Effects of short term metformin administration on androgens in diabetic men

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ABSTRACT

Objective: Metformin, an oral hypoglycemic agent, has several other metabolic and hormonal effects. This study aims at identifying the metabolic effect of metformin on androgens in diabetic men.

Methods: The study was conducted at The National Center for Diabetes Endocrinology and Genetics, Jordan University Hospital, Amman, Jordan from April 2001 to September 2001. We studied 15 men with type 2 diabetes mellitus by measuring fasting serum glucose, insulin, glycosylated hemoglobin, total and free testosterone, sex hormone binding globulin, dehydroepiandrosterone sulphate, 17-OH progesterone, luteinizing hormone, and follicle stimulating hormone before and after a short course of metformin.

Results: There was a significant decrease in fasting serum glucose and glycosylated hemoglobin and increase in the level of 17-OH progesterone. The remainder of the measured parameters did not show any significant change. Although serum glucose and glycosylated hemoglobin decreased insulin levels were not changed.

Conclusion: In contrast to normal men there was no change in androgen levels in diabetics but the 17-OH progesterone was elevated.

Saudi Med J 2004; Vol. 25 (1): 75-78

Metformin, a biguanide, is used as an oral hypoglycemic agent.[1-3] The primary mechanism of action is the improvement of insulin sensitivity in the liver and muscles and suppression of hepatic glucose production through the inhibition of gluconeogenesis and glycogenolysis.[4,5] The United Kingdom Prospective Diabetic Study (UKPDS) has shown that metformin reduces mortality in obese patients with coronary artery disease.[6] In addition, it is used to treat the state of hyperinsulinemia due to insulin resistance associated with Polycystic Ovary syndrome (PCOS).[7] Several studies have shown that metformin reduces serum testosterone and increases sex hormone binding globulin (SHBG) in women with or without PCOS.[7-9] Recently, we have explored the effect of short-term metformin administration on androgens in normal men, which demonstrated reduction in total testosterone, free testosterone, and in 17-OH progesterone and an increase in SHBG and dehydroepiandrosterone (DHEA-S).[10] The effect of metformin combined with hypocaloric diet has been explored in diabetic men where it resulted in significant reduction in free testosterone level in obese non-diabetic men who were used as control subjects with a significant increase in SHBG, while in the obese diabetic men there was a significant reduction in total testosterone level only.[11] The purpose of this study is to report the metabolic effects of metformin on androgens in diabetic men as a short-term therapy.

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Received 10th June 2003. Accepted for publication in final form 28th September 2003.

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Methods. ***Patients selection.*** Fifteen diabetic men with type 2 diabetes mellitus (DM) with an age range of 36-60 years, were enrolled in this study. The diagnosis of diabetes was made according to American Diabetes Association in 8 of them who were newly diagnosed.[12] Seven of our patients were diagnosed previously with a median duration of DM of 4 years. None of our patients was on any other treatment at the time metformin was started. A complete physical examination was performed, including height, weight and blood pressure measurements. After an overnight fasting of 8 hours, a baseline venous blood sample was obtained at 8 a.m. for fasting plasma glucose and insulin. Pooled blood samples were obtained at 0 time, 30 and 60 minutes interval for measurement of total and free testosterone, SHBG, DHEA-S, 17-OH progesterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH). Thereafter, each subject was given metformin, 1500 mg per day in 3 divided doses for a mean of 4.5 weeks. At the end of this period, blood specimens were obtained for the same parameters in the same fashion as the pretreatment samples.

Laboratory procedures. The serum from blood samples was separated immediately after collection. Total testosterone was analyzed by radioimmunoassay (RIA) using a commercial kit with a sensitivity of 0.059 ng/ml (Dia Sorin Incorporation Industrial, Italy). Free testosterone and 17-hydroxyprogesterone were analyzed by RIA using commercial kits from Diagnostic Products Corporation (DPC) with sensitivities of 0.15 pg/ml (conversion factor to pmol/L =3.48) and 0.2 nmol/l (Diagnostic Products Corporation, USA, Los Angeles). Sex hormone binding globulin was measured by Immunoradiometric Assay (IRMA) using kits with a sensitivity of 0.04 nmol/l. (Diagnostic Products Corporation, USA, Los Angeles). Dehydroepiandrosterone was analyzed by RIA using commercial kits from Diagnostic System Laboratories with a sensitivity of 0.046 mol/l. Samples were analyzed for gonadotrophic (LH and FSH) and insulin by microparticle enzyme immunoassay (MEIA) using IMX, ABBOTT Diagnostics Instruments from (ABBOTT Laboratory Diagnostic Division, USA) with a sensitivity of 0.5 IU/L, 0.2 IU/L and1.0μU/ml. Blood glucose was analyzed by oxidative methods and glycosylated hemoglobin (HbA1C) was carried out by High Performance Liquid Chromatography (HPLC) Japan.

Statistical analysis. Data were analyzed using Epi info version 6, software. The paired student t-test was used to assess the statistical significance of the differences in serum levels of the measured hormones.

Results. ***The effect of metformin on body weight and blood pressure.*** The mean body weight did not change after metformin. The mean blood pressure dropped from 128.5/83.2 mm Hg before metformin to 119/80.4 mm Hg, but this drop was not statistically significant.

The effect of metformin on glucose and insulin levels. The mean fasting blood glucose decreased significantly after treatment and the mean HbA1C also decreased significantly. There was no significant difference between baseline levels of insulin before and after metformin therapy as the mean baseline insulin was 11 μIU/ml ± 6.7 and became 11.1 μIU/ml ± 6 (**Table 1**).

The effect of metformin on androgens and gonadotropins levels. **Table 2** shows the effect of metformin on androgen and gonadotropin level. The 17-OH progesterone levels increased significantly after metformin, meanwhile, there were no significant changes in total and free testosterone levels, serum DHEA-S and gonadotropins (LH and FSH) (**Table 2**).

Table 1 - The effect of metformin on blood glucose, HbA1C and insulin level.

Variable	Before metformin Mean ± SD	After metformin Mean ± SD	*p* value
Fasting blood glucose mg/dl	181.9 ± 55.8	123.6 ± 22.1	0.002
HbA1C	8.7 ± 1.6	7.8 ± 1.0	0.001
Serum insulin level μU/ml	11 ± 6.7	11.1 ± 6.0	0.8

p values are obtained by the pair t-test,
normal values for glycosylated hemoglobin (HbA1C) 4.2-6.2%

Table 2 - The effect of metformin on androgens gonadotropins level and sex hormone binding globulin.

Variable	Before metformin Mean ± SD	After metformin Mean ± SD	*p* value
Total testosterone (ng/ml)	3.4 ± 1.2	3.2 ± 1.2	0.6
Free testosterone (pg/ml)	12 ± 3.9	12 ± 4	0.8
SHBG (nmol/l)	18.7 ± 7.1	18.4 ± 6.5	0.7
DHEA-S (μmol/l)	3.5 ± 1.7	3.7 ± 2	0.1
17-OH progesterone (nmol/l)	3.5 ± 1.8	3.7 ± 1.4	0.002
LH (IU/L)	5.5 ± 2	5.9 ± 2.3	0.1
FSH (IU/L)	10 ± 9.7	10.1 ± 9.8	0.8

SHBG - sex hormone binding globulin,
DHEA-S - dehydroepiandrosterone

Discussion. Our study presents the metabolic effect of metformin on blood glucose and androgens in diabetic men. Significant reduction in glucose and HbA1C after metformin treatment is shown in our study but there was no change in insulin levels. This is consistent with previous studies.[4,5,13-15] Several studies have shown that metformin improved glucose tolerance in diabetic individuals through the increase in sensitivity of the hepatic and peripheral tissue to the action of insulin irrespective of the changes in its level.[1,2,16] Our patients were insulin resistant according to the Homeostasis Model Assessment (HOMA).[17] The insulin resistance decreased significantly with the short-term metformin therapy such that the mean insulin resistance dropped from 5.9 ± 4.2 to 3.5 ± 1.8 (p=0.032). Previous studies have provided evidence that insulin is a regulatory factor of serum SHBG[18,19] and showed an inverse correlation between serum insulin and SHBG in women[20] and in type 2 diabetic men.[21] We have published some data revealing that metformin causes a rise in SHBG in normal healthy men.[10] In this study, there was no change in SHBG or insulin levels, but there was a significant decrease in insulin resistance. This suggests that metformin blunts the inverse correlation between serum insulin and serums SHBG in type 2 diabetic men unlike its effect in normal men. The study of Ozata et al[11] investigated a combined effect of metformin and hypocaloric diet on plasma testosterone and leptin in obese men. Also, their study cohort was composed of obese men with and without type 2 diabetes. It is somewhat difficult to compare our results to theirs as they have 2 combined effectors, metformin and hypocaloric diet in men with one common factor, which is obesity. It is known that in type 2 male diabetics the androgen levels are low in comparison with normal individuals,[22] which may suggest that they cannot get any lower with metformin namely basal level has already crossed the threshold of metformin effect. Our study was not designed to test for this model and we think that further investigation would be of interest.

In type 2 DM, DHEA-S levels decrease secondary to low 17-20 lyase activity and high 17-hydroxylase activity mediated by the high insulin.[23,24] In our study DHEA-S did not change while 17-OH progesterone increased. This suggests that metformin does not modify the insulin effect on the 17-20 lyase activity but sensitizes the 17-OH to the effect of insulin in diabetics. Our findings indicate that metformin has no direct effect on androgen in diabetic men. The increase in the 17-OH progesterone level needs further investigation.

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