Chou SH et al., 2010 [24]	in vitro (human)	adrenocortical carcinoma tissue (n=48)	+	+	protein	not associated with obesity	not examined	low frequency of AdipoR1 expression
Ramanjaneya M et al., 2011 [20]	in vitro (cell line)	H295R human adrenocortical cell line	+	+	mRNA and protein	not examined	increased cortisol production	adiponectin stimulated H295R, which resulted in increased cortisol secretion and an AMPK, ERK1/2-mediated up-regulation of the steroidogenic acute regulatory (StAR) protein, the first mediator of cholesterol metabolism
Babińska A et al., 2017 [26]	in vitro (human)	adrenal cortical carcinoma tissue (n=20), adrenal cortical adenoma and nodular hyperplasia	+	+	protein	not examined	hormonal overproduction was determined in 12 cases with adrenal cortical carcinoma, a statistically	assessment of immunohistochemical expression of AdipoR1 and AdipoR2 revealed that they

		(n=63)					significant correlation was determined for steroidogenic factor 1 (SF1), insulin growth factor 2 (IGF2), AdipoR1 and AdipoR2 according to multivariate analysis with respectively 14%, 22%, 23%, 36% higher odds ratio of an adrenal cortical carcinoma diagnosis adjusted for hormonal activity, age, gender, and tumor size	may be useful markers in the diagnostic process of uncertain adrenal cortical carcinoma cases
Babińska A et al., 2018 [25]	in vitro (human)	non-functioning adrenal incidentaloma tissue: adrenal adenoma (n=16) and nodular hyperplasia (n=26) – control group (n=42)	+	+	protein	statistically significant negative correlation between BMI and expression of AdipoR1 and AdipoR2 in patients with SCS, negatively correlation between BMI and expression of AdipoR2 in patients with PHEO	in univariate analysis in SCS patients: AdipoR2 expression was significantly lower as compared to individuals without SCS and cortisol levels after 1 mg dexamethasone suppression test correlated with AdipoR1 and AdipoR2 expression, in PHEO patients: there was a statistically significant, positive correlation between AdipoR1 expression and 24-h urinary metanephrine excretion, but in multivariate analysis these correlations were not significant after inclusion of the variable BMI	78 patients with subclinical hormone secretion
	in vitro (human)	subclinical Cushing's syndrome (n=38): adrenal cortex adenoma (n=23) and nodular hyperplasia (n=15) tissues	+	+	protein			
	in vitro (human)	pheochromocytoma tissue (n=40)	+	+	protein			

References:

1. Bednarczuk T, Bolanowski M, Sworczak K, Górnicka B, Cieszanowski A, Otto M, et al. Adrenal incidentaloma in adults - management recommendations by the Polish Society of Endocrinology. Endokrynol Pol. 2016;67(2):234-258. doi: 10.5603/EP.a2016.0039.
2. Bhat HS, Tiyadath BN. Management of Adrenal Masses. Indian J Surg Oncol. 2017;8(1):67-73. doi: 10.1007/s13193-016-0597-y.
3. Bittner JG, Brunt LM. Evaluation and management of adrenal incidentaloma. J Surg Oncol. 2012;106(5):557-564. doi: 10.1002/jso.23161.
4. Cichocki A, Samsel R, Papierska L, Roszkowska-Purska K, Nowak K, Jodkiewicz Z, et al. Adrenal tumour bigger than 5 cm - what could it be? An analysis of 139 cases. Endokrynol Pol. 2017;68(4):411-415. doi: 10.5603/EP.a2017.0039.
5. Androulakis II, Kaltsas G, Piaditis G, Grossman AB. The clinical significance of adrenal incidentalomas. Eur J Clin Invest. 2011;41(5):552-560. doi: 10.1111/j.1365-2362.2010.02436.x.
6. Griffing GT. A-I-D-S: the new endocrine epidemic. J Clin Endocrinol Metab. 1994;79(6):1530-1531.
7. Babińska A, Siekierska-Hellmann M, Błaut K, Lewczuk A, Wiśniewski P, Gnacińska M, et al. Hormonal activity in clinically silent adrenal incidentalomas. Arch Med Sci. 2012;8(1):97-103. doi: 10.5114/aoms.2012.27288.
8. Mannelli M, Lenders JW, Pacak K, Parenti G, Eisenhofer G. Subclinical phaeochromocytoma. Best Pract Res Clin Endocrinol Metab. 2012;26(4):507-515. doi: 10.1016/j.beem.2011.10.008.
9. Libè R, Dall'Asta C, Barbetta L, Baccarelli A, Beck-Peccoz P, Ambrosi B. Long-term follow-up study of patients with adrenal incidentalomas. Eur J Endocrinol. 2002;147(4):489-494.
10. Elenkova A, Matrozova J, Zacharieva S, Kirilov G, Kalinov K. Adiponectin - A possible factor in the pathogenesis of carbohydrate metabolism disturbances in patients with pheochromocytoma. Cytokine. 2010;50(3):306-310. doi: 10.1016/j.cyto.2010.03.011.
11. Emral R, Aydoğan Bİ, Köse AD, Demir Ö, Çorapçıoğlu D. Could a nonfunctional adrenal incidentaloma be a risk factor for increased carotid intima-media thickness and metabolic syndrome. Endocrinol Diabetes Nutr. 2019; pii: S2530-0164(19)30037-0. doi: 10.1016/j.endinu.2019.01.007.

12. Tuna MM, Imga NN, Doğan BA, Yılmaz FM, Topçuoğlu C, Akbaba G, et al. Non-functioning adrenal incidentalomas are associated with higher hypertension prevalence and higher risk of atherosclerosis. J Endocrinol Invest. 2014;37(8):765-768. doi: 10.1007/s40618-014-0106-5.
13. Dogruk Unal A, Ayturk S, Aldemir D, Bascil Tutuncu N. Serum Adiponectin Level as a Predictor of Subclinical Cushing's Syndrome in Patients with Adrenal Incidentaloma. Int J Endocrinol. 2016;2016:8519362. doi: 10.1155/2016/8519362.
14. Babinska A, Kaszubowski M, Sworczak K. Adipokine and cytokine levels in non-functioning adrenal incidentalomas (NFAI). Endocr J. 2018;65(8):849-858. doi: 10.1507/endocrj.EJ18-0066.
15. Taya M, Paroder V, Bellin E, Haramati LB. The relationship between adrenal incidentalomas and mortality risk. Eur Radiol. 2019. doi: 10.1007/s00330-019-06202-y.
16. Di Dalmazi G, Vicennati V, Garelli S, Casadio E, Rinaldi E, Giampalma E, et al. Cardiovascular events and mortality in patients with adrenal incidentalomas that are either non-secreting or associated with intermediate phenotype or subclinical Cushing's syndrome: a 15-year retrospective study. Lancet Diabetes Endocrinol. 2014;2(5):396-405. doi: 10.1016/S2213-8587(13)70211-0.
17. Prins JB. Adipose tissue as an endocrine organ. Best Pract Res Clin Endocrinol Metab. 2002;16(4):639-651.
18. Smitka K, Marešová D. Adipose Tissue as an Endocrine Organ: An Update on Pro-inflammatory and Anti-inflammatory Microenvironment. Prague Med Rep. 2015;116(2):87-111. doi: 10.14712/23362936.2015.49.
19. Kargi AY, Iacobellis G. Adipose tissue and adrenal glands: novel pathophysiological mechanisms and clinical applications. Int J Endocrinol. 2014;2014:614074. doi: 10.1155/2014/614074.
20. Ramanjaneya M, Conner AC, Brown JE, Chen J, Digby JE, Barber TM, et al. Adiponectin (15-36) stimulates steroidogenic acute regulatory (StAR) protein expression and cortisol production in human adrenocortical cells: role of AMPK and MAPK kinase pathways. Biochim Biophys Acta. 2011;1813(5):802-809. doi: 10.1016/j.bbamcr.2011.02.010.

21. Rossi GP, Sticchi D, Giuliani L, Bernante P, Zavattiero S, Pessina AC, et al. Adiponectin receptor expression in the human adrenal cortex and aldosterone-producing adenomas. Int J Mol Med. 2006;17(6):975-980.
22. Li P, Sun F, Cao HM, Ma QY, Pan CM, Ma JH, et al. Expression of adiponectin receptors in mouse adrenal glands and the adrenocortical Y-1 cell line: adiponectin regulates steroidogenesis. Biochem Biophys Res Commun. 2009;390(4):1208-1213. doi: 10.1016/j.bbrc.2009.10.122.
23. Paschke L, Zemleduch T, Rucinski M, Ziolkowska A, Szyszka M, Malendowicz LK. Adiponectin and adiponectin receptor system in the rat adrenal gland: ontogenetic and physiologic regulation, and its involvement in regulating adrenocortical growth and steroidogenesis. Peptides. 2010;31(9):1715-1724. doi: 10.1016/j.peptides.2010.06.007.
24. Chou SH, Tseleni-Balafouta S, Moon HS, Chamberland JP, Liu X, Kavantzas N, et al. Adiponectin receptor expression in human malignant tissues. Horm Cancer. 2010;1(3):136-145. doi: 10.1007/s12672-010-0017-7.
25. Babińska A, Pęksa R, Świątkowska-Stodulska R, Wiśniewski P, Sworczak K. Expression of adiponectin and leptin receptors in adrenal incidentaloma patients with subclinical hormone secretion. Cancer Biomark. 2018;22(2):325-332. doi: 10.3233/CBM-171049.
26. Babińska A, Pęksa R, Wiśniewski P, Świątkowska-Stodulska R, Sworczak K. Diagnostic and prognostic role of SF1, IGF2, Ki67, p53, adiponectin, and leptin receptors in human adrenal cortical tumors. J Surg Oncol. 2017;116(3):427-433. doi: 10.1002/jso.24665.
27. Isobe K, Fu L, Tatsuno I, Takahashi H, Nissato S, Hara H, et al. Adiponectin and adiponectin receptors in human pheochromocytoma. J Atheroscler Thromb. 2009;16(4):442-447.
28. Ehrhart-Bornstein M, Lamounier-Zepter V, Schraven A, Langenbach J, Willenberg HS, Barthel A, et al. Human adipocytes secrete mineralocorticoid-releasing factors. Proc Natl Acad Sci U S A. 2003;100(24):14211-14216.
29. Ehrhart-Bornstein M, Arakelyan K, Krug AW, Scherbaum WA, Bornstein SR. Fat cells may be the obesity-hypertension link: human adipogenic factors stimulate aldosterone secretion from adrenocortical cells. Endocr Res. 2004;30(4):865-870.
30. Ermetici F, Malavazos AE, Corbetta S, Morricone L, Dall'Asta C, Corsi MM, et al. Adipokine levels and cardiovascular risk in patients with adrenal incidentaloma. Metabolism. 2007;56(5):686-692. doi: 10.1016/j.metabol.2006.12.018.

31. Letizia C, Petramala L, Di Gioia CR, Chiappetta C, Zinnamosca L, Marinelli C, et al. Leptin and adiponectin mRNA expression from the adipose tissue surrounding the adrenal neoplasia. J Clin Endocrinol Metab. 2015;100(1):E101-104. doi: 10.1210/jc.2014-2274.
32. Lazúrová I, Spišáková D, Wagnerová H, Habalová V, Dravecká I, Darina P, et al. Clinically silent adrenal adenomas - their relation to the metabolic syndrome and to GNB3 C825T gene polymorphism. Wien Klin Wochenschr. 2011;123(19-20):618-622. doi: 10.1007/s00508-011-0064-2.
33. Reincke M, Beuschlein F, Slawik M, Borm K. Molecular adrenocortical tumourigenesis. Eur J Clin Invest. 2000;30 Suppl 3:63-68.
34. Akkus G, Evran M, Sert M, Tetiker T. Adipocytokines in Non-functional Adrenal Incidentalomas and Relation with Insulin Resistance Parameters. Endocr Metab Immune Disord Drug Targets. 2019;19(3):326-332. doi: 10.2174/1871530318666181009112042.
35. Ashizawa N, Takagi M, Seto S, Suzuki S, Yano K. Serum adiponectin and leptin in a patient with Cushing's syndrome before and after adrenalectomy. Intern Med. 2007;46(7):383-385.
36. Makimura H, Mizuno TM, Bergen H, Mobbs CV. Adiponectin is stimulated by adrenalectomy in ob/ob mice and is highly correlated with resistin mRNA. Am J Physiol Endocrinol Metab. 2002;283(6):E1266-1271. doi: 10.1152/ajpendo.00227.2002.
37. Okauchi Y, Ishibashi C, Shu K, Adachi S, Mineo I. Decreased Serum Adiponectin Level during Catecholamine Crisis in an Obese Patient with Pheochromocytoma. Intern Med. 2018;57(9):1253-1257. doi: 10.2169/internalmedicine.9089-17.
38. Bosanska L, Petrak O, Zelinka T, Mraz M, Widimsky J Jr, Haluzik M. The effect of pheochromocytoma treatment on subclinical inflammation and endocrine function of adipose tissue. Physiol Res. 2009;58(3):319-325.
39. Monticone S, Burrello J, Tizzani D, Bertello C, Viola A, Buffolo F, et al. Prevalence and Clinical Manifestations of Primary Aldosteronism Encountered in Primary Care Practice. J Am Coll Cardiol. 2017;69(14):1811-1820. doi: 10.1016/j.jacc.2017.01.052.
40. Dick SM, Queiroz M, Bernardi BL, Dall'Agnol A, Brondani LA, Silveiro SP. Update in diagnosis and management of primary aldosteronism. Clin Chem Lab Med. 2018;56(3):360-372. doi: 10.1515/cclm-2017-0217.

41. Urbanet R, Pilon C, Calcagno A, Peschechera A, Hubert EL, Giacchetti G, et al. Analysis of insulin sensitivity in adipose tissue of patients with primary aldosteronism. J Clin Endocrinol Metab. 2010;95(8):4037-4042. doi: 10.1210/jc.2010-0097.
42. Rojas E, Rodríguez-Molina D, Bolli P, Israili ZH, Faría J, Fidilio E, et al. The role of adiponectin in endothelial dysfunction and hypertension. Curr Hypertens Rep. 2014;16(8):463. doi: 10.1007/s11906-014-0463-7.