THE EFFECT OF METFORMIN ON WEIGHT LOSS IN OBESITY

By

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ABSTRACT

In seven hospitalised obese patients (one diabetic, two with questionable diabetes, and four non-diabetic subjects) the average weight loss on a 1250 calorie diet was 20 per cent greater with than without metformin. The weight loss depended on the dosage of metformin. Based on the present results and investigations the outline of a new investigation is presented.

A tendency to weight loss in obese diabetics treated with phenformin, a biguanide, has been postulated and a decreased lipogenic effect of the preparation discussed (Weller et al. 1962; Radding et al. 1962; Williams 1962; Grodsky et al. 1963).

Since the weight loss was observed in out-patients, without special control of the intake of calories and, since the biguanides have some anorexigenic effect which might involve a lessened intake of calories (Patel & Stowers 1964) the author found it of interest to investigate the possible effect of biguanides on weight loss in obese patients taking a fixed amount of calories during a stay in hospital. The preparation metformin (dimethylbiguanide hydrochloride) was used, and each patient acted as her own control.

METHODS AND MATERIALS

Principles and Methods. During the trial 7 patients were hospitalised. After examinations on a full diet they were given a diet of 1250 calories starting 5–35 days after

admission. In 4 patients the diet contained 77 g protein, 55 g fat, and 97 g carbohydrate, and in 3 patients 95 g protein, 34 g fat and 140 g carbohydrate. While on this diet the patients were put on and off metformin for periods of 4 to 23 days, always starting and ending with a period without metformin of 7–20 and 5–11 days, respectively.

The patients were instructed about the importance of eating the whole diet and nothing but the diet, to take the same amount of daily exercise and not to alter their intake of table salt. The intake of food was strictly supervised, and only alterations in the amount of vegetables eaten were allowed. The patients were up and about in the ward, and the same amount of extra (preferably outside) exercise was taken every day, supervised by nurses, and a physiotherapist.

Every morning the patients were weighed on (the same) one of two ordinary hospital scales, at the same time, wearing the same kind of clothing etc. and nearly always by the same nurse.

Glucose tolerance tests were made in five patients (oral) and in four patients (intravenous). In two, the 24-hour blood sugar (fasting and at 11 a.m. and at 2 and 8 p.m.) was determined on a full diet before the trial. In addition, in three patients the blood-sugar was measured while fasting, at 11 a.m. and at 2 p.m. on several days during the trial. The capillary blood-sugar method was that of Hagedorn-Jensen. Other pilot biochemical studies were also performed.

The Patients. In Table 1, some data on the seven female patients are given. They were middle-aged to old with obesity of varying degree. The number of trial days varied from 21–59 days, an average of 40 days.

In addition to the main diagnosis of obesity, slight deviations from the normal were found in 5 of the patients. Patient no. 6, however, had cardiac insufficiency on admission and was first on the trial after 35 days, when her weight had decreased from 95.5 to 84.0 kg with the help of digitalis, diuretics, and diet, and when her weight had proved stationary for 14 days with digitalis as the only medication. Patient no. 7 had untreated manifest maturity onset diabetes with a fasting blood-sugar of 186 mg/100 ml and a 24-hour blood-sugar over 200 mg/100 ml and glucosuria of 4 g/24 h.

4 patients were non-diabetics. Patient no. 2 on two occasions had a completely normal oral glucose-tolerance test but a k value of 0.90 as judged by an intravenous test on two occasions. One of her children was an insulin-treated diabetic. This patient had given birth to a baby weighing 4800 g and had a slight rubiosis faciei. Patient no. 4 had an »in-between« oral glucose-tolerance test, neither normal nor clearly diabetic, whereas the intravenous test gave a k value of 1.24. These two patients are here designated as questionable diabetics.

Dosage of metformin. The maximum daily dosage of metformin (Glucophage®, Rona) during the periods of treatment was 1500 mg in one, 2000 mg in two, 3000 mg in two and 4000 mg in two patients. The tolerance to metformin was good (for single initial loose stools vide infra). After the first one or two days there were no complaints at all.

Another patient had 2–5 loose stools daily during the metformin treatment period and was thus not included in the material.

Medicine. Patient no. 6 had a digitalis preparation daily for 5 days a week. Patient no. 1 had a chlorprothixeni preparation (Truxal®, Lundbeck) for 3 days during her final period off metformin.

Exceptions from the general scheme. 2 patients were tried on diets with 1700 (patient no. 3) and 1850 calories (patient no. 2) on and off metformin before they were given the diet with 1250 calories. 2 patients had no food at all for 48 hours (water and tea
**Table 1.**
Data on the patients.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Diagnoses (besides obesity)</th>
<th>Glucose-tolerance test</th>
<th>Length of trial (days)</th>
<th>Weight loss (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>162</td>
<td>96.5</td>
<td>Slight hypertension</td>
<td>Oral: N</td>
<td>24</td>
<td>4.8</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>159</td>
<td>99.5</td>
<td>Questionable diabetes*</td>
<td>Intravenous: N (twice)</td>
<td>59</td>
<td>10.5</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>170</td>
<td>118.8</td>
<td>Slight hypertension</td>
<td>Oral: N</td>
<td>55</td>
<td>12.3</td>
</tr>
<tr>
<td>4</td>
<td>51</td>
<td>150</td>
<td>88.3</td>
<td>Questionable diabetes*</td>
<td>Oral: Abnormal</td>
<td>30</td>
<td>6.8</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>157</td>
<td>78.5</td>
<td>Slight hypertension</td>
<td>Oral: 24-hour</td>
<td>45</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>blood-sugar</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>149</td>
<td>84.0</td>
<td>Compensated cardiac insufficiency*</td>
<td>Oral: N</td>
<td>44</td>
<td>5.3</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>171</td>
<td>113.2</td>
<td>Diabetes*</td>
<td>Oral: N</td>
<td>21</td>
<td>4.5</td>
</tr>
</tbody>
</table>

*) see text.
allowed), patient no. 5 before and patient no. 3 after metformin had been administered. Patient no. 3 had a 4-day, patient no. 7 a 14-day period with metformin as the final period.

Patients nos. 2 and 3 who, together, were in the trial for 114 days (Table 1) had together 5 free days out of the hospital, 1 metformin day (weight loss 0.2 kg), and 4 days without metformin (average daily weight loss 0.3 kg). 1 patient (no. 4) was unable to eat the meat dish on one metformin day.

In altogether 5 initial days of metformin, 4 patients had more than 1 stool daily, while this happened once for one patient off metformin. Another patient no. 7 had 2 normal stools daily on 10 of 14 metformin days (Fig. 3).

RESULTS

When all patients and regimens are pooled (Table 2), the average daily weight loss for the group was found to be about 20 per cent greater on metformin, or (by chance) the same weight loss of 25 kg was obtained on metformin in 128 days instead of 150 days. In Fig. 1 the average daily weight loss on and off metformin for each patient is compared.

The dose of metformin appears to play an important role in weight loss (Fig. 2). Apparently, after the initial weight loss, these patients scarcely lose weight on a diet of 1250 calories without metformin, whereas weight loss is induced or accelerated by metformin, though in a daily dose of 3000 to 4000 mg. Similarly, only after the dose of metformin has been pushed to 4000 mg

* Including 48 hours without food.
Fig. 1.
Average daily weight loss with and without metformin in 7 obese patients.
Diet: see text.

Fig. 2.
Loss of weight in relation to dose of metformin. Diet: 1250 calories (cases nos. 5 and 6).

daily is the weight loss accelerated again after the initial weight loss in case no. 7 (Fig. 3). Fig. 4 shows the effect of metformin when different amounts of calories are ingested. The weight is constant on a 1700 calorie diet, but weight loss is induced by metformin. On a 1250 calorie diet the patient loses weight, and the two metformin periods accelerate this loss. In comparison with the results in Fig. 2 the more reducing effect of a diet with 1250 calories in this more obese patient and the smaller dose of metformin during shorter periods should be taken into account. Metformin again induces a weight loss after starvation.
In Figs. 2 and 4 the result of 48 hours’ fast is shown. Both patients react in a typical way with an immediate large weight loss followed by no change or a slight rise in weight for several days on a 1250 calorie diet.

The pilot studies on blood-sugar, pH and base excess (capillary blood), cholesterol and protein bound iodine (venous blood), 17-KS and 17-KGS (24-hour urine) have all given the expected results: Small decreases, of the same magnitude as known from weight loss in obese subjects. An excess of base of -3.5 meq/l was the only pathological value measured and was seen in a patient off metformin when she had had no food for 48 hours.
Comments

When evaluating the results in Table 2 and Fig. 1, the following should be kept in mind: 4 days without any food at all are included in the 150 days without metformin. Likewise the weight loss on non-metformin days was favoured by the inclusion of the »initial« dehydration weight loss which occurs when obese patients start treatment with a reducing diet.

This boosting of the weight loss on non-metformin days was done to compensate for the inaccuracies of the trial on the metformin days, mentioned previously. However, there is also the fact that the »initial loose stool days« comprised 5 of 128 days on metformin, only, and that no correlation between weight loss and number of stools could be found (see e. g. Fig. 3).

The negligible effect of metformin in patients nos. 1 and 2 (Table 2, Fig. 1) can easily be explained by the fact that no. 1 had 1500 mg, no. 2, 2000 mg of metformin daily for short periods, a dose too small to have any effect on weight. (These patients were the first to be studied).

The reason why the average daily weight loss is higher without metformin in case no. 7 (Table 2) is the lacking terminal period without metformin (Fig. 3), causing an undue preponderance of the initial dehydration weight loss.

DISCUSSION

The aim of the trial was to determine the possible effect of metformin on weight, but not, a priori, to produce a large loss of weight. Therefore, too much importance should not be attached to the average loss being just 20 per cent greater with the metformin. More important is the fact that the daily dose has to be as large as 3–4000 mg metformin in order to produce an increased weight loss on a 1250 calorie diet.

With or without metabolic ward facilities, investigations of this kind are difficult to perform, but attractive, since the mechanism of the effect of metformin is unknown. Although the author is rather convinced that metformin has had a reducing effect which is not due to a lessened intake of calories, the study, so far, may not be fully convincing to others. Here as a supplement to the present results two groups of obese subjects should be treated with a 1500 calorie diet with one group taking 3000–4000 mg metformin daily.

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REFERENCES


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