Preliminary Report of Hypoglycemic Response in Obese Metabolic Syndrome Males Treated with Metformin after Weight Loss Intervention

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A B S T R A C T

We conducted this study to determine the degree of obesity influence on the hypoglycemic response of growth hormone and cortisol after weight loss of 5%. A total of 45 non-diabetic, male subjects followed in the outpatient endocrinological departments were divided into three groups comprising 15 subjects in each group, based upon body mass index (BMI) to healthy, overweight and obese group. Metformin was administered in the dose of 50 mg daily to the overweight and obese participants. Cortisol was measured at 0, 60 and 120 minutes. Growth hormone (GH) was measured at –15, 0, 30, 60, 90 and 120 minutes.Values of cortisol and GH were compared upon changes in hypothalamo-pituitary-adrenal (HPA) response to insulin induced hypoglycemia initially and after weight loss of 5% for overweight and obese participants.The BMI of the healthy group ranged 20.0–24.5 kg/m^2 (median: 22.8); overweight group ranged 25.9–29.7 kg/m^2 (median: 28.3); and obese group ranged 30.9–34.6 kg/m^2 (median: 32.6). There were no significant differencesof cortisol values among groups at 0 (χ^2=2.0; p=0.365); 60 (χ^2=0.754; P=0.686) and at 120 minutes (χ^2=0.466; p=0.792). The comparisons among groups were significant for differences of GH values at –15 (χ^2=25.0; p<0.01); 0 (χ^2=16.2; p<0.01); 30 (χ^2=16.2; p<0.01); 60 (χ^2=32.8; p<0.01); 90 (χ^2=30.2; p<0.01) and at 120 minutes (χ^2=27.3; p<0.01).Healthy and obese subjects significantly differed in growth hormone response at –15 (Z=4.67; p<0.01); 0 (Z=3.83; p<0.01); 60 (Z=2.78; p=0.05); 90 (Z=4.67; p<0.01) and at 120 minutes (Z=4.23; p<0.01).Changes on the various levels of HPA axis, when it is activated by a stress as it is the case in insulin-induced hypoglycemia correspond to the degree of obesity. Weight loss of 5% was not enough for restoration of a normal stimulated growth hormone release and did not influence on the level of cortisol.

Key words: *obesity, cortisol, growth hormone*

Introduction

Obesity is becoming a global epidemic. Besides an altered metabolic profile, a variety of adaptations/alterations occur in the individual as adipose tissue accumulates in excess amounts because the adipose tissue is not simply a passive storehouse for fat but an endocrine organ[1]. Growth hormone (GH) secretion, either spontaneous or evoked by provocative stimuli, is markedly blunted in obesity[2]. GH secretion is mainly controlled by the hypothalamus through the stimulating action of GH-releasing hormone and the inhibiting influence of somatostatin, which are in turn switched off and on, respectively, by the pituitary hormone. This functional loop is modulated by central (neurotransmitters and neuropeptides) and peripheral factors (insulin like growth factor 1, non esterified fatty acids, leptin, etc.)[2]. Cortisol secretion has been examined extensively in obesity because when abnormalities have been observed, evidence suggests that these are mainly because of abnormal regulation of the HPA axis and also peripheral modulations result in cortisol exposure of tissues[3].

The literature appears to support the concept that reduced feedback stimulability of the HPA axis is present

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in obesity which may explain the empirical findings of a combination of normal cortisol production and subnormal plasma cortisol concentration in the obese individuals[4]. Most obese subjects are characterized by significant insulin resistance, although many still have normal oral glucose tolerance and metformin exerts favourable effects on insulin sensitivity[5,6]. Studies accumulated in the past decade point out that metformin possesses beneficial action on lipid and glucose metabolism so these effects when combined lead to an integrated approach as we used in our study. Hence, we aimed to analyze hypoglycemic response in obese metabolic syndrome males treated with metformin after weight loss intervention.

Subjects and Methods

A total of 45 male subjects aged ≥30 years without history of pituitary, thyroid, adrenal dysfunction and diabetes mellitus were recruited from a primary health care. No subjects were being treated with topical, inhaled or oral corticosteroid preparations or had received such treatment in the year prior to the study.

The study protocol was approved by the Hospital Ethical Committee; all subjects gave their informed, written consent to participate in the study. The standard clinic examination included a physician interview, a physical examination and laboratory tests. All subjects, except healthy, were educated on menu planning, nutrient calculating, exercise and changes in their daily lifestyles by the endocrinologists. Metformin was administered in the daily dose of 50 mg on the beginning of the investigation. All subjects, except healthy, were checked monthly. At the end of 4.3±2.6 months which corresponds to decrease of 5% of initial body weight subjects were reexaminated. Body weight was taken while the patients barefooted and in light clothing, using a digital weighting machine (Seca, Marsden, UK) to the nearest 0,1 kg. Standing height was measured without shoes to the nearest cm using a Harpenden stadiometer (Holtain Ltd., Crymych, UK) with the shoulders in a relaxed position and the arms hanging freely. BMI was calculated as the ratio of weight (kilograms) to the square of height (meters). Subject's BMI was classified according to WHO classification, as being healthy (BMI; 20.0 to 24.9 kg/m^2), overweight (BMI; 25.0 to 29.9 kg/m^2) and obese (BMI; 30.0 to 34.9 kg/m^2)[7]. All subjects were divided into three groups comprising 15 subjects in each group, based upon BMI. Waist and hip circumference were both measured in a transverse plane, at the level of the umbilicus and greater trochanters, respectively.

All participants underwent two insulin tolerance tests (ITT) (0.15 U insulin i.v./kg body weight) after an overnight fast. ITT was performed on the beginning and after 5% of weight reduction, except healthygroup. All tests commenced at 08:0 AM and blood was drawn at –15, 0, 15, 30, 45, 60, 75, 90, 105 and 120 minutes for determination of plasma glucose. Serum cortisol was measured at 0, 60 and 120 minutes. GH was measured at –15, 0, 30, 60, 90 and 120 minutes.Our participants experienced symptomatic hypoglycemia and their blood glucose level reached nadir of 2.2 mmol/L or less. Patients received 20% glucose intravenously if hypoglycaemia was severe. The highest amounts of glucose given were 10–18 g delivered in boluses of 4–6 g every 5–10 minutes in order to avoid greater blood glucose fluctuations. Others received substantially less. These small amounts of glucose could not abolish the stimulatory effect of hypoglycaemia on GH and cortisol secretion as consequent blood glucose increments were in the range of 0.5–1.5 mmol/L leaving the patients still mildly hypoglycaemic. Laboratory testing was done under similar conditions.Serum cortisol was measured by radioimmunoassay (Immunotech a Beckman coulter company, Prague, Czech Republic). The inter and intra-assay coefficients of variation (CV) were 9.2% and 5.8%. Growth hormone was measured by immunoradiometric assay (BioSource Europe S.A., Belgium). The inter and intra-assay coefficients of variation (CV) were 6.7% and 1.0%. Glucose was measured by (Olympus AU 270 analyzer, Olympus Mishima Co., Shizuoka, Japan).

Data analysis was performed using the Statistica version 7.0. Numeric data are presented as median(minimum – maximum). Kolmogorov-Smirnov test was used for assumption of normality. The values of cortisol and GH among groups were tested by the Kruskal-Wallis test and the difference between healthy and obesegroups in growth hormone values was calculated by Mann-Whitney test. A p value <0.05 was considered to indicate statistical significance.

Results

The healthy subject´s age ranged between 37.6–48.0 years with a median age of 40.1. The overweightsubjects hada median age of 41.5 years (ranging between 38.0–47.4 years). The obesesubject´s age ranged between 36.8–47.3 years with a median age of 41.3.

The healthy subject´s BMI ranged between 20.0–24.5 kg/m^2 with a median BMI of 22.8. The overweight subjects had a median BMI of 28.3 kg/m^2 (ranging between 25.9–29.7). The obese subject´s BMI ranged between 30.9–34.6 kg/m^2 with a median BMI of 32.6.

The healthy subject´s waist circumferenceranged between 84.0–95.0 cm with a median of 87.0 and hip circumference ranged between 95.0–106.0 cm with a median of 101.0. The overweight subjects had a median of waist circumference of 101.0 cm (ranging between 95.0–107.0) and hip circumference ranged between 102.0–120.0 cm with a median of 105.0. The obese subject´s waist circumference ranged between 101.0–123.0 cm with a median of 110.0 and hip circumference ranged between 104.0–117.0 cm with a median of 109.0.

Cortisol values were observed at the beginning of the study and after 5% reduction of weight, except healthy participants (Figures 1, 2 and 3).

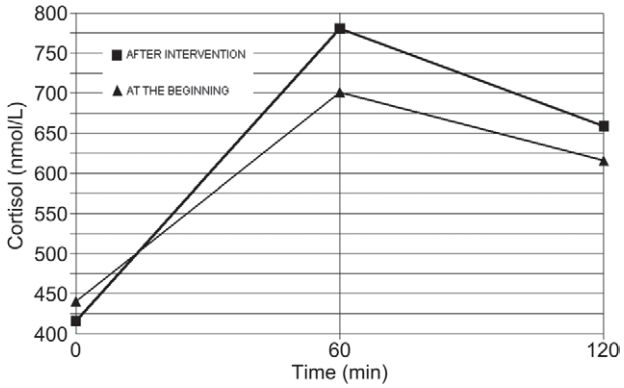

Fig. 1. Cortisol (C) values of healthy group at the beginning and after intervention.

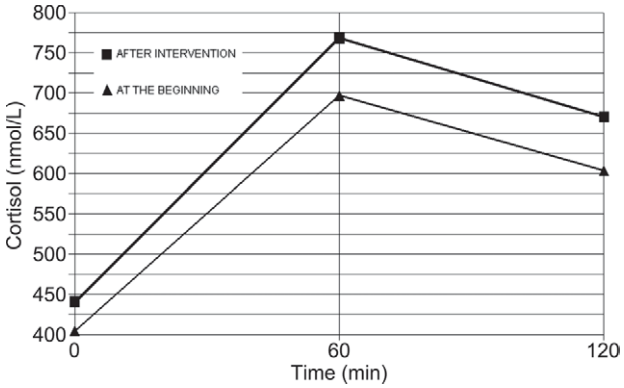

Fig. 2. Cortisol (C) values of overweight group at the beginning and after intervention.

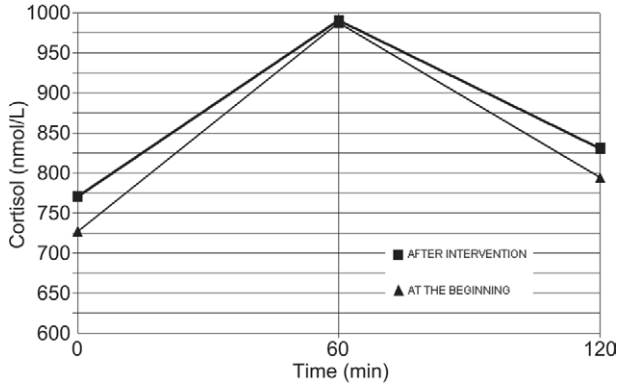

Fig. 3. Cortisol (C) values of obese group at the beginning and after intervention.

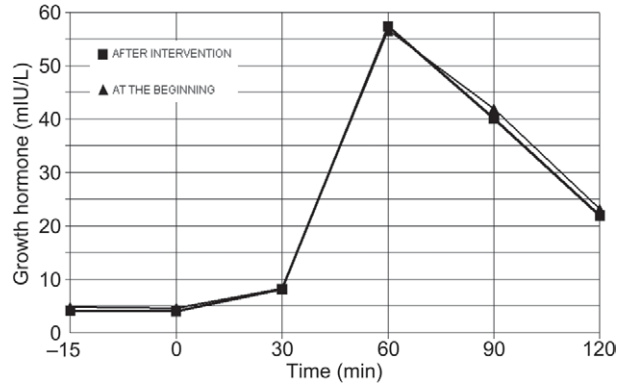

Fig. 4. Growth hormone (GH) values of healthy group at the beginning and after intervention.

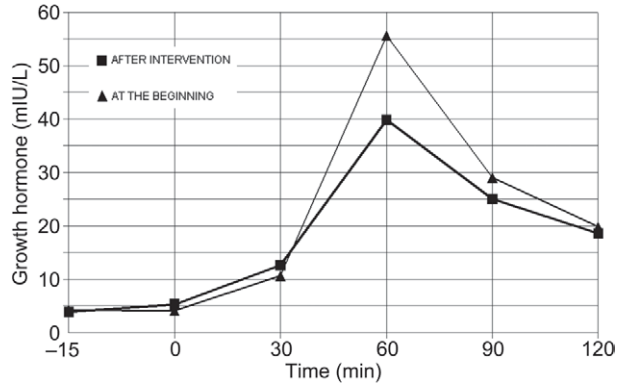

Fig. 5. Growth hormone (GH) values of overweight group at the beginning and after intervention.

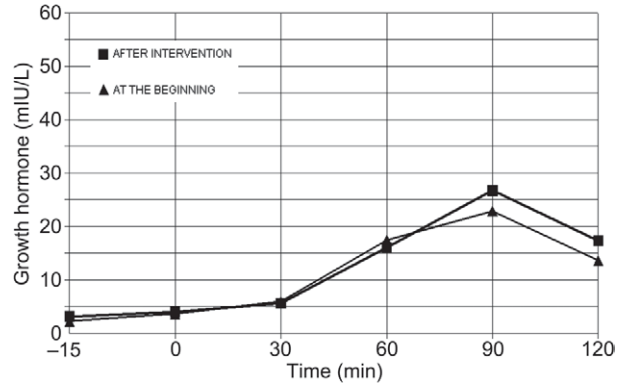

Fig. 6. Growth hormone (GH) values of obese group at the beginning and after intervention.

There was no significant difference of cortisol values among groups at 0 (χ^2=2.0; p=0.365); 60 (χ^2=0.754; p=0.686) and at 120 minutes (χ^2=0.466; p=0.792).

GH values were measured at the beginning of the study and after 5% reduction of weight, except healthy participants (Figures 4, 5 and 6). The differences of cortisol and GH values between measures in healthy, overweight and obese participants are shown in the first table (Table 1).

The comparisons among groups were significant for differences of GH values at –15 (χ^2=25.0; p<0.01); 0 (χ^2=16.2; p<0.01); 30 (χ^2=16.2; p<0.01); 60 (χ^2=32.8; p<0.01); 90 (χ^2=30.2; p<0.01) and at 120 minutes (χ^2=27.3; p<0.01).

TABLE 1
DIFFERENCES OF CORTISOL AND GH VALUES BETWEEN TWO MEASURES IN HEALTHY, OVERWEIGHT AND OBESE PARTICIPANTS

Differences basal – after	Healthy group Median (min.–max.)	Overweight group Median (min.–max.)	Obese group Median (min.–max.)
GH at –15 min	–0.3 (–2.2 – 0.2)	–0.4 (–1.9 – 1.0)	1.0 (0.5 – 1.4)
GH at 0 min	0.0 (–1.8 – 0.3)	1.2 (–1.0 – 2.1)	0.4 (0.0 – 0.9)
GH at 30 min	–0.3 (–1.2 – 1.1)	2.2 (–2.2 – 4.0)	–0.2 (–1.6 – 0.7)
GH at 60 min	0.7 (–6.0 – 5.7)	–16.0 (–18.5 – –11.8)	–1.5 (–4.1 – 3.6)
GH at 90 min	–1.9 (–5.7 – 0.7)	–3.7 (–5.9 – –0.9)	3.9 (1.3 – 6.3)
GH at 120 min	0.0 (–3.8 – 3.5)	–1.8 (–6.5 – 0.8)	3.9 (1.1 – 7.6)
C at 0 min	–15.0 (–114.5 – 159.9)	6.0 (–145.8 – 226.7)	61.9 (–90.8 – 149.4)
C at 60 min	60.6 (–173.9 – 520.7)	64.7 (–51.0 – 230.3)	46.0 (–111.7 – 252.6)
C at 120 min	10.2 (–103.9 – 240.3)	49.9 (–170.0 – 189.6)	49.0 (–110.8 – 251.5)

Healthy and overweight subjects significantly differed in growth hormone response at 0 ($Z=2.87$; $p=0.04$); 30 ($Z=3.47$; $p=0.01$) and at 60 minutes ($Z=4.67$; $p<0.01$).

Healthy and obese subjects significantly differed in growth hormone response at –15 ($Z=4.67$; $p<0.01$); 0 ($Z=3.83$; $p<0.01$); 60 ($Z=2.78$; $p=0.05$); 90 ($Z=4.67$; $p<0.01$) and at 120 minutes ($Z=4.23$; $p<0.01$).

Overweight and obese subjects significantly differed in growth hormone response at –15 ($Z=3.95$; $p<0.01$); 0 ($Z=2.07$; $p=0.038$); 30 ($Z=3.47$; $p=0.01$); 60 ($Z=4.67$; $p<0.01$); 90 ($Z=4.67$; $p<0.01$) and at 120 minutes ($Z=4.67$; $p<0.01$).

Discussion and Conclusion

The insulin tolerance test assesses the integrity of the entire central nervous system – pituitary – end organ axis[8]. Our results clearly indicate that GH secretion in response to insulin induced hypoglycaemia is markedly attenuated in obese subjects.Reduced central serotonin activity in the obese might affect GH response to insulin induced hypoglycaemia, because the serotoninergic mechanism is involved in the mediation of this response through somatostatin inhibition. Since the endogenous somatostatin is augmented in obesity, this would seem to explain the reduced GH response to insulin tolerance test[9]. The previously noted recovery of GH responses to insulin induced hypoglycaemia with weight reduction therefore suggests that endogenous secretion of growth hormone – releasing factor is probably unimpaired in obese persons[10]. Scacchi et al. assumed that defect of GH secretion in obesity appears to be adaptive phenomenon, since it is completely reversed by the normalization of body weight[2]. On the other hand, our study did not show complete restoration of a normal stimulated growth hormone release. We noticed at –15, 0, 90 and 120 minutes enhancing of GH response in obese subjects but still insufficient in comparison with healthy group.The limitations of our investigation might be in a presence of small sample of subjects and modest achieved weight loss of 5%.

There is no evidence of increased cortisol production in obese subjects, as it has been shown in our results. Studies on overall feedback stimulation reported in the literature have utilized insulin-induced hypoglycaemia as the stimulus, not lowering of plasma cortisol levels by some mechanism (such as increased metabolic removal)[4]. Many authors reported decreased cortisol response to hypoglycemia[11–15]. Obese subjects in our investigation maintained the same cortisol response after weight loss of 5%. Bell at al. also reported normal cortisol response[16]. The possibility that intracellular hypercortisolism is present and may play a causative role, requires further investigation. Cortisol may work through several mechanisms including an increase in hepatic glucose production by stimulation of gluconeogenesis, increase in peripheral insulin resistance, and stimulation of lipoprotein lipase in abdominal adipocytes, which in turn increases intra-abdominal fat depots[15,16]. Abdominal obesity is associated with relative functional hypercortisolism. The origin of the hyperactivity of the hypothalamo-pituitary-adrenal axis and the resulting hypercortisolism may be genetically determined by abnormality of CRH secretion and an exaggerated neuroendocrine response to environmental stress, or both.In addition to HPA axis activation, a parallel central activation of the sympathetic nervous system occurs[3].

Metformin, the biguanide most widely used for the treatmentof type 2 diabetes mellitus, may be useful in aiding weightloss or at least keep their weightstable[17,18]. It suppresses endogenous glucoseproduction and may also act as an insulin sensitizer. Indeed, metformin might enhance weight loss more effectivelyin obese patients whose BMI is greater than 35 kg/m^2, becausethat is when insulin resistance, a potential mediator of weightgain and inhibitor of weight loss, becomes more prevalent[19]. Evidence is insufficient to conclude that metformin can serveas a treatment of overweight or grade I obesity in adults whodo not have diabetes mellitus[20]. Our data are in agreement with the above reported studies, although a different population was investigated. Changes on the various levels of HPA axis correspond to the degree of obesity.

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PRELIMINARNO IZVJEŠĆE O HIPOTALAMO-PITUITARNO-ADRENALNOM ODGOVORU NA HIPOGLIKEMIJU U METFORMINOM LIJEČENIH DEBELIH MUŠKARACA S METABOLIČKIM SINDROMOM NAKON GUBITKA TJELESNE TEŽINE

SAŽETAK

Cilj istraživanja je utvrditi utjecaj različitog stupnja debljine na lučenje hormona rasta i kortizola kao odgovor na hipoglikemiju nakon gubitka 5% tjelesne težine. Ukupno 45 muškaraca s metaboličkim sindromom, podijeljeno je prema indeksu tjelesne mase (ITM) u 3 skupine po 15 ispitanika i to u zdravu, preuhranjenu i pretilu skupinu. Metformin je dat u dozi od 50 mg dnevno preuhranjenim i pretilim ispitanicima. Kortizol je mjeren u 0, 60 i 120 minuti. Hormon rasta (HR) je mjeren u –15, 0, 30, 60, 90 i 120 minuti.Vrijednosti kortizola i HR su analizirane na početku i nakon gubitka 5% tjelesne težine za preuhranjene i debele ispitanike kao odgovor na inzulinom induciranu hipoglikemiju. ITM zdravih ispitanika bio je u rasponu od 20,0–24,5 kg/m^2 (median: 22,8); preuhranjenih 25,9–29,7 kg/m^2 (median: 28,3); i pretilih od 30,9–34,6 kg/m^2 (median: 32,6). Analizirajući vrijednosti kortizola nije nađeno razlike među grupama u 0 (χ^2=2,0; p=0,365); 60 (χ^2=0,754; p=0,686) i 120 minuti (χ^2=0,466; p=0,792). Značajne su razlike među grupama za vrijednosti HR u –15 (χ^2=25,0; p<0,01); 0 (χ^2=16, 2; p<0,01); 30 (χ^2=16, 2; p<0,01); 60 (χ^2=32, 8; p<0,01); 90 (χ^2= 30,2; p<0,01) i 120 minuti (χ^2=27,3; p<0,01). Zdravii pretili ispitanici značajno se razlikuju u izlučivanju hormona rasta u –15 (Z=4, 67; p<0,01); 0 (Z=3, 83; p<0,01); 60 (Z=2, 78; p=0,05); 90 (Z=4,67; p<0,01) i 120 minuti (Z=4,23; p<0,01).Promjene na različitim razinama hipotalamo-pituitarno-adrenalne osovine kada je potaknuta stresom kao što je slučaj u inzulinom induciranoj hipoglikemiji odgovaraju stupnju debljine. Gubitak tjelesne težine od 5% nije dovoljan za uspostavu normalnog oslobađanja hormona rasta i ne utječe na vrijednosti kortizola.