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Influence of Dimethylbiguanide (Metformin®) on Carbohydrate Metabolism in Obese, Non-Diabetic Women

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Summary. The authors have studied the influence of 2 weeks' treatment of 15 non-diabetic, obese subjects with 2 g of Metformin daily, on intravenous glucose tolerance and plasma insulin levels. Blood glucose fasting and during the IVGTT were not influenced by treatment, but the insulin levels and the insulin/glucose ratios were significantly decreased. This points to a decreased insulin resistance.

Influence du traitement à la Metformine sur le métabolisme glucidique chez des femmes obèses non diabétiques

Résumé. Les auteurs ont étudié chez 15 obèses non diabétiques, l'influence d'un traitement à la Metformine (2 g/jour pendant quinze jours) sur la glycémie et le taux d'insulinémie à jeun et après une surcharge glucosée intraveineuse. Le traitement n'influence ni la glycémie à jeun, ni la glycémie après surcharge intraveineuse ni la constante d'assimilation du glucose. L'insulinémie à jeun et après surcharge glucosée est cependant nettement diminuée, de même que le rapport insulinémié/glycémie. Ceci semble indiquer une réduction de la résistance à l'insuline observée chez les obèses non diabétiques.

Zusammenfassung. Die Autoren untersuchten an 15 übergewichtigen, nicht diabetischen Patienten die Beeinflussung des Kohlenhydratstoffwechsels und der Insulin-Sekretion durch eine Behandlung mit Metformin (2 g/Tag). Die Blutzuckerwerte, nüchtern und während des intravenösen G.T.T., wurden nicht beeinflußt. Auch die K-Werte zeigten trotz eines leichten Abfalls unter der Behandlung keine statistisch signifikante Abweichung von den Ausgangswerten. Die Insulinspiegel, nüchtern und nach Glucose, waren jedoch unter der Behandlung signifikant gesenkt und der Insulin/Glucose-Quotient erniedrigt. Dies läßt auf eine partielle Aufhebung der Insulinresistenz bei übergewichtigen Patienten schließen.

Key words: Obesity, insulin resistance, insulin plasma levels, biguanides, Metformin.

After an oral or intravenous glucose load, insulin levels generally increase to higher values in obese non-diabetic subjects than in individuals of normal weight [14, 17, 19, 21, 22, 28]. This can be interpreted as evidence for an insulin resistance, which is also suggested by the results of forearm metabolism studies [24] and the decreased hypoglycaemic action of exogenous insulin in obesity [1].

Since it has been suggested that dimethylbiguanide might act by relieving insulin resistance [28, 29, 30], it was of interest to us to investigate whether the administration of dimethylbiguanide might normalize the insulin levels in obese non-diabetic patients during a glucose load.

Material and Methods

Subjects selected for this study were obese women ($n = 15$), with a body weight at least 25% in excess of ideal body weight, who were non-diabetic as evidenced by a normal oral glucose tolerance test and by a glucose assimilation coefficient (K) greater than 1.0 during the intravenous glucose tolerance test [7]. 15 normal subjects, matched for age and sex, served as controls. All subjects were on a normal diet before and during the whole period of the study. The IVGTT was performed after an overnight fast by injecting rapidly, at 9 a.m., 50% glucose at a dose of 0.66 ml per kg bodyweight.

Blood glucose levels were determined by the *o*-toluidine method [10] adapted for the autoanalyzer. The K value [7] was determined by the method of least squares, using the glycaemia values obtained at 10, 15, 30, 45 and 60 min. Plasma insulin levels were determined by the radioimmunoassay method of Yalow and Berson [32] just before and 3, 7, 10, 15, 30, 45, 60 and 90 min after the beginning of the rapid glucose injection.

All patients received dimethylbiguanide, 2 g daily, in 4 divided doses of 0.5 g for 15 days. On day 15, 1 g of dimethylbiguanide was given at 7 a.m. and an IVGTT was repeated at 9 a.m. Results were evaluated statistically, using the t test of Student. For comparison with the normal group this t test was calculated on the differences of the mean values; the effects of dimethylbiguanide were evaluated by means of statistical analysis (Student's t test) of the absolute changes in paired samples (before and after treatment in the same subject) of blood glucose, serum insulin and insulin/glucose ratios. All subjects followed a normal diet during the study and weights did not change significantly.

Results

Prior to dimethylbiguanide treatment (Table 1) the mean fasting glucose level was identical in the obese and in the control group; the mean glucose assimilation

coefficient although normal (1.38 ± 0.12^1), was however significantly lower ($P < 0.001$) in the obese than in the non-obese control group (2.07 ± 0.10^1). During the IVGTT, glucose levels were slightly, and insulin levels significantly ($P < 0.01$), higher in the obese than in the control group; insulin/glucose ratios were similarly significantly increased (Table 3) in the obese group, both in the fasting condition and during the IVGTT.

After treatment with dimethylbiguanide 2 g daily for 15 days, the following observations were made (Table 2):

Table 1. *Glucose and insulin levels in normal controls (n = 15) and obese non-diabetics (n = 15)*

Glucose levels (mg/100 ml)					Insulin levels (μU/ml)			
	Normal Controls	Obese	d	p	Controls	Obese	d	p
0	88±2[a]	89±3	1± 3	—	12± 2	32± 4	20± 4	<0.001
3	277±6	302±8	25±11	0.05	112±10	232±27	120±29	0.001
7	244±7	266±7	22±10	0.05	91± 8	182±22	91±23	0.01
10	208±6	222±7	14± 9	0.2	69± 9	140±16	71±18	0.01
15	178±6	198±8	20±10	0.05	48± 6	122±16	74±17	0.01
30	127±9	160±8	33±12	0.05	37± 4	96±12	59±13	0.001
45	91±9	121±6	30±11	0.05	25± 3	78± 8	53± 9	0.001
60	79±4	104±5	25± 7	0.01	18± 2	67± 5	49± 5	0.001
90	77±3	80±3	3± 4	—	9± 1	48± 6	39± 6	0.001
K	2.07±0.10	1.38±0.12		0.001				

[a] SEM $= \sqrt{\frac{\Sigma d^2}{n(n-1)}}$

Table 2. *Influence of dimethylbiguanide on blood glucose and insulin levels in obese non-diabetic women during i.v. glucose load*

Glucose levels (mg/100 ml)					Insulin levels (μU/ml)			
Time (min)	Before	After	d	p	Before	After	d	p
0	89±3[a]	86±2	− 3± 4	ns	32± 4	22± 2	−10± 3	<0.01
3	302±8	288±7	−14±10	ns	232±27	173±16	−54±13	0.05
7	266±7	264±5	− 2± 9	ns	182±22	124±13	−58±18	0.01
10	222±7	218±9	− 4±11	ns	140±16	102± 9	−38±14	0.02
15	198±8	193±8	− 6±11	ns	122±16	84±11	−38±14	0.02
30	160±8	154±7	− 6±10	ns	96±12	76± 8	−20±11	0.1
45	121±6	124±8	+ 3± 9	ns	78±13	59±13	−19±13	0.2
60	104±5	105±7	1± 9	ns	67± 5	51± 5	−16± 7	0.05
90	80±3	80±3			48± 6	29± 4	−19± 4	0.001
K	1.38±0.12	1.54±0.16		ns				

[a] SEM $= \sqrt{\frac{\Sigma d^2}{n(n-1)}}$

Table 3. *Insulin/glucose ratios (μU/mg/100 ml) after rapid i.v. glucose (0.66 g/kg) injection in normal controls (n = 15) and in obese non-diabetics (n = 15)*

Time (min)	Normal controls ($n = 15$)	Obese before treatment ($n = 15$)	d	p	Obese after DMBG treatment ($n = 15$)	d (after-before treatment)	p
0	15.2±1.7[a]	36.2±3.8	17.0±4.2		25.7±2.8	−10.5±3	<0.01
3	44.2±2.8	76.8±6.7	32.6±7.3		61.8±5.8	−15.0±6.1	0.05
7	37.1±2.8	68.4±4.9	31.3±5.6		47.0±3.9	−11.4±4.3	0.05
10	33.3±3.2	64.0±5.2	30.7±6.1		46.3±4.6	−17.7±4.8	0.01
15	27.2±3.8	61.1±7.2	33.9±8.1		43.5±5.8	−17.6±6.5	0.02
30	28.8±3.3	60.0±7.0	31.2±7.8		42.8±4.1	−17.2±6.5	0.01
45	27.4±3.1	64.4±4.4	37.0±5.4		47.6±5.2	−16.9±5.0	0.01
60	22.5±2.1	64.4±5.8	41.9±6.2		48.5±4.5	−15.9±5.1	0.01
90	12.5±1.6	62.3±4.1	39.8±4.4		36.2±3.8	−26.1±4.0	0.01

[a] SEM $= \sqrt{\frac{\Sigma d^2}{n(n-1)}}$

1 S.D. $= \sqrt{\frac{\Sigma d^2}{n-1}}$

1. Neither fasting nor IVGTT blood glucose levels were significantly changed by dimethylbiguanide treatment.
2. Similarly the mean K value was not significantly changed.
3. Fasting plasma insulin levels were significantly decreased after treatment (mean $= 22 \pm 2$ μU/ml) although still higher than in the normal control group (mean $= 12 \pm 2$ μU/ml).
4. IVGTT insulin levels were significantly decreased, although still higher than in normal, non-obese subjects (Table 1).
5. Insulin/glucose ratios were significantly decreased after dimethylbiguanide treatment (Table 3).

Discussion

It is well known that in obese subjects, insulin levels in response to an oral or intravenous GTT [3, 12, 16, 21, 22] are increased in comparison with normal subjects having similar glucose levels, suggesting the existence of an insulin resistance in obesity. However, as both the oral and intravenous glucose tolerance tests are within the normal range, these patients are not classified as (chemical) diabetics according to usual criteria. We observed that the increased insulin response is already evident 3 min after the glucose load, proving that there is no delay in insulin release in non-diabetic obesity. This is in accordance with the results of Chiles *et al.* [6] who, after oral glucose administration to obese subjects, found only a delay in insulin release when glucose tolerance was mildly impaired.

As far as the influence of short-term dimethylbiguanide treatment is concerned, our results show that glucose levels, both in the fasting state and after an intravenous glucose load, were not significantly different from the pretreatment levels, notwithstanding a tendency towards slightly decreased levels. Similarly the glucose assimilation coefficient was not significantly influenced by this short-term treatment, confirming earlier observations [15]. The insulin response and the insulin/glucose ratios on the other hand were significantly decreased after treatment, suggesting a greater effectiveness of insulin. Results reported in the literature concerning influence of long-term metformin treatment [8, 15] are difficult to interpret in view of reduction in body weight, which by itself improves glucose assimilation. Most studies on the influence of biguanides on plasma glucose and insulin levels were performed in obese, mildly *diabetic* patients [2, 20] and the decrease in insulin levels might be considered to be a consequence of the hypoglycaemic effect of biguanides observed in these patients. Vague [31], studying the influence of the administration of 1.5 g of metformin to obese, *non-diabetic* subjects, observed a decrease in glucose and insulin levels after oral administration of glucose. Here again it might be argued that the decreased insulin levels were the consequence of the decrease in glycaemia, itself eventually the consequence of a decreased glucose absorption, as suggested by Czyzyk [9]. Grodsky *et al.* [13] after administration of phenformin to five non-diabetic, obese patients did not observe a decrease in glycaemia after an I.V. glucose load, but reported decreased insulin levels. The method used for the determination of plasma insulin was however rather unreliable, making the interpretation of the insulin levels rather hazardous.

It is evident from our results that metformin may decrease insulin levels in obese non-diabetic subjects, independent of any significant decrease in glycaemia. The mechanism of this effect is still problematical. An increase in biological half life of insulin is unlikely: indeed it can be calculated from our results that the rate of decrease in plasma insulin after the glucose load is practically unchanged by treatment. Qualitative differences in the insulin secreted after biguanide treatment, on the other hand, are for the moment purely hypothetical.

A direct stimulatory effect of biguanides on glucose utilization by peripheral muscle tissue [5] might be one of the factors contributing to a greater effectiveness of insulin. An argument for this hypothesis is the observation by Searle *et al.* [26], of an increased Cori cycle activity and increased glucose turnover in non-diabetic human subjects under the influence of phenformin. This might decrease the need for extra insulin in obese subjects and explain the decreased insulin levels in the presence of an unchanged glycaemia. Similarly, inhibition of gluconeogenesis by biguanides might also decrease the insulin requirements. However, according to Kreisberg [18], as well as to Searle and Cavalieri [27], gluconeogenesis is normal under phenformin treatment of non-diabetic obese subjects. Since increased insulin levels play a role in hypertriglyceridaemia and lipogenesis [23] and maintenance of obesity, the decrease of insulin levels observed after biguanide treatment may be considered as a desirable effect which, by promoting fat mobilization and lipolysis [25] might contribute to a loss in body weight; in this way biguanides might contribute to break the vicious circle of obesity → insulin resistance → hypersecretion of insulin → increased food intake → lipogenesis → obesity, leading finally to the development of maturity-onset diabetes.

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