КЛИНИЧКИ ИСТРАЖУВАЊА

АНДРОИД /НОЗЕ И НОЗЕ /ТРУП ИНДЕКСИ ОДРЕДЕНИ СО АБСОРПЦИМЕТРИЈА СО ДВОЈНО-ЕНЕРГЕТСКИ Х-ЗРАЦИ КАЈ КУШИНГ И НЕ-КУШИНГ ЗДЕБЕЛЕНИ ЖЕНИ

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Извадок

Целта на ова истражување беше да изврши проценка на централната дебелина, која е основна карактеристика на Кушинговиот синдром (КС), со апсорпциометрија со двојно-енергетски х-зраци и да се одредат индекси кои прецизно ги диференцираат КС од не-КС задебелените жени. Кај 12 жени со КС и 12 контролни здебелени жени (КД) со соодветен ИТМ како и кај 12 контролни здрави жени (К) со нормален ИТМ беа испитувани ДХА параметрите: регионална (труп, раце и нозе), ткивна (ТМ) и масна маса (ММ), како и дијагностичката точност (ДТ) на пресечните точки (ПТ) на нивните количници. Најдобра диференцираност на КС од К обезбеди ПТ од 0,24 за андроид/нозе ТМ количникот со ДТ од 100%, додека ПТ на количникот нозе/труп ТМ (0,67) имаше ДТ од 95,83%. Андроид/нозе ММ за ПТ од 0,25 ги диференцираше КС од К со ДТ од 100%, и нозе/труп ММ количникот од 0,69 ги диференцираше КС од К со ДТ од 91,67%. Андроид/нозе ТМ (ПТ 0,27) и нозе/труп ТМ количниците (ПТ 0,62) ги диференцираа КС од КД со ДТ од 87,5%. Заклучок: Индексите андроид/нозе и нозе/труп ТМ и ММ ја откриваат екстремната централна дистрибуција на телесните маснотии кај КС, значајно ги диференцираат КС од К и КД, и можат да бидат употребувани како ДХА индекси за екстремна централна абдоминална дебелина кај КС и не-КС здебелените жени. Андроид/нозе индексот има повисока ДТ и предиктивна вредност на екстремната висцерална дебелина кај КС, споредено со нозе/труп индексот.

CLINICAL SCIENCE

ANDROID/LEGS AND LEGS/TRUNK INDEXES DETERMINED WITH DUAL-ENERGY X-RAY ABSORPTIOMETRY IN CUSHING'S AND NON CUSHING'S OBESE WOMEN

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Abstract

The aim of this study was to evaluate the central obesity, which is a main characteristic of Cushing's syndrome (CS), with dual-energy x-ray absorptiometry (DXA) and to determine DXA indexes that precisely differentiate CS from non CS obese women. In 12 CS women and 12 control obese (CO) with appropriate BMI which was not significantly different from CS, and 12 healthy control women (C) with normal BMI, the following DXA parameters were evaluated: regional (trunk, android and legs) tissue (TM) and fat mass (FM), and also the diagnostic accuracy (DG) for their ratio index cut-off points (CP). The best differentiation of CS from C obtained CP of 0.24 for android/legs TM ratio with DG of 100%, while CP for legs/trunk TM ratio (0.67) had DG of 95.83%. Android/legs FM ratio CP of 0.25 differentiated CS from C for DG of 100% and legs/trunk FM ratio of 0.69 differentiated CS from C for DG of 91.67%. Android/legs TM ratio (CP 0.27) and legs/trunk TM ratio (CP 0.62) differentiated CS from CO with DG of 87.5%. Conclusion: DXA indexes android/legs and legs/trunk TM and FM discovered extreme central body fat distribution in CS, differentiated them significantly from C and CO, and could be used as DXA indexes of extreme central, abdominal obesity in CS and non CS obese women. Android/legs index had higher DG and predictive value of extreme visceral obesity in CS, compared to legs/trunk index.

Introduction

The core abnormality of CS is extreme central, visceral, abdominal obesity. Chronic hypercortisolemia due to Cushing's disease (CD) results in abnormal adipose tissue distribution.[1] Measurements of body composition and body fat distribution have provided a research tool to study the metabolic effects of aging, obesity, and various diseases such as CS.[2] Obesity and central body fat distribution are known risk factors for cardiovascular and metabolic diseases. Dual-energy X-ray absorptiometry (DXA) body composition and fat distribution assessment may be useful in studies related to obesity-associated disease risk.[3] DXA is a gold standard for assessment of bone health and body composition, because of its reliability, precision and the fact that it is based on a three-compartment model.[4] Published studies have shown a good correlation between central abdominal fat by DXA and visceral fat by computed tomography or magnetic resonance imaging.[5,6] DXA method determines absolute (kg) and relative (%) total, bone, lean and fat body mass and separately their regional values on arms, legs, head and trunk (includes ribs, pelvis, abdominal, thoracic and lumbar spine).[7] Shubeska-Stratrova S. (2015), showed that the ratios of non-significantly different central and peripheral regional parts of the body precisely differentiated patients with CS and non CS obese, and confirmed central body fat distribution in CS. Relationships between central regional tissue and fat mass to peripheral regional parts of the body in CS are needed as diagnostic DXA indexes of central obesity.[8]

The aim of this study was to evaluate the central obesity with DXA indexes android/legs and legs/trunk tissue mass (TM) and fat mass (FM) and to determine their diagnostic accuracy and predictive value in precise differentiation of CS from non CS obese women

Material and Methods

This transversal study was organized and realized at the University Clinic of Endocrinology, Diabetes and Metabolic Disorders, University „Ss Cyril and Methodius", Medical Faculty in Skopje. Central obesity was evaluated in two groups of obese women. One group of obese women (N=12) had Cushing's syndrome (Cushing's syndrome group, CS), diagnosed with standard clinical examinations; hormonal and metabolic parameters; anthropometry; and dual-energy x-ray absorptiometry (DXA). The other group (N=12) comprised control obese women (CO) without Cushing's syndrome or other clinical condition. These two groups were matched according to age and BMI, which mean values were 39.92 ± 12.62 y and 29.63 ± 3.96 kg/m2 in CS, and 36.4 ± 13.72 y and 29.56 ± 3.57 kg/m^2 in CO. The results of CS and CO were compared with a group of healthy woman with normal BMI, assigned as a control healthy group (C) with mean age of 36.8 ± 12.09 y and mean BMI of 22.29 ± 1.37 kg/m^2. All examinees were premenopausal. CS had not received any treatment at the time of assessment and had typical signs and symptoms of Cushing's syndrome including extreme central obesity, which was discovered with anthropometry and DXA. All investigated women gave a personal permission to be included in this study and have been treated according to the Declaration of Helsinki.

DXA assessment was performed with DXA System Lunar DPX-NT, which uses enCore Windows-XP Professional OS computer. The entire body of each subject was scanned. During DXA scan, the subject was in a supine position while the x-ray scanner performed a series of transverse scans, measured at 1cm intervals from the top of the head to the bottom of the toes. The DXA machine was calibrated daily in accordance with the manufacturer's guidelines to ensure adequate quality control. The following regional (segmental) DXA indicators were determined: trunk, android and legs tissue (TM) and fat mass (FM) in kg; and segmental ratios between central and peripheral parts of the body an-

droid/legs (A/legs) and legs/trunk tissue and fat mass ratios.

Statistical analysis was done with SPSS for Windows, version 14.0. Variables were presented as means ± standard deviations. Differences between the groups were tested by unpaired t-test and ANOVA was used to compare the measurements with normal distribution. Level of significance was set at $p < 0.05$. Cut-off point values were determined for all DXA indexes and their specificity, sensitivity, positive and negative predictive value and diagnostic accuracy (DG) were evaluated in the following way:

- Sensitivity (true positive rate) is the probability that a test result – extreme visceral obesity will be positive when the CS disease is present.

- Specificity (true negative rate) is the probability that a test result will be negative; there is no extreme central body fat distribution, when the disease is not present in C and CO.

- Positive predictive value (PPV): the proportion of those with a positive test result (extreme central body fat distribution) who actually have a disease (CS).

- Negative predictive value (NPV): the proportion of those with a negative test result (without extreme central obesity) who do not have a disease (C and CO).

- Diagnostic accuracy (effectiveness) was expressed as a proportion of correctly classified subjects (true positive rate + true negative rate) among all subjects.

Results

Table 1.   Differences in regional tissue and fat mass in Cushing's and non Cushing's obese women compared with healthy controls

Variable (kg)	Investigated groups		Significance (p)			
	CS[1]	CO	C	CS/CO	CS/C	CO/C
Trunk tissue mass	39.12 ± 7.39	35.57 ± 6.24	26.8 ± 3.07	NS[2]	<0.001	0.001
Android tissue mass	6.67 ± 1.4	5.77 ± 1.39	3.83 ± 0.55	NS	<0.001	<0.001
Legs tissue mass	21.08 ± 5.68	24.58 ± 3.77	20.59 ± 2.4	0.048	NS	NS
Trunk fat mass	19.76 ± 4.96	16.39 ± 3.6	9.48 ± 2.33	0.037	<0.001	<0.001
Android fat mass	3.65 ± 1.00	2.85 ± 0.85	1.32 ± 0.40	0.018	<0.001	<0.001
Legs fat mass	9.82 ± 3.77	11.83 ± 2.54	8.5 ± 1.73	NS	NS	0.007

[1] CS, obese women with Cushing's syndrome; CO control obese women; C, control healthy women; [2]NS, not significant

Differences in regional TM and FM between investigated groups are shown in Table 1. Trunk and android TM are not significantly higher in CS compared to CO. Trunk and android FM were higher in CS compared to CO with a very small significant difference (p=0.037 and p=0.018). Trunk and android TM and FM values in C were significantly lower compared to CS and CO (p<0.001).

Legs lean mass (LM) and FM were estimated separately. Mean value of legs LM in CS was 11.26 ± 2.10 kg and it was significantly lower (p<0.042) compared to CO who had mean value of 12.76 ± 1.91 kg. Mean value of legs LM in C was 12.09 ± 1.01 kg. Legs FM was not significantly different between CS and CO (p>0.05). Legs TM was lower in CS compared to CO with a small significant difference (p<0.048).

Table 2. Differences in tissue and fat mass ratios indexes in Cushing's and non Cushing's obese women compared with healthy controls

Index tissue and fat mass ratios	Investigated groups			Significance (p)		
	CS[1]	CO	C	CS/CO	CS/C	CO/C
Android/Legs TMR[2]	0.33 ± 0.05	0.23 ± 0.04	0.19 ± 0.03	<0.001	<0.001	0.01
Android/Legs FMR	0.40 ± 0.11	0.24 ± 0.06	0.15 ± 0.04	<0.001	<0.001	0.014
Legs/trunk TMR	0.53 ± 0.07	0.69 ± 0.08	0.77 ± 0.09	<0.001	<0.001	0.01
Legs/trunk FMR	0.49 ± 0.14	0.73 ± 0.13	0.92 ± 0.18	<0.001	<0.001	0.005

[1]CS, obese women with Cushing's syndrome; CO control obese women; C, control healthy women; [2]TMR, tissue mass ratio; FMR, fat mass ratio

Android/legs TM and FM ratios indexes were significantly higher in CS compared to CO and C (p<0.001). Legs/trunk TM and FM ratios indexes values were significantly lower in CS compared to CO and C (p<0.001). The results are shown in Table 2.

Table 3. Cut-off points of tissue and fat mass ratio indexes that best differentiated Cushing's, non Cushing's obese and healthy controls

Index mass ratios		Cut-off point	S[1] (%)	SP (%)	PPV (%)	NPV (%)	DG (%)
Android/Legs (CS-C)[2]	TMR	0.24	100	100	100	100	100
	FMR	0.25	100	100	100	100	100
Android/Legs (CS-CO)	TMR	0.27	91.67	83.33	84.62	90.91	87.5
	FMR	0.26	100	66.67	75	100	83.33
Legs/trunk (CS-C)	TMR	0.67	100	91.67	92.31	100	95.83
	FMR	0.69	91.67	91.67	91.67	91.67	91.67
Legs/trunk (CS-CO)	TMR	0.62	91.67	83.33	84.62	90.91	87.5
	FMR	0.65	83.33	75	76.92	81.82	79.17

[1]S, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; DG, diagnostic accuracy; [2]CS, obese women with Cushing's syndrome; CO control obese women; C, control healthy normal weight women; TMR, tissue mass ratio; FMR, fat mass ratio

Cut-off points of TM and FM ratio indexes and their DG are shown in Table 3. Cut-off point value of 0.24 for android/legs TM ratio and 0.25 for android/legs FM ratio, differentiated the best CS and C for DG of 100%. Cut-off point of legs/trunk (0.67) TM ratio had DG of 95.83% and legs/trunk FM ratio cut-off point (0.69) had DG of 91.67% in differentiation of CS from C. CS and CO were differentiated the best for A/legs ratio TM cut-off point value of 0.27 and legs/trunk TM ratio cut-off point value of 0.62 with DG of 87.5%. Android/legs ratio FM cut-off point value of 0.26 differentiated CS and CO for DG of 83.3

Discussion

CS patients are characterized with extreme central, visceral body fat distribution.[9] Android obesity in CS and in non-CS abdominal obese with the metabolic syndrome, which is predominantly visceral, intra-abdominal, is more predictive of adipose-related comorbidities than gynecoid obesity,

which has a relatively peripheral (gluteal) distribution. There is growing evidence that intra-abdominal adipose tissue, rather than total body fat, is a risk factor for metabolic conditions associated with obesity. For this reason, the evaluation of intra-abdominal adipose tissue is clinically important.[10,11] Because of that, effective methods for assessing visceral fat are important to investigate its role for the increased health risks in obesity.[12,13,14] There is an increased interest in the evaluation of various methods for assessment of body composition and fat distribution.

DXA provide useful information on fat and lean masses as single measurement in an individual, particularly with respect to limb lean mass. A recent study has suggested that central fat distribution measured with DXA is a useful marker of insulin sensitivity in healthy subjects, and that a simple measurement of total (visceral plus anterior and posterior subcutaneous fat) abdominal fat mass is highly predictive of health risks and may be as valuable as measuring intra-abdominal fat depots.[15,16]

DXA is a good alternative to CT for predicting abdominal fat in the elderly population.[17] This method allows us to determine more accurately the degree of obesity of a particular patient as well as body fat distribution.[2,4]

DXA is used to quantify abdominal fat mass.[18] Central abdominal fat measured by DXA includes the visceral fat at this region plus anterior and posterior subcutaneous fat, and it highly correlates with intra-abdominal (visceral) fat measured by CT or MRI.1[9-27] A strong correlation exists between DXA and CT values for total abdominal fat.[17,22]

Patients with CS had less than a twofold increase in subcutaneous fat and greater than a fivefold increase in intra-abdominal fat compared with values in healthy subjects. These findings suggest that fat in different body compartments responds differently to disease processes and that DXA can be used to measure these changes.[28,29]

A reduction of the total adipose tissue volume and a redistribution of adipose tissue from visceral to peripheral depots were found by using a multiscan CT technique after normalization of the hypercortisolic state in women with CS.[30] The first study concerning the measurements of body composition in CS using DXA and CT was published by Wajchenberg.[31] Patients with CS had no increase in total body fat or the trunk region, but had a higher intra-abdominal fat area compared to obese subjects.

The study of Schafroth showed on a subgroup of 12 CS patients that trunk fat mass was significantly elevated, compared to obese controls (19.2 kg vs. 14.7 kg, p < 0.01), whereas total fat mass was not significantly increased.[9] The results of our study are very similar to the study of Schafroth. Trunk and android TM values were not significantly different between CS and CO, and trunk (19.76±4.96 kg) and android FM (16.39±3.6 kg) values were higher in CS with a small significant difference (p=0.38 and p=0.018). Trunk and android TM and FM levels in C were significantly lower than CS and CO because of significantly lower BMI in C. These data indicate that these regional DXA measurements cannot be used as indicators of visceral obesity in CS as well as CO.

Age and menopausal status have no influence on the differences in fat mass and its distribution between CS, CO and C, because evaluated women in this study were age matched and all of them are premenopausal.

The study of Burt et al. in 2006 concluded that FM was higher and LBM lower in CS patients. However, there was a greater abnormality of regional body composition in patients with CS who exhibited a lower limb lean mass and a greater truncal fat.[32] Truncal fat represented a greater proportion of total FM in CS (52.5 ± 1.8% vs. 46.9 ± 1.3%, p = 0.014) than in normal subjects.[32] The results of the Burth study were confirmed in this study in which legs FM was not different among CS and CO, but legs TM was lower in CS compared to CO with a small significant difference as a result of lower legs LM.

In Jebb's study Cushing disease patients had higher visceral versus total adipose tissue ratios, suggesting that glucocorticoids play a pivotal role in the pathogenesis of central obesity.[1]

This study represents continuation of the previous study of Shubeska-Stratrova, which indicated the need of determination of cut-off point values for different DXA body segmental indexes in order to evaluate their diagnostic value. In the previous study, DXA indexes were presented by ratios of central to peripheral segmental parts of the body that best differentiated CS from C and CO. DXA indexes of central body fat distribution in CS also could be a gold standard, diagnostic criterion of extreme central, visceral obesity in C and CO (non CS).[8]

In this study it was found that android/legs and legs/trunk TM and FM ratios differentiated CS and CO with very high significance (p<0.001) and discovered extreme central body fat distribution in CS.

Lower legs/trunk TM values differentiated better CS from CO than legs/trunk FM, because of lower legs LM in legs TM in CS compared to CO, and very low significant higher trunk FM in CS compared to CO (p<0.037). Therefore, legs/trunk TM ratio had higher DG (87.5%) than legs/trunk FM ratio (79.17%).

Legs TM and FM were not significantly different between CS and C, but trunk and android TM and FM were significantly higher in CS than C (p<0.001). Therefore, android/trunk TM ratio differentiated CS and C with DG of 95.83% and android/trunk FM ratio differentiated them for DG of 91.67%.

Cut-off point value of 0.24 for android/legs TM ratio and 0.25 for android/legs FM ratio differentiated the best CS and C for sensitivity, specificity, predictive value and DG of 100%. Legs/trunk TM ratio cut-off point 0.67 differentiated CS and C for sensitivity of 100% and DG of 95.83%, and legs/trunk FM ratio cut-off point value of 0.69 differentiated them for DG of 91.67%.

Cut-off point value of 0.27 for android/legs TM ratio, and 0.62 for legs/trunk TM ratio differentiated CS and CO for DG of 87.5%. Android/legs FM ratio cut-off point value of 0.26 differentiated CS and CO for sensitivity of 100% and DG of 83.33%. Legs/trunk FM ratio cut-off point value of 0.65 had the lowest DG of 79.17% in differentiation of CS and CO.

In medical diagnosis a perfect predictor described as 100% sensitive means that all individuals with CS are correctly identified as sick – with extreme visceral obesity. It is most important not to avoid individuals with extreme visceral obesity and to take care of them on time irrespective of the fact whether they are CS patients or metabolic syndrome patients with extreme visceral obesity.[9]

Conclusions

DXA indexes android/legs and legs/trunk TM and FM ratios discovered extreme central body fat distribution in CS; differentiated them significantly from C and CO, and could be used as DXA indexes of extreme central, visceral, abdominal obesity in CS and non CS obese women. Android/legs index had higher DG and predictive value of extreme visceral obesity in CS and non CS than legs/trunk index. These data confirmed android/legs TM and FM ratio as a better DXA index of central obesity in CS and non CS obese, and also confirmed that central against peripheral parts of the body relations are better predictors of central, abdominal obesity in CS and CO.

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