The studied integral biochemistry blood parameters of experimental animals throughout the whole experiment were within the physiological oscillations.

When investigating the effect of soy protein isolate on the functional state of the central nervous system of rats in the «open» field conditions it was established that in the tested doses it did not reduce locomotors activity of rats in the number of squares crossed test and orientation response in the test of «mink reflex» compared to the control.

Macroscopic investigations of internal organs of rats received soy protein isolate within 28 days were without features: all organs were correctly positioned, the cavities without effusions and adhesions. Serous membranes were smooth, nitidous. Airway was available: the lungs were elastic, airy, on the incision spot of normal color. Heart, kidneys, liver, spleen, thymus, gastrointestinal organs, adrenals, testes were of normal shape, texture, color and sizes.

Thus, the conducted research of soy protein isolate showed that it did not affect the basic integral indicators.

**Conclusions**

1. Soy protein isolate is non-toxic, does not cause locally-irritating exposure on to the skin and irritated effect on conjunctiva, it has no cumulating and sensitizing properties.
2. Macroscopic studies conducted at the end of the experiment found that soy protein isolate with prolonged introducing in doses more than 7 times higher than the recommended single process does not cause local irritant and systemic toxicity.
3. The test soy protein isolate can be attributed to non-toxic, (relatively harmless by S.D. Zaugolnikov) and low-hazard (IV class of danger according to State Standard Certifications 12.1.007) food additives.

**References:**

7. Standards for research on chemistry № 23 “Thorough toxicological evaluation — the classic method” of March 22, 1996.

Metabolic disorders in patients with adrenal incidentalomas

**Abstract:** In our study metabolic disorders was the basic component in manifestations of adrenal incidentalomas to be contributed by dislipidemia, high BMI, age, high levels of hormones and glucose, and to be confirmed by significant changes in the parameters as compared with those in the control group and those in group of patients without metabolic disorders. In addition, significant correlation was established between frequency of metabolic disorders and subclinical hormonal activity, high levels of cortisol and aldosterone, in particular.

**Keywords:** hormones, adrenal incidentalomas, metabolic disorders.
Adrenal incidentalomas are basically the tumors producing no hormones, but thorough biochemical and morphological evaluations in some patients are reported to detect subclinically excessive production of adrenal hormones [1, 53–57; 2, 23–26; 3, 284–289; 4, 40–48; 5, 1309–1311]. According to literature, pheochromocytomas occur in 1.5–11% of patients; primary aldosteromas can be seen in 1.5–3.5%, and subclinical autonomous glucocorticoid secretion, that is, subclinical Cushing’s syndrome is diagnosed in 1–29%. Furthermore, in patients with adrenal incidentaloma the prevalence of cardiovascular risk factors, which are known to be components of the metabolic syndrome, to name arterial hypertension (AH), impaired glucose tolerance (IGT), adverse lipid profiles and obesity, is higher than the one in general population [6, 61–66; 7, 327–339; 8, 1440–1448; 9, 4872–4878; 10, 89–97; 11, 217–223; 12, 423–439]. Some authors consider adenomas as causes of the metabolic syndrome [13, 998–1003], but the tumors could be its direct consequence. Reincke M. hypothesized that adrenal incidentalomas could be the unrecognized manifestations of the metabolic syndrome [14, 757–761]. The work was initiated to study metabolic and hormonal statuses in patients with adrenal incidentalomas.

Materials and methods
Clinical, hormonal and biochemical parameters were comparatively examined in ninety eight patients with adrenal incidentalomas referred to the Center for the Scientific and Clinical Study of Endocrinology, Uzbekistan Public Health Ministry. Twenty two patients with arterial hypertension but without any adrenal pathology were included into the control group. All patients underwent computer tomography of the adrenals. Concentrations of cortisol and aldosterone, as well as 24-hour urinary catecholamines, such as adrenaline, noradrenaline and dopamine were measured in each patient and in the controls. Biochemical investigation included measurement of total cholesterol, high density lipoproteins (HDL), low density lipoproteins (LDL), triglycerides, and blood electrolytes, such as, potassium, sodium and chloride. Glycemic parameters, including fasting and 2-hour postprandial glycemia were measured in all examinees by means of oral glucose tolerance test (OGTT). Body mass index and plasma renin activity were assessed in every examinee. All the parameters above were analyzed separately by a size of the neoplasm, by deviations in serum cortisol and aldosterone, and urine catecholamines, and by presence of metabolic disorders.

Results and discussion
By a size of an adrenal neoplasm all patients were divided into three groups. Of 98 patients, 57 patients (58.2%) included into the first group had adrenal neoplasms with a size < 1 cm. In 17 patients (17.4%) of the second group adrenal neoplasms varied from 1 to 3 cm. In twenty four patients (24.5%) of the third group adrenal neoplasms exceed 3 cm in size.

Mean age of 57 patients with adrenal neoplasms less than 1 cm in size was 33.7 ± 2.2 years. Mean duration of arterial hypertension was 3.83 ± 1.01 years. In this group of patients (n=57) subclinically elevated levels of cortisol were found in 7 patients (12.3%), hyperaldosteronism could be seen in 4 (7%); in 3 patients (5.3%) concentrations of 24-hour urinary catecholamines were found increased. Mean age of patients in the second group was 39.8 ± 2.9 years, mean duration of arterial hypertension was 6.26 ± 2.2 years. There were 5 cases (29.4%) of subclinical Cushing’s syndrome, 3 cases (17.6%) of hyperaldosteronism (P < 0.05 versus the size of neoplasms under 1 cm); urinary catecholamines were found elevated in 15 patients (88.2%). As compared with the patients in the first and second groups, significantly higher concentrations of hormones were found in patients with the largest adrenal neoplasms. Thus, subclinical Cushing’s syndrome and hyperaldosteronism were found in 9 (37.5%) and 4 (16.7%) patients, respectively (P< 0.05 versus the size of neoplasms under 1 cm); significantly higher concentrations of catecholamines were registered in 18 (75%). In this group of patients mean age was 39.5 ± 2.85 years, mean duration of arterial hypertension was 4.21 ± 1.3 years.

As it can be seen, frequency of subclinically elevated concentrations of adrenal hormones, cortisol and aldosterone, in particular, is directly proportional to increase in the size of adrenal incidentaloma. As to catecholamines, their elevated levels were not confirmed as statistically significant; adequate clinical presentation was absent.

Regardless of a neoplasm’s size, initial examination helped detecting hypercortisolism and hyperaldosteronism in 21 (21.4%) and 11 (11.2%) patients, respectively; significantly higher concentrations of catecholamines were found in 79 (80.6%) patients to confirm lower sensitivity of catecholamines in diagnosis of adrenal neoplasms.

Next, we compared parameter and frequency of metabolic disorders between patients with adrenal incidentalomas of various sizes and the subjects in the control group. In the first group arterial hypertension was registered in 42 of 57 patients (73.7%); its mean duration was the least one as compared with the values in other groups of patients and in the controls (3.83 ± 1 years) (P<0.05). Adverse body mass index (BMI) was found in 32 patients (56.2%). In this group metabolic disorders were registered in 38 patients (66.6%). Dislipidemia was found in 38.5% (n=22). As to carbohydrate metabolism disorders, the impaired fasting glucose (IFG), the impaired glucose tolerance (IGT) and diabetes mellitus were registered in 3 (5.3%), 7 (12.2%) and 3 (5.3%) patients, respectively.

Of 17 patients in the second group metabolic disorders were registered in 12 (70.1%) and included dislipidemia (n=7, 41.2%) and higher BMI (n=13, 76.5%). Carbohydrate metabolism disorders were found in 8 patients (47.1%) and included one case of the impaired fasting glucose (5.9%), 4 cases of the impaired glucose tolerance (23.5%) and 3 cases of diabetes mellitus (17.7%). In this group arterial hypertension was registered in 76.5% of patients (n=13) with the highest mean duration as compared with the values in other groups of patients and in the controls (6.26 ± 2.2 years).

Of twenty four patients with the largest adrenal incidentalomas (size < 3 cm) various metabolic disorders were found in 18 (75%), and this frequency is the highest one as compared with the values in other groups (66.6% and 70.1% of patients in the first and second groups, respectively). In this group adverse BMI was registered in 13 patients (54.2%), dislipidemia was found in 11 (45.8%). Carbohydrate metabolism disorders were found in 8 patients (33.3%) and included 3 cases of the impaired fasting glucose (12.5%), one case of impaired glucose tolerance (4.1%) and 4 cases of diabetes mellitus (16.6%). Arterial hypertension was found in 20 patients (83.3%).

Thus, the larger the sizes of adrenal neoplasms were the higher was frequency of metabolic disorders. As compared with the controls, in patients with adrenal neoplasms significant changes could be seen in concentrations of glucose, HDL and triglycerides as well as in BMI and arterial pressure; parameters of both lipid and carbohydrate metabolism tended to increase quite clearly.

To assess the role of subclinical hormonal activity in progression of metabolic disorders we studied incidence of the metabolic syndrome components in patients with subclinical Cushing’s syndrome, hyperaldosteronism and those with pheochromocytoma.

In our study subclinical Cushing’s syndrome was registered in 21 of 98 patients (21.4%), 77 (78.6%) patients had concentrations of cortisol within normal limits. We have managed to demonstrate clear correlation between onset and progression of metabolic disorders and high concentrations of cortisol (Table 1).
Section 7. Medical science

Table 1. – Correlation between frequency of metabolic disorders and concentrations of cortisol in patients with incidentalomas (n=98)

<table>
<thead>
<tr>
<th></th>
<th>AH</th>
<th>High BMI</th>
<th>DLP</th>
<th>CMD</th>
<th>IFG</th>
<th>IGT</th>
<th>DM</th>
<th>MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated cortisol</td>
<td>17 (80.9%)</td>
<td>15 (71.4%)</td>
<td>14* (66.7%)</td>
<td>9</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Normal cortisol</td>
<td>58 (75.3%)</td>
<td>43 (55.8%)</td>
<td>26 (33.7%)</td>
<td>20</td>
<td>5</td>
<td>8</td>
<td>7</td>
<td>51</td>
</tr>
</tbody>
</table>

Notes: AH — arterial hypertension, BMI — body mass index, DLP — dislipidemia, CMD — carbohydrate metabolism disorders, IFG — impaired fasting glucose, IGT — impaired glucose tolerance, DM — diabetes mellitus, MD — metabolic disorders.

* P<0.01 vs a group with normal cortisol

Next, we studied effect of concentrations of aldosterone on clinical symptoms of adrenal incidentalomas. Aldosterone plays a central role in the regulation of blood pressure increasing reabsorption of ions and water in the kidney, to cause the conservation of sodium, to decrease plasma renin, to accelerate secretion of potassium, and by this to cause hypoglycemia, increase in water retention, and increase in blood pressure and blood volume. When dysregulated, aldosterone is pathogenic and contributes to the development and progression of cardiovascular and renal disease. In our study subclinically elevated concentrations of aldosterone were registered in 11 patients (11.2%) with adrenal incidentalomas, its concentrations within normal limits were found in 87 patients (88.7%) (Table 2).

Table 2. – Correlation between concentrations of aldosterone and biochemical parameters in patients with adrenal incidentalomas (n=98)

<table>
<thead>
<tr>
<th></th>
<th>AH</th>
<th>High BMI</th>
<th>DLP</th>
<th>CMD</th>
<th>IFG</th>
<th>IGT</th>
<th>DM</th>
<th>MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated aldosterone</td>
<td>10 (90.1%)</td>
<td>6 (54.5%)</td>
<td>7 (63.6%)</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Normal aldosterone</td>
<td>65 (74.7%)</td>
<td>52 (59.7%)</td>
<td>33 (37.9%)</td>
<td>25</td>
<td>5</td>
<td>11</td>
<td>9</td>
<td>59</td>
</tr>
</tbody>
</table>

Notes: AH — arterial hypertension, BMI — body mass index, DLP — dislipidemia, CMD — carbohydrate metabolism disorders, IFG — impaired fasting glucose, IGT — impaired glucose tolerance, DM — diabetes mellitus, MD — metabolic disorders.

In our study concentrations of aldosterone were found to vary from 82.32 ± 5.1 pg/ml to 195.33 ± 12.5 pg/ml to be significantly higher than those in the control group (P<0.001) and in patients with normal aldosterone (P<0.001). PAC/PRA (plasma aldosterone concentration/plasma renin activity) ratio was 125.8, that is, the one not exceeding the cut-off value of 140. Of note, mean age of patients with normal aldosterone was 35.22 ± 1.35 years, while the one not exceeding the cut-off value of 140. Mean arterial blood pressure was 171.9 ± 4.84 and 105 ± 2.78 mm Hg, respectively. It should be noted that though mean concentrations of cortisol were found to vary from 82.32 ± 5.1 pg/ml to 195.33 ± 12.5 pg/ml, increase in neither cortisol nor catecholamines was registered among patients with high concentrations of aldosterone. No changes were found in the concentrations of potassium and plasma renin either. Furthermore, in patients with hyperaldosteronism incidence of the metabolic syndrome was almost as high as the one in patients with hypercortisolism. In those with hyperaldosteronism incidence of arterial hypertension was high, adverse BMI and diabetes mellitus occurred less frequently.

Pheochromocytomas, tumors associated with incidentalomas producing catecholamines are of special interest. Due to its non-specific properties it is difficult to diagnose pheochromocytomas intra vitam. In our study elevated concentrations of adrenaline were found in 79 of 98 patients (80%); levels of noradrenaline and dopamine were elevated in 59 (60%) and 27 (27.5%) patients, respectively. But clinical picture typical of pheochromocytoma could be seen in 7 patients (7.1%) only. Postoperatively pheochromocytoma was diagnosed in 9 (9.2%). Due to low specificity of the assay to measure catecholamines we did not make the point to analyze clinical, biochemical and hormonal parameters in association with their concentrations.

Presence or absence of the metabolic syndrome in patients with adrenal incidentalomas was the next aspect for us to analyze clinical-paraclinical parameters of the patients. None metabolic disorders were found in 30 of 98 examinees (30%); some or other components of the metabolic syndrome could be seen in 68 patients (70%). To clarify the causes of metabolic disorders we have performed a comparative analysis of clinical, biochemical and hormonal parameters.

Mean age of patients with adrenal incidentalomas without any metabolic disorders was 30.3 ± 1.83 years (P<0.01). There were 16 men (53%) and 14 (47%) women among them. Nineteen patients (63.3%) had arterial hypertension with mean duration of 2.68 ± 0.79 years (P<0.001 vs the values in the controls). Mean arterial pressure was 166.6 ± 6.3/106.6 ± 3.53 mm Hg, mean BMI value was 22.7 kg/m². There were no differences in mean concentrations of hormones between this group and the controls, though high cortisol was registered in 13.3% (n4) and high aldosterone was found in 6.67% (n2). High concentrations of adrenaline, noradrenaline and dopamine were found in 22 (73.33%), 17 (56.76%) and 6 (20%) patients, respectively. Parameters of lipid profile were within normal limits and did not differ from those in the controls. There were no carbohydrate metabolism disorders, and, consequently, pathological conditions, such as impaired fasting glucose, impaired glucose tolerance and diabetes mellitus in this group of patients.

The metabolic syndrome was registered in 68 of 98 patients (70%) with adrenal incidentalomas (mean age 39.1 ± 1.58 years). There was similar frequency of metabolic disorders in men and women. Arterial hypertension was registered in 56 patients of this group (82.4%). Mean duration of arterial hypertension was 5.68 ± 0.91 years, that is, significantly higher as compared with the one in patients without metabolic syndrome (P<0.05). Mean systolic and diastolic arterial pressure was 171.9 ± 4.84 and 105 ± 2.78 mm Hg, respectively. It should be noted that though mean concentrations of hormones were not different from the normal ones, isolated increase in levels of some hormones took place. Thus, hypercortisolism and hyperaldosteronism were registered in 1/4 (25%) and in
9 patients (13.34%), respectively. Elevated levels of adrenaline, nor-adrenaline and dopamine were found in 57 (83.8%), 42 (61.7%) and 21 (30.8%) patients, respectively. Total cholesterol (n=26, 38.2%), triglycerides (n=24, 35.3%), HDL (n=21, 30.9%) increased, while LDL (n=40, 58.8%) reduced. Body mass index was found adverse in 58 (85.3%) patients; mean BMI in this group of patients was 28.6 ± 0.43 kg/m². Carbohydrate metabolism disorders were found in 29 (42.6%) patients and included impaired fasting glucose (n=7, 10.2%), impaired glucose tolerance (n=12, 17.6%) and diabetes mellitus (n=10, 14.7%).

To sum up, it should be noted that metabolic disorders was the basic component in manifestations of adrenal incidentalomas to be contributed by dislipidemia, high BMI, age, high levels of hormones and glucose, and to be confirmed by significant changes in the parameters as compared with those in the control group and those in group of patients without metabolic disorders. In addition, significant correlation was established between frequency of metabolic disorders and subclinical hormonal activity, high levels of cortisol and aldosterone, in particular.

**Conclusions**

Potential sources of hormonal activity, adrenal incidentalomas in our study were accompanied by subclinical Cushing’s syndrome and hyperaldosteronism in 21.4% and 11.2%, respectively; in 9.2% it was silent pheochromocytoma. The larger the neoplasm the higher was frequency of cases of subclinical hormonal activity. Metabolic disorders were registered in 70%; higher body mass index was found in 85.3%, dislipidemia and carbohydrate metabolism disorders occurred in 58.8% and 42.6%, respectively. Frequency of metabolic disorders was proportional to the size of adrenal incidentalomas. In our study it varied from 66.6% in patients with neoplasms less than 1 cm to 75% in patients with neoplasms more than 3 cm in size (P<0.05). Significant correlation was found between subclinical hormonal activity and metabolic disorders.

**References:**