Dynamics of Anthropometric Indicators in Women of Fertile Age with Cushing’s Syndrome After Surgical and Drug Treatment

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Abstract

We studied the dynamics of anthropometric indicators in 153 women of fertile age with Cushing’s syndrome, who applied for excess weight, lack of menstruation and infertility in the RSSPMC of Endocrinology of the PHM of the Republic of Uzbekistan, from 2000 to the present. The control group consisted of 20 women with obesity of varying degrees and without menstrual irregularities.

According to the classification of the American Association of Endocrinologists from 2012, all female patients with SC registered since 2000 (the dead are not included) were distributed according to etiology as follows: 1 g. - patients with ACTH-dependent CS – 115 (75.2%), 2 g. - with ACTH-independent CS - 35 (22.9%) and group 3 - patients with ACTH-ectopic CS - 3 (1.9%). 6 months after surgical and drug treatment, in groups 1 and 2 of patients there was a significant improvement compared with the average OT, OB, OT / OB data before treatment, while in patients of 3 groups there were significant changes in the average OT, OB, OT values / OB after 6 months of treatment not established.

Keywords: Cushing’s Syndrome, Fertile Age, RSSPMC.

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RELEVANCE

The leading pathogenetic factor in the development of the clinical picture in endogenous hypercorticism is hypercortisolemia, which is proved by the development of similar symptoms during long-term treatment with synthetic glucocorticoids (drug-induced Cushing’s syndrome). In this regard, clinical manifestations in various forms of endogenous hypercorticism (ACTH-dependent and ACTH-independent) are of the same type and can be considered together [1-5].

The clinical picture of hypercorticism includes dysplastic obesity, trophic skin changes, arterial hypertension, systemic osteoporosis, myopathy, steroid diabetes mellitus, hypogonadism, secondary immunodeficiency, steroid encephalopathy and emotional and mental disorders. Most researchers note the relative rarity of the presence of all symptoms both in the advanced stage and in relapse of the disease [6-10].

Dysplastic obesity is one of the most striking and common symptoms of endogenous hypercorticism (observed in 90% of patients). Excessive fat deposition is noted in the trunk, abdomen, and face. On the upper and lower extremities, on the contrary, there is a decrease in fat deposits, the limbs are "thin" compared to other parts of the body. In patients with a severe course of the disease (usually young people), obesity may be absent, but a characteristic redistribution of the subcutaneous fat layer is observed to one degree or another [11].

Thus, changes in the appearance of patients during the initial examination (increase in body weight, redistribution of fatty tissue, skin manifestations) suggest the presence of SC. At the same time, the dynamics of changes in the patient's appearance at the stages of treatment indicates remission or relapse of the disease even before a more detailed examination [12].

Reduction of body weight and reduction of the distribution of adipose tissue is one of the main indicators of the effectiveness of the treatment When complete, stable remission is achieved, body weight can decrease by up to 40% In 15-25% of patients after bilateral adrenalectomy performed for ACTH-HSC, micronucleal dysplasia and macronucleal hyperplasia of the adrenal glands, excess body weight persists. This may be due to the hypothalamic genesis of obesity (with ACTH-HSC), as well as the use of unreasonably high doses of glucocorticoids during replacement therapy [12-15].

In almost all patients after corticosteroma removal (in the absence of malignant growth and distant metastases), body weight and distribution of subcutaneous fat are normalized.
in the first 6 months [16-18].

Based on the above, early diagnosis, the study of long-term treatment results and the development of optimal algorithms for diagnosis and treatment, monitoring of quality of life is relevant both in scientific and practical terms [19-20].

The above determines the relevance of research aimed at developing an integrated approach to the treatment of obesity in young women with SC, taking into account the peculiarities of metabolic and hormonal imbalances, eating behavior and reproductive disorders, which can improve the quality of life of patients and reduce the risk of obesity-related diseases.

There are very few publications in the literature devoted to evaluating the effectiveness of surgical treatment of SC, taking into account the study of anthropometry indicators. The stimulating factor for the performance of this work was also the lack of sufficient information about the condition of patients after surgical treatment in terms of the dynamics of anthropometric indicators. These data can solve the problems of rehabilitation of patients and their return to a full lifestyle.

All this was the reason for this study.

THE PURPOSE OF THE STUDY

To study the dynamics of anthropometric indicators in women of fertile age with SC before and 6 months after treatment.

MATERIAL AND METHODS

The dynamics of anthropometric indicators was studied in 153 out of 212 women with Cushing's Syndrome who applied for excess weight, lack of menstruation and infertility in the RSNPCE of the Ministry of Health of the Republic of Uzbekistan, starting from 2000 to the present. The control group consisted of 20 women with obesity of various degrees and without menstrual disorders.

According to the classification of the American Association of Endocrinologists from 2012, all female patients with SC who have been registered since 2000 (the deceased are not included) were distributed according to etiology as follows: 1 gr. – patients with ACTH-dependent SC – 115 (75.2%), 2 gr. - with ACTH-independent SC – 35 (22.9%) and group 3 – patients with ACTH-ectopic SC – 3 (1.9%). The average age was 27.58 ± 3.4 years (from 17 to 49 years). The duration of the disease averaged 4.2± 0.2 years. The age of patients in group 1 ranged from 20 to 39 years and averaged 28.3 ± 0.64 years. In the 2nd group of 22-37 years, on average 30.4 ± 0.51 years and in the 3rd group - an average of 29.4 ± 0.51 years, respectively.

All patients underwent a complex of studies that included general clinical (general blood and urine analysis), biochemical (blood glucose, rovi electrolytes, urea, creatinine, lipid spectrum), hormonal (ACTH, LH, FSH, prolactin, free testosterone, blood cortisol, free testosterone, estradiol, progesterone, insulin, etc.) Ultrasound of internal and genital organs, as well as magnetic resonance imaging (MRI) of the Turkish saddle and computed tomography (CT) of the adrenal glands, chest X-ray, spine X-ray. In addition, patients underwent a study of the rhythm of secretion of daily cortisol in the blood, determination of free cortisol in daily urine, as well as a large sample with dexamethasone. If necessary, a glucose-tolerance test was performed.

Anthropometric study - was carried out immediately during the initial examination, in dynamics and included the determination of height, MT, determination of body mass index (BMI) (Quetelet index), calculated by the formula: BMI (kg/m2) = (MT, kg) / (height, m).

According to the BMI values recommended by WHO (1997), the degree of obesity was determined. Determination of the nature of the distribution of adipose tissue was carried out in accordance with the coefficient (ratio) of the length of the waist circumference (FROM) to the length of the hip circumference (ABOUT). The OT/O ratio of more than 0.85 was regarded on the basis of WHO recommendations (1997) as abdominal obesity (AO), less than the specified value – as glucose-femoral (GFO).

When prescribing therapy regimens, first of all, we relied on various international guidelines – Management of obesity 115, National Guideline (Scottish Intercollegiate Guidelines Network, Part of NHS Quality Scotland, 2010, 96 pages); and others.

The methods of treatment of ACTH-ZSC were surgical (TAG and AE, surgical treatment of ACTH of ectopic foci), radiation therapy (LT) and drug therapy (MT), as well as combination therapy (CTe).

All patients with SC received treatment in the Department of Neuroendocrinology and Neurosurgery of the RSNPCE of the Ministry of Health of the Republic of Uzbekistan named after Academician E.H. Turakulov. Transnasal pituitary adenomectomy (TAG) was performed primarily in 107 (50.5%) patients with ACTH-HSC, of which 10 (9.3%) were performed secondarily (Prof. Powell M.P. (Great Britain, London), MD Fayzullaev R.B., MD Makhkamov K.I.). Adrenalectomy was performed in only 43 (20.3%) patients, of them with ACTH-ZSC in 11 patients. All patients with surgical treatment developed compensation for the condition on the background of HRT (they were prescribed prednisone therapy at a dose of 5 to 15 mg).

The patients were prescribed non-drug therapy and drug therapy. Non-drug therapy included general recommendations for measuring weight every day before and after exercise therapy, counting daily calories, as well as giving up easily digestible carbohydrates. Drug therapy included the following schemes:

Group 1 was prescribed a combination of siofor 1000 mg per day + veroshpiron 100 mg twice a week + iodamin 100 mg in the morning + levothyroxine 50 mg in the morning +
antidepressants courses (amitriptyll, phenibut, rexetin, etc.). Group 2 was assigned a combination of siofor 1000 mg per day + veroshpiron 15 mg in the morning + levothyroxin 50 mg in the morning + reducsin 15 mg in the morning after meals + antidepressants courses (amitriptyll, phenibut, rexetin, etc.). Group 3 was assigned a combination of iodmarin 100 mg in the morning + levothyroxine 50 mg in the morning.

The obtained data were processed using computer programs Microsoft Excel and STATISTICA 6. The average values (M) and standard deviations of the averages (m) were calculated. The reliability of the differences in the level between the groups was assessed by the value of the confidence interval and the Student's criterion (p). The differences were considered statistically significant at p<0.05.

**RESULTS**

It was found that remission was achieved in 82.4±5.63% of women of fertile age, and in 17.6±5.63% of patients in general, remission was not achieved. Table 1 shows the activity of the hypercerciticism process in various forms of the disease.

Table 1: Characteristics of the condition of patients with SC according to the register (n=153)

<table>
<thead>
<tr>
<th>№</th>
<th>Condition of patients</th>
<th>ACTG ESC (%±m) n=115</th>
<th>ACTG ESC (%±m) n=35</th>
<th>ACTG ESC (%±m) n=3</th>
<th>Total (%±m) n=153</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Remission n=126</td>
<td>77,4±3,22</td>
<td>97,1±4,12 ***</td>
<td>100,0±2,83</td>
<td>82,4±5,63</td>
</tr>
<tr>
<td>2</td>
<td>n=27</td>
<td>22,6±2,63</td>
<td>2,9±1,83*</td>
<td>0,0</td>
<td>17,6±5,63</td>
</tr>
</tbody>
</table>

Note: - the significance of differences compared to ACTH-dependent SC, where p < 0.001. (NDR-patients who have not achieved remission, P- patients who have developed a relapse)

As can be seen from Table 1, a high frequency of remission was found in patients with ACTH-NSC, which amounted to 97.1±4.12% of cases, and only in 1 case (2.9%) a relapse of the disease developed due to an unfavorable outcome with the development of metastases after surgery for adrenal carcinoma.

According to the research results of G.D. Narimova, in 2018, 71% of patients with SC in the Republic of Uzbekistan achieved remission [7]. Moreover, the lowest remission was observed in patients with ACTH–HSC and amounted to 65.3%, which is consistent with the literature data.

Table 2 presents the data of anthropometry by groups before treatment. As can be seen from Table 2, patients with grade 1 BMI were most common in all groups.

Further, to perform the study, we calculated other anthropometric data for groups before treatment. As can be seen from Table 2, our study was dominated by persons with grade 2 obesity – 104 cases out of 153 (67.9%). Obesity of the 1st degree was observed in the second place in terms of frequency – 35 cases (22.8%) and obesity of the 3rd degree – 15 cases (9.8%) in the third place.

Table 2: Average BMI values by groups before treatment

<table>
<thead>
<tr>
<th>№</th>
<th>Group</th>
<th>30,0-34,9 kg/m²</th>
<th>35,0-39,9 kg/m²</th>
<th>≥40 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>group</td>
<td>n=25</td>
<td>n=9</td>
<td>n=4</td>
</tr>
<tr>
<td>2</td>
<td>group</td>
<td>n=9</td>
<td>n=12</td>
<td>n=9</td>
</tr>
<tr>
<td>3</td>
<td>group</td>
<td>n=1</td>
<td>n=1</td>
<td>n=1</td>
</tr>
</tbody>
</table>

Total 35 104 15

Table 3 shows the data FROM, ABOUT, FROM/ABOUT by groups before treatment. As can be seen from Table 3, the average values of OT, OT, OT/OB corresponded to the degree of BMI by group and increased with its increase.

Table 3: Average values FROM, ABOUT, FROM/ABOUT by groups before surgical treatment

<table>
<thead>
<tr>
<th>Gro</th>
<th>30,0-34,9 kg/m²</th>
<th>35,0-39,9 kg/m²</th>
<th>≥40 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 group</td>
<td>OT O B</td>
<td>OT OB</td>
<td>OT O B</td>
</tr>
<tr>
<td>2 group</td>
<td>85, 1±13, 8</td>
<td>89, 9±11, 6</td>
<td>0,9±0, 0, 0</td>
</tr>
<tr>
<td>3 group</td>
<td>86, 3±11, 5</td>
<td>88, 7±10, 9</td>
<td>0,9±0, 0, 0</td>
</tr>
<tr>
<td>4 group</td>
<td>87, 2±11, 3</td>
<td>89, 2±10, 9</td>
<td>0,9±0, 0, 0</td>
</tr>
</tbody>
</table>

In the postoperative period, the patients were prescribed non-drug and drug therapy according to the above schemes in groups.
Table 4 shows the anthropometry data by groups 6 months after treatment.

Table 4: Average BMI values by group 6 months after treatment

<table>
<thead>
<tr>
<th>№</th>
<th>Group</th>
<th>30.0-34.9 kg/m²</th>
<th>35.0-39.9 kg/m²</th>
<th>≥40 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 group</td>
<td>n=106</td>
<td>26.7 ± 3.5*</td>
<td>34.2 ± 2.9*</td>
</tr>
<tr>
<td>2</td>
<td>2 group</td>
<td>n=22</td>
<td>28.1 ± 3.2*</td>
<td>33.4 ± 3.2*</td>
</tr>
<tr>
<td>3</td>
<td>3 group</td>
<td>n=3</td>
<td>32.8 ± 3.4</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>131</td>
<td>21</td>
<td>1</td>
</tr>
</tbody>
</table>

As can be seen from Table 4, in all groups of patients there was a significant decrease in BMI of 1 and 2 degrees 6 months after surgical and drug treatment. At the same time, in patients of group 3 with a grade 3 BMI, a tendency to decrease BMI was achieved after 6 months.

In addition, fertility recovery and pregnancy were achieved in group 1 patients without stimulation treatment – in 23.0% of cases (in 30 patients).

Table 5 shows the data of OT, OT, OB/OT by group 6 months after treatment.

As can be seen from Table 5, in groups 1 and 2 of patients, there was a significant improvement in indicators compared to the average data from, ABOUT, FROM / ABOUT before treatment, while in patients of group 3, there were no significant changes in the average values FROM, ABOUT, FROM / ABOUT after 6 months of treatment.

Table 5: The average values of OT, OB, OT / OB in groups 6 months after treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>30.0-34.9 kg/m²</th>
<th>35.0-39.9 kg/m²</th>
<th>≥40 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80.1 ± 6.4</td>
<td>82.1 ± 8.3*</td>
<td>100.4 ± 8.9</td>
</tr>
<tr>
<td>2</td>
<td>79.1 ± 4.3</td>
<td>83.2 ± 8.4*</td>
<td>105.4 ± 8.9</td>
</tr>
<tr>
<td>3</td>
<td>89.4 ± 9.4</td>
<td>91.5 ± 12.3</td>
<td>106.7 ± 11.7</td>
</tr>
</tbody>
</table>

**DISCUSSION OF THE RESULTS OBTAINED**

Like many pathological conditions, SC contributes to the development of other complications, including obesity and impaired reproductive function [7]. Despite this functional state of the gonads in SC, at the same time, the issues of overweight therapy in SC, a combination of drug and non-drug treatment in the postoperative period are still insufficiently studied. In the literature, there are only some works devoted to this issue, in which they are limited to studying the level of total estrogens [15, 17, 18].

Back in 1990, Manusharova R A, VeĭNberg M E described the main parameters of the reproductive system in 121 women with Itsenko-Cushing's disease and 87 with primary obesity before and after therapy. Itsenko-Cushing's disease was treated with drugs affecting the adrenal glands (chloditan, destruction of one or both adrenal glands, unilateral or bilateral adrenalectomy) and the hypotalamic-pituitary zone (paradole, peritol, nakom, X-ray therapy). Combination therapy of primary obesity included a low-calorie diet (approximately 1200 kcal) with 1-2 fasting days per week, a set of therapeutic exercises, physiotherapy and balneotherapy. The obtained results allowed the authors to conclude that pathogenetic therapy leading to stable clinical and hormonal remission of Itsenko-Cushing's disease and weight loss in primary obesity, as a rule, leads to the restoration of the functioning of the reproductive system in such patients [129].

According to our research, 6 months after the surgical treatment and the performance of medication, as well as non-drug treatment, significant shifts from the initial data appeared in group I and II, namely, a significant decrease in BMI, OT, OT/OT was observed. While in patients of group 3 there were no significant changes in BMI, OT, OB / OB after 6 months of treatment. In addition, positive changes in weight also affected the reproductive function of the patients: spontaneous fertility recovery was observed and pregnancy was achieved in group 1 patients – in 23.0% of cases (in 30 patients).

**CONCLUSIONS**

1. Thus, the inclusion in the traditional treatment of patients with SC of various groups in the postoperative period of drug and non-drug treatment contributes to a significant improvement in clinical indicators - a decrease in BMI, which indirectly indicates that in the studied groups of women obesity is one of the makers of reproductive function disorders.

2. Optimization of the treatment of obesity in women of reproductive age with SC is based on the compilation of individual programs, the choice of which is determined by the values of anthropometric indicators, the state of hormonal and metabolic status, the peculiarities of eating behavior and the personal-emotional sphere, the state of menstrual and
reproductive function.

3. Carrying out a complex of therapeutic measures, taking into account the developed algorithm of individual selection of obesity therapy, allows you to effectively reduce and maintain the achieved body weight, contributes to the improvement of somatic and reproductive health in women of childbearing age with SC.

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