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Oral glucose tolerance test as a screening tool in diagnostics of steroid-induced glucose intolerance – preliminary report

Doustny test obciążenia glukozą jako test przesiewowy w diagnostyce zaburzeń gospodarki węglowodanowej indukowanej przewlekłym leczeniem glikokortykosteroidami – doniesienie wstępne

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Keywords

steroid-induced hyperglycemia, steroid-induced diabetes, OGTT, chronic steroid treatment

Słowa kluczowe

hiperglikemia posteroidowa, cukrzyca posteroidowa, doustny test obciążania glukozą, przewlekła steroidoterapia

Summary

Introduction. Glucocorticoids (GCS) are used in chronic treatment of many connective tissue diseases, however they can also cause many adverse events such as impairment in glucose metabolism. Since pre-diabetes or diabetes lead to macro- and microangiopathy it is crucial to properly detect and manage these conditions. The current guidelines recommend to screen patients chronically treated with GCS using fasting plasma glucose levels while these medicaments cause mainly postprandial hyperglycemia.

Aim. The aim of the study was to assess the usefulness of oral glucose tolerance test (OGTT) in screening of patients chronically treated with glucocorticoids without previously diagnosed pre-diabetes or diabetes. The second study's objective was to evaluate the relation between occurrence of steroid-induced impairment in glucose metabolism and time, dose and type of steroid, BMI, WHR, HbA1c, HOMA-IR, Matsuda Index and family history of diabetes.

Material and methods. In 30 patients diagnosed with connective tissue diseases OGTT was performed. All participants underwent clinical and biochemical evaluation. Then they were divided into two groups. Group 1 (10 patients) was found to have steroid-induced IGT or diabetes and group 2 (20 patients) had normal glucose metabolism. Statistical analysis comparing two groups was performed with STATA13 software.

Results. 26% of patients had pre-diabetes or diabetes diagnosed only during OGTT. There was no difference between groups in time of treatment, type or daily dose of steroids, BMI, WHR, percentage total body or trunk fat and HOMA-IR. The statistical significance was reached for cumulative dose of steroids – it was surprisingly lower in the group with IGT.

Conclusions. The oral glucose tolerance test should be performed in every patients chronically treated with GCS as it is the only way to effectively detect the impairment in glucose metabolism.

Streszczenie

Wstęp. Glikokortykoidy (GKS) wykorzystywane są w leczeniu wielu schorzeń, między innymi chorób układowych tkanki łącznej. Niestety, wywołują one również wiele działań niepożądanych, w tym zaburzenia metabolizmu glukozy. Z uwagi na to, że stan przedcukrzycowy i cukrzyca prowadzą do makro- i mikroangiopatii, niezmiernie ważne jest, by prawidłowo rozpoznawać i leczyć te zaburzenia. Obecne wytyczne dotyczące rozpoznawania cukrzycy u pacjentów przewlekle leczonych steroidami zalecają wykonywanie przesiewowych oznaczeń stężenia glukozy na czczo, podczas gdy GKS powodują głównie hiperglikemie poposiłkowe.

Cel pracy. Ocena przydatności doustnego testu obciążenia glukozą jako testu przesiewowego w diagnostyce zaburzeń gospodarki węglowodanowej wśród pacjentów przewlekle leczonych glikokortykosteroidami (powyżej 3 miesięcy), u których nie stwierdzono stanu przedcukrzycowego lub cukrzycy przed włączeniem do badania. Drugim celem badania było zaobserwowanie zależności pomiędzy występowaniem nieprawidłowości

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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w metabolizmie glukozy indukowanej steroidami a czasem leczenia, dawką i rodzajem glikokortykoidu, BMI, WHR, procentową zawartością tkanki tłuszczowej (tułowia i całkowitą), HbA1c, HOMA-IR, Matsuda Index i wywiadem rodzinnym w kierunku cukrzycy.

Materiał i metody. U 30 pacjentów z układową chorobą tkanki łącznej wykonano OGTT. Wszyscy uczestnicy badania odbyli ocenę kliniczną i biochemiczną, a następnie zostali podzieleni na dwie grupy. Do grupy I zakwalifikowano 10 chorych, u których stwierdzono nieprawidłową tolerancję glukozy lub cukrzycę, a do grupy II 20 badanych z prawidłowym metabolizmem glukozy. Wykonano analizę statystyczną i porównano obie grupy, wykorzystując program STATA 13.

Wyniki. U 26% badanych stwierdzono upośledzoną tolerancję glukozy lub cukrzycę dopiero na podstawie OGTT. Nie wykazano różnic pomiędzy grupami w: czasie steroidoterapii, aktualnej dawce dobowej i rodzaju steroidu, BMI, WHR, całkowitej procentowej zawartości tkanki tłuszczowej i procentowej zawartości tkanki tłuszczowej tułowia oraz wskaźniku insulinooporności HOMA. Co zaskakujące, to w grupie z zaburzeniami tolerancji glukozy stwierdzono znamiennie niższą kumulacyjną dawkę steroidu.

Wnioski. Wyniki prezentowanego badania pokazują, iż w grupie pacjentów leczonych przewlekle glikokortykoidami, opieranie diagnostyki cukrzycy jedynie na oznaczaniu stężeń glukozy na czczo jest nieprzydatne. Zaburzeń tych nie przewidują również: BMI, WHR, czas steroidoterapii, dawka i rodzaj glikokortykoidu, wskaźnik HOMA czy wywiad rodzinny w kierunku cukrzycy. Rekomendujemy wykonanie doustnego testu obciążenia glukozą u wszystkich pacjentów leczonych glikokortykoidami powyżej 3 miesięcy, gdyż w tej grupie pacjentów jest to najskuteczniejsze badanie przesiewowe.

INTRODUCTION

Oral glucocorticoids (GCS) are widely used in treatment of many diseases. Despite their unquestionable positive effects in treatment of autoimmune and inflammatory disorders they are not free from serious adverse events such as impairment in glucose metabolism (1). GCS cause hyperglycemia by several mechanisms:

- enhancing liver gluconeogenesis (rise in glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activity) (2),
- increasing the glycogen production in liver (through inactivation of glycogen phosphorylase and activation of glycogen synthetase) (2),
- reducing glucose uptake in liver, muscles and adipose tissue,
- inducing the insulin resistance and β-cells dysfunction (2, 3).

The GCS treatment can worsen the glycemic control in patients with pre-existing diabetes or pre-diabetes but can also lead to development of these conditions "de novo". Some authors estimate the prevalence of new-onset steroid-induced diabetes on 10-20% (4) while in other four studies researchers did not find any case of this disease (5). Probably this is due to the fact that mentioned studies were carried out on patients using small doses of GCS (≤ 10 mg of prednisone) while the risk of hyperglycemia that require treatment was found to be dependent on the daily dose of steroids (OR 10.34 when using > 120 mg/d of hydrocortisone equivalent and OR 1.77 for a dose 1-39 mg/d) (6). Not only the dose but also the type of steroid is important. Patients using dexamethasone are thirty times and using prednisone four times more prone to developing impairment in glucose metabolism than patients treated with hydrocortisone (7). In the study conducted by Da Silva the risk factors for developing the new-onset diabetes after GCS were identified as the same as for type 2 diabetes: pre-diabetes, obesity, positive family history and previous gestational diabetes (5). However, the study published in 2012, comparing individuals with pre-existing type 2 diabetes and with new-onset steroid-induced diabetes, both chronically treated with GCS, gave interesting results (8). Patients with type 2 diabetes had more positive family history and macrovascular complications as well as a higher body mass index. Interestingly, the retinopathy was not observed in any of the patients with new-onset diabetes, what may suggest shorter exposure to hyperglycemia (8). This indicates that steroid-induced diabetes may be more than just simply unmasking previously existing impairment in glucose metabolism, and probably its development is dependent on other additional, probably genetic, factors.

Unfortunately, there are no available evidence based medicine data on how to detect, prevent and manage steroid-induced hyperglycemia or diabetes. The only recommendations are based on opinion of experts (9, 10). Every patient before initiating treatment with GCS should be screened to determine plasma fasting glucose. If any abnormalities are found, oral glucose tolerance test (OGTT) should be performed and depending on the result further management need to be introduced as stated in the current guidelines for diagnosis of diabetes (11-13). If GCS treatment was already initiated The European League Against Rheumatism (EULAR) recommends regular testing for plasma fasting glucose (FPG) and "standard care" (9, 10).

In American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" from 2016, in International Diabetes Federation Global Guidelines (IDF) released in 2012 or in Polish Diabetes Association Guidelines 2016 there are no separate recommendations for diagnosing and treatment of steroid-induced diabetes (11-13). This is surprising, taking into consideration fact that steroids are the most common cause of drug-induced diabetes (3). In 2003 the international guidelines concerning diagnosis and management of new-onset diabetes after transplantation ware released (14). It is recommended to determine plasma fasting glucose once a week during treatment for the first four weeks after surgery and then after 3, 6 and

12 months and once a year afterwards. However, this does not reflect the action of GCS which increase mainly postprandial glucose concentrations while fasting glucose levels are within normal range (3). In 2014 Lansang (15) proposed to diagnose the steroid-induced diabetes based on the "random plasma glucose ≥ 200 mg/dl (preferably in the afternoon or two hours after a meal) with classical symptoms of hyperglycemia" or as stated in ADA guidelines (FPG ≥ 126 mg/dl, HbA1c ≥ 6.5% or 2-hour value of glucose ≥ 200 mg/24 in OGTT) (11, 15). Still this is not much different from previous general guidelines for diagnosing diabetes (16, 17). There is a current need to create practical recommendations on how to detect diabetes in patients chronically treated with glucocorticoids, based on the wide knowledge about GCS and their effect on glucose metabolism.

AIM

The aim of the study was to evaluate the OGTT as a screening test in patients chronically treated with GCS who were not previously diagnosed with impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or diabetes. The second objective was to determine the relation between occurrence of steroid-induced impairment in glucose metabolism and time, dose and type of steroid, body mass index (BMI), waist-to hip ratio (WHR), HbA1c, Homeostasis Model Assessment (HOMA-IR), Matsuda Index and family history (FH) of diabetes. The preliminary report of the study is presented.

MATERIAL AND METHODS

30 patients diagnosed with systemic connective tissue diseases admitted to the Department of Endocrinology of Centre of Postgraduate Medical Education in Warsaw were evaluated for major side effects of chronic glucocorticoid treatment.

All participants met the inclusion criteria:

- glucocorticoid treatment lasting for at least three months,
- documented lack of IFG, IGT or diabetes (according to definition of IDF 2012).

The exclusion criteria were as follows:

- pregnancy,
- diagnosed IFG, IGT or diabetes before corticoid treatment,
- corticoid treatment for less than three months,
- diagnosed hypercortisolemia before corticoid treatment,
- cancer,
- liver or renal failure.

The study was approved by the Bioethics Committee and all patients gave their written consent to participate in the study.

All participants underwent clinical and biochemical evaluation including:

- medical history of the daily, cumulative dose and type of GCS,
- waist and hip circumference – Waist-hip (WHR) was calculated,
- body composition assessment – percentage total body fat and percentage fat trunk was measured using densitometer with "Total body" option (General Electric Healthcare model Lunar Prodigy Advance). Body composition measurement with dual-energy X-ray absorptiometry (DEXA) is more accurate than body mass index to determine body fat distribution,
- weight and height – body mass index (BMI) was calculated,
- lipid profile and HbA1c%,
- OGTT – the blood samples for glucose and insulin were collected in basic state and every thirty minutes until two hours after administering 75 g of glucose (without the morning dose of steroid),
- family history of diabetes.

Two insulin resistance indexes which have a good correlation with euglycemic insulin clamp were calculated (18, 19):

1. HOMA-IR = glucose x insulin / 405 (glucose mg/dl; insulin μIU/ml).
2. Matsuda Index (18): http://mmatsuda.diabetes-smc.jp/MIndex.html – the area under the curve is calculated using insulin and glucose samples from 0, 30, 60, 90 and 120 minutes of OGTT. The whole body insulin resistance is defined as equal or lower than 2.5.

Statistical analysis comparing two groups was performed with STATA13 software. The measured continuous parameters were described by the minimum and maximum value, mean and median. Compatibility with a normal distribution was checked with test of Shapiro-Wilk and equality of variance with Bartlett's test. Next, the obtained mean of the two groups was compared using Student's t test for two variables. In the absence of normal distribution of one of the variables, the nonparametric U-Mann-Whitney-Wilcoxon test was used. When inequality of variances of normally distributed variables was found the Welch test was performed.

RESULTS

The study included 30 patients during chronic glucocorticoid therapy – 25 females and 5 males of median age 55 (20-77) and 60 (35-65), respectively. 8 patients suffered from systemic lupus erythematosus (SLE), 8 with rheumatoid arthritis, 3 were diagnosed with mixed connective tissue disease, 5 with polymyalgia rheumatica, 1 with Wegener granulomatosis and 2 with polymyositis.

Based on results obtained from OGTT participants were divided into two groups. Group 1 (33% of total patients) included 9 women with impaired glucose tolerance and 1 man with diabetes. Only three patients in this group had IFG coincide with IGT. One patient diagnosed with diabetes had normal level of fasting plasma glucose. Patients from group 2, 16 women and 4 men, had normal glucose metabolism. The statistical analysis was performed to compare both groups. Results are presented in table 1. Although there was no statistical significance in age between groups it is clearly seen that patients in group 1 were almost 10 years older. There was no difference between groups in time of treatment,

type or daily dose of steroids, BMI, WHR, percentage total body or trunk fat and HOMA-IR. The cumulative dose of steroids was greater in group 2 (fig. 1). The mean levels of HbA1c were higher in group 1 (fig. 2). The Matsuda Index was lower in participants with IGT and diabetes which indicates on the whole body insulin resistance in this group (fig. 3).

11 patients were treated with statins (3 patients in group 1; 8 patients in group 2). 6 patients from group 2 and 4 patient in group 1 had family history of diabetes.

DISCUSSION

Glucocorticoids are one of the most common drugs used in treatment of connective tissue diseases. Often the treatment is chronic (or even lifelong) and patients cannot reduce their daily dose because of exacerbation of the underlying disease. Meanwhile they can develop complications related to the use of GCS. As pre-diabetes and diabetes can lead to serious long-term complications such as cardiovascular diseases, chronic renal failure, neuropathy or retinopathy we should properly diagnose and treat these conditions. As GCS are medicaments that are the most common cause of drug-induced diabetes it is extremely important to identify high-risk factors among this group of patients. As stated in the current guidelines they should be screened based on the FPG (9-14) and are not even within high-risk individuals in whom we should actively search for diabetes (11-13). In the present study 23% of patients had impaired glucose tolerance (3 of them with coincide FPG) or diabetes identified only in OGTT and all of them had FPG levels within normal range before joining the study. It is clearly seen that following the recommendations as for general population we are not able to properly detect the impairment in glucose metabo-

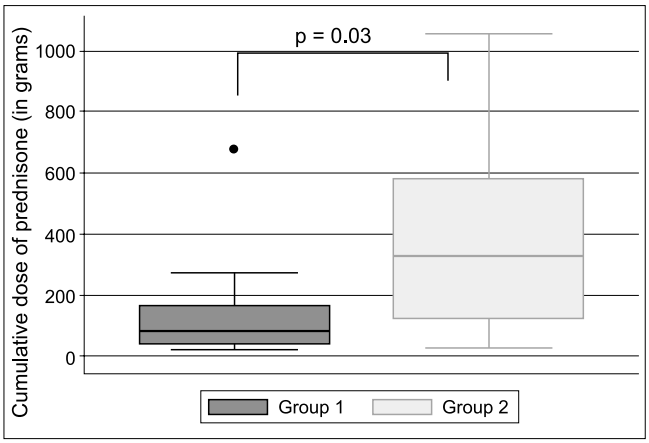

Fig. 1. The cumulative dose in prednisone equivalent in both groups

Tab. 1. Patients characteristics and differences between group 1 with steroid-induced glucose intolerance detected in OGTT and group 2 with normal glucose metabolism in OGTT

Characteristic of patients	Group 1 (n = 10)	Group 2 (n = 20)	P value
Age (yr) mean/median	33-77 57.4/60.5	20-65 48.05/53	p = 0.07
Time of steroid treatment (in days) mean/median	182-8721 2208.5/552.5	84-10 662 3457.3/2610	p = 0.147
Daily dose (in milligrams) (equivalent of prednisone) mean/median	1.25-30 8.875/6.875	2.5-50 11.75/5.625	p = 0.74
Cumulative dose (in grams) (equivalent of prednisone) mean/median	22.18-67.8 156.7/84.1	27.3-1058.5 389.19/330.46	p = 0.03
Type of steroid (number of patients) Methylprednisolone Prednisolone	7 12	3 8	p = 0.59
BMI (kg/m^2) mean/median	20.8-31.25 27/26.89	16.4-44.62 26.33/24.56	p = 0.36
WHR (cm) mean/median	0.74-0.97 0.88/0.89	0.74-1.15 0.9/0.88	p = 0.66
Percentage fat trunk (%) mean/median	22.2-50.6 40.77/44.25	27-50 40.46/42.2	p = 0.92
Percentage total body fat (%) mean/median	19.5-48 39.43/43.65	25.9-47.6 38.10/39.4	p = 0.18
Total cholesterol (mg/dl) mean/median	133-230.36 186.6/188.3	86.55-429.69 214.78/210.87	p = 0.15
LDL cholesterol (mg/dl) mean/median	67.36-137.47 97.84/104.105	34.64-286.1 117.52/104.895	p = 0.57
HDL cholesterol (mg/dl) mean/median	31-94.07 69.52/69.815	36.27-170.77 72.83/65.42	p = 0.92
TG (mg/dl) mean/median	70.19-152.21 96.127/82.825	39.35-355.75 121.91/102.67	p = 0.5
HbA1c (%) mean/median	5.4-6.5 6.04/6.1	4.6-6.3 5.62/5.6	p = 0.037
HOMA-IR mean/median	1.34-4.4 2.65/2.63	0.6-7.78 2.16/1.68	p = 0.065
Matsuda Index mean/median	1.846-4.157 3.132/3.159	1.84-12.25 5.288/4.686	p = 0.0049

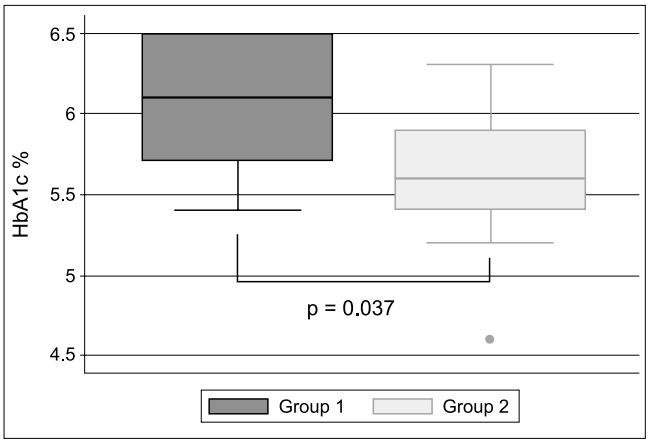

Fig. 2. The HbA1c in both groups

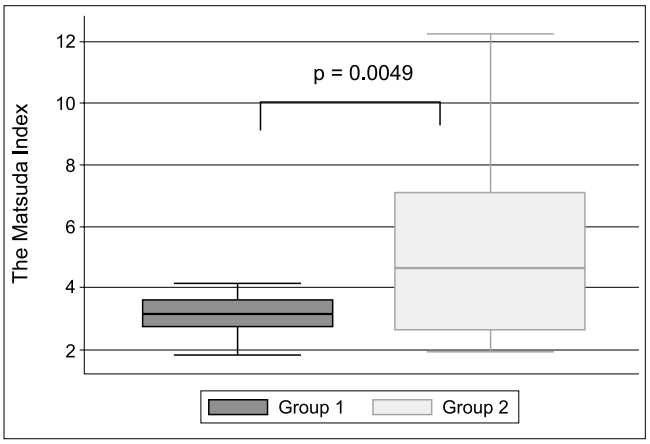

Fig. 3. The Matsuda Index in both groups

lism in patients chronically treated with glucocorticoids. Moreover, the obtained results from the present study indicate that based on "Cushingoid appearence", BMI, WHR, HOMA-IR, percentage total body or trunk fat, family history of diabetes, daily or cumulative dose, type of steroid and time of treatment it was impossible to predict the impairment in glucose metabolism or distinguish high-risk individuals. Although the mean HbA1c levels were higher in group 1 no threshold value was observed which could be useful to foresee IGT or diabetes (fig. 2). No difference in HOMA-IR between groups clearly shows that using only FPG and fasting insulin levels to diagnose insulin resistance or predict disturbances in glucose metabolism in this group of patients is unhelpful. Still the whole body insulin resistance is present in group 1 as expressed by lower Matsuda Index (fig. 3). It indicates that muscle and liver insulin resistance does not occur in every patient treated with GCS but only in predisposed individuals. This observation and no difference between groups in other analyzed parameters suggest that there are additional factors, probably genetic, that trigger the glucose metabolism impairment in this population.

After the study four patients from group 1 required treatment with metformin. In other cases the hyperglycemia was well managed by diet with a low glycemic index.

In many cases the glucocorticoid treatment is continued for many years or is even lifelong. Although, there is a possibility that glucocorticoid-induced IGT or diabetes will improve after reducing the dose or withdrawal of the medication, by that time patients are exposed to hyperglycemia and its serious consequences.

CONCLUSIONS

The OGTT is a useful and the only standardized tool to properly detect glucose intolerance or diabetes in patients chronically treated with glucocorticoids. We recommend performing OGTT in every patient treated with GCS for more than 3 months regardless of other risk factors of diabetes.

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