Insulin Secretion and Body Composition in Obesity

By Ashraf Z. El-Khodary, Michael F. Ball, Ibrahim M. Oweiss, and John J. Canary

Plasma immunoreactive insulin levels were measured before and for 6 hr following a 100 g oral glucose load in ten normal volunteers and 17 grossly obese subjects. Eleven of the obese had an abnormal glucose tolerance, five of whom were overt diabetics. Twelve of the obese were restudied after significant weight reduction (thinned obese). Eight thinned obese subjects were also restudied 6–12 mo after completion of the weight reduction protocol. Body composition was measured in each subject prior to testing. Obesity was associated with hyperinsulinemia in the fasting state and in response to oral glucose. The obese diabetics demonstrated a delay and an impairment of insulin secretion in response to glucose. After weight reduction, elevated fasting plasma insulin levels fell in all. Insulin response to oral glucose was not different in the thinned obese with normal glucose tolerance from that observed in the normal volunteers. There was significant correlation between both fasting plasma insulin and total measurable insulin following the glucose load, and total body fat in the obese and thinned obese nondiabetics, but not in the obese overt diabetics. There was, however, significant correlation between fasting plasma insulin levels and total body fat in the diabetics who had a normal fasting blood sugar. These data indicate that the hyperinsulinemia of obesity is clearly related to the increase in total body fat. Carbohydrate intolerance occurs in those obese individuals with a limited pancreatic insulin secretory reserve, which fails to compensate for the increase in total body fat.

Hyperinsulinemia occurs in obesity irrespective of the state of carbohydrate tolerance.14 Weight loss results in an improvement in glucose tolerance in the diabetic obese and in a reduction of the hyperinsulinemia in both the nondiabetic and diabetic obese.8,5

From the Department of Medicine, Georgetown University School of Medicine, and the School of Economics and Statistics, Georgetown University, Washington, D.C.

Received for publication January 10, 1972.

Supported in part by Grant TM 5041 from the National Institutes of Arthritis and Metabolic Diseases; by Research Grant RD 2224-M from the Social and Rehabilitation Service of the Department of Health, Education and Welfare; by General Research Support Grant FR 5360 from the Division of Research Facilities and Resources, National Institutes of Health; by grants from Life Insurance Medical Research Fund and the Washington Heart Association; and the facilities of the Georgetown University Clinical Study Unit, supported by the National Institutes of Health (FR-60).

Ashraf Z. El-Khodary, M.D.: Assistant Professor of Medicine, Laval University School of Medicine, St. Sacrement Hospital, Quebec, Canada; formerly Assistant Professor of Medicine, Georgetown University School of Medicine, Washington, D.C. Michael F. Ball, M.D., F.A.C.P.: Assistant Professor of Medicine, Georgetown University School of Medicine, Washington, D.C. Established Investigator of the American Heart Association. Ibrahim Oweiss, Ph.D.: Assistant Professor of Economics, School of Economics and Statistics, Georgetown University, Washington, D.C. John J. Canary, M.D., F.A.C.P.: Professor of Medicine; Director, Division of Endocrinology, Georgetown University School of Medicine, Washington, D.C.
Although hyperinsulinemia in obesity has been attributed to insulin resistance, localization of the cause of the insulin resistance remains speculative. Studies of glucose uptake in the perfused forearm suggest that the insulin resistance of obesity is in muscle.\textsuperscript{7,8} In contrast, Salans et al. demonstrated diminished insulin sensitivity in adipose tissue samples from obese subjects and suggested that adipose tissue reponsiveness to insulin was dependent on adipose cell size.\textsuperscript{9} Seltzer et al. agreed that obesity induces peripheral insulin resistance but further indicated that there was no difference in the magnitude of insulin response to glucose between obese and normal weight nondiabetic subjects and concluded that insulin secretion was impaired in both normal weight and obese diabetic patients.\textsuperscript{3}

To further clarify the factors that contribute to hyperinsulinemia and the apparent paradoxical occurrence of glucose intolerance in obese subjects, we investigated the relationship between the major components of body weight and plasma insulin levels in the basal state and in response to oral glucose in patients with and without carbohydrate intolerance, prior to and following weight reduction.

**MATERIALS AND METHODS**

Ten normal volunteers were chosen from the House Staff and the Nursing Staff of the Georgetown University Hospital. All were nondiabetic with no family history of diabetes. Five males and five females were studied, varying in age from 24 to 37, with a mean age of 28 yr. Their average body weight was 67.7 kg, ranging from 49.2 to 85.0 kg. All were within 5\% of ideal body weight, according to the 1959 Metropolitan Life Insurance Tables.\textsuperscript{10} Fat constituted less than 20\% of the body weight of each male subject and less than 30\% of the body weight of the female subjects.

Seventeen subjects comprised the obese group. These patients had a mean age of 21, ranging from 16 to 40 yr. Body weight ranged from 86 to 178 kg, with a mean of 135 kg. Fat comprised 29-48\% of the total body weight in the males and 44-53\% in the females.

The normal volunteers and the obese were studied on the Clinical Research Facility of the Georgetown University Hospital. Both groups were on an unrestricted diet prior to admission to the study. Each subject received 300 g carbohydrate daily, included in a total dietary intake of 2600-3000 kcal, during a period of equilibration ranging from 3 days to 1 wk. During this period, all subjects were in positive caloric balance as judged by their daily weights, which either remained steady or increased.

A 6-hr glucose tolerance test was carried out after each subject had received a 100-g oral glucose load. The test was performed at complete bed rest, following an overnight fast. Blood was drawn while fasting and at 30 min, 1, 2, 3, 4, 5, and 6 hr after the glucose load. Each sample was analyzed for blood sugar and plasma immunoreactive insulin. Blood glucose determinations were performed on the day of the test, utilizing an autoanalyzer. Plasma for immunoreactive insulin levels was frozen at \(-20^\circ\text{C}\) until assayed by the double-antibody immunoassay of Morgan and Lazarow as modified by Soeldner and Slone.\textsuperscript{11,12} The minimal sensitivity of this assay is 1.0 mU/ml in this laboratory, and the assay is reproducible within \(\pm12\%\). Total body fat and the fat-free body were calculated from the measured total body water and body density, determined by the method of Siri as modified in this laboratory.\textsuperscript{13,14}

The obese patients remained on the metabolic ward for a period of 6–9 mo, during which they were fed 1000–1500 kcal, liquid metabolic diets in which 40\% of the calories were derived from carbohydrate, 20\% from protein, and 40\% from fat. Although physical exercise was encouraged during this period of hospitalization, its effect on insulin secretion
and carbohydrate metabolism was not evaluated. After considerable weight loss or return to normal body composition, i.e., total body fat comprising less than 20% of the body weight of the males and less than 30% of the body weight of the females,15 the thinned obese patients were placed on 1500–2000 kcal diets, containing at least 200 g carbohydrate for 3 days–1 wk. This diet was supplemented with soft drinks to provide a daily 300 g carbohydrate intake. During this short refeeding period all subjects gained weight. The glucose tolerance test and measurements of body composition were then repeated. Eight thinned, obese subjects were also restudied 6–12 mo after their discharge from the metabolic ward. During that interval they were on unrestricted diets and had returned to normal physical activities outside the hospital.

RESULTS

Fasting Insulin Levels and the Insulin Response to Glucose (Table 1)

Normal Volunteers: The mean fasting plasma insulin level in the normal volunteers was 11.0±2.7 (SEM) μU/ml. (Standard error of the mean is the estimate of variance used throughout the text.) Seven of the ten subjects had a peak plasma insulin response 30 min after the oral glucose load; in three subjects the peak level was recorded 1 hr after glucose ingestion. The mean peak plasma insulin level irrespective of time was 114.4±17.3 μU/ml. The mean total plasma insulin (sum of plasma insulin levels measured over the 6-hr period following the glucose load) was 231.9±25.0 μU/ml.

Obese group: Using the criteria defined by Fajans and Conn, the obese group was divided into obese nondiabetics and obese diabetics.16 The diabetic group was subdivided into chemical diabetics and overt diabetics (fasting blood sugar [FBS] 105 or above). None of the diabetic subjects had been treated for diabetes.

The mean fasting plasma insulin in the obese nondiabetics was 25.5±2.7 μU/ml, which was significantly higher than that observed in the normal volunteers (p<0.005). Of the six obese nondiabetic subjects, four had a peak plasma insulin level 30 min after the glucose load, and two had a peak plasma insulin level 1 hr after glucose ingestion. The mean peak plasma insulin level irrespective of time in this group was 239.2±17.9 μU/ml, which was significantly greater than that observed in the normal volunteers despite comparable blood glucose levels (p<0.001). The mean total plasma insulin in the obese nondiabetics was much higher than that recorded in the normal volunteers (p<0.001).

The mean fasting plasma insulin level in the obese diabetics as a group was 57.8±10.7 μU/ml, which was significantly higher than that observed in the normal volunteers and the obese nondiabetics (p<0.001, p<0.02, respectively). The mean fasting plasma insulin level in the overt diabetics was not statistically different from that observed in the chemical diabetics. The peak plasma insulin levels were not detected in any obese diabetic until at least 1 hr after the glucose load. Peak plasma insulin response varied considerably among individual patients in each of the two diabetic groups irrespective of the blood glucose levels. The mean peak plasma insulin level in the obese, overt diabetics irrespective of time was significantly higher than that observed in the normal volunteers (p<0.02); however, it was not
Table 1. Plasma Insulin Concentrations in Response to Oral Glucose

<table>
<thead>
<tr>
<th></th>
<th>Weight (kg)</th>
<th>F.F.B.</th>
<th>T.B.F.</th>
<th>0</th>
<th>30 min</th>
<th>1 hr</th>
<th>2 hr</th>
<th>3 hr</th>
<th>4 hr</th>
<th>5 hr</th>
<th>6 hr</th>
<th>Peak</th>
<th>Total Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (10)†</td>
<td></td>
<td></td>
<td></td>
<td>67.8</td>
<td>55.9</td>
<td>11.8</td>
<td>11.0</td>
<td>94.4</td>
<td>67.1</td>
<td>31.1</td>
<td>16.7</td>
<td>10.8</td>
<td>8.7</td>
</tr>
<tr>
<td>SEM</td>
<td>± 4.2</td>
<td>±3.9</td>
<td>±1.2</td>
<td>11.0</td>
<td>94.4</td>
<td>67.1</td>
<td>31.1</td>
<td>16.7</td>
<td>10.8</td>
<td>8.7</td>
<td>6.1</td>
<td>1144</td>
<td>231.9</td>
</tr>
<tr>
<td>Mean blood sugar (mg/100 ml)</td>
<td></td>
<td></td>
<td></td>
<td>127.9</td>
<td>71.1</td>
<td>56.8</td>
<td>25.5</td>
<td>205.2</td>
<td>190.2</td>
<td>106.3</td>
<td>104.5</td>
<td>48.7</td>
<td>23.8</td>
</tr>
<tr>
<td>SEM</td>
<td>±12.3</td>
<td>±7.8</td>
<td>±6.1</td>
<td>205.2</td>
<td>190.2</td>
<td>106.3</td>
<td>104.5</td>
<td>48.7</td>
<td>23.8</td>
<td>23.6</td>
<td>239.2</td>
<td>702.0</td>
<td></td>
</tr>
<tr>
<td>Obese nondiabetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (6)</td>
<td></td>
<td></td>
<td></td>
<td>127.9</td>
<td>71.1</td>
<td>56.8</td>
<td>25.5</td>
<td>205.2</td>
<td>190.2</td>
<td>106.3</td>
<td>104.5</td>
<td>48.7</td>
<td>23.8</td>
</tr>
<tr>
<td>SEM</td>
<td>±12.3</td>
<td>±7.8</td>
<td>±6.1</td>
<td>205.2</td>
<td>190.2</td>
<td>106.3</td>
<td>104.5</td>
<td>48.7</td>
<td>23.8</td>
<td>23.6</td>
<td>239.2</td>
<td>702.0</td>
<td></td>
</tr>
<tr>
<td>Obese diabetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (6)</td>
<td>131.0</td>
<td>74.0</td>
<td>57.0</td>
<td>39.0</td>
<td>237.5</td>
<td>284.0</td>
<td>266.0</td>
<td>121.0</td>
<td>57.7</td>
<td>49.2</td>
<td>35.8</td>
<td>35.8</td>
<td>302.0</td>
</tr>
<tr>
<td>SEM</td>
<td>±12.5</td>
<td>±7.7</td>
<td>±7.6</td>
<td>237.5</td>
<td>284.0</td>
<td>266.0</td>
<td>121.0</td>
<td>57.7</td>
<td>49.2</td>
<td>35.8</td>
<td>302.0</td>
<td>1052.0</td>
<td></td>
</tr>
<tr>
<td>Mean blood sugar (mg/100 ml)</td>
<td></td>
<td></td>
<td></td>
<td>91.7</td>
<td>154.8</td>
<td>172.2</td>
<td>134.7</td>
<td>96.5</td>
<td>82.0</td>
<td>83.3</td>
<td>91.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>±3.5</td>
<td>±6.3</td>
<td>±7.3</td>
<td>154.8</td>
<td>172.2</td>
<td>134.7</td>
<td>96.5</td>
<td>82.0</td>
<td>83.3</td>
<td>91.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>----------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>149.9</td>
<td>81.0</td>
<td>68.9</td>
<td>79.4</td>
<td>172.0</td>
<td>413.0</td>
<td>292.2</td>
<td>257.2</td>
<td>154.0</td>
<td>95.2</td>
<td>62.8</td>
<td>473.0</td>
</tr>
<tr>
<td>SEM</td>
<td>±14.0</td>
<td>±8.2</td>
<td>±9.0</td>
<td>±18.2</td>
<td>±37.0</td>
<td>±119.1</td>
<td>±80.9</td>
<td>±90.8</td>
<td>±74.2</td>
<td>±31.2</td>
<td>±19.9</td>
<td>±122.4</td>
<td></td>
</tr>
<tr>
<td>Mean blood sugar (mg/100 ml)</td>
<td>127.2</td>
<td>186.6</td>
<td>222.4</td>
<td>199.0</td>
<td>175.8</td>
<td>148.0</td>
<td>113.0</td>
<td>102.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>±17.3</td>
<td>±37.3</td>
<td>±33.4</td>
<td>±45.1</td>
<td>±31.3</td>
<td>±26.1</td>
<td>±16.0</td>
<td>±12.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thinned obese subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nondiabetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (10)</td>
<td>80.9</td>
<td>62.0</td>
<td>18.9</td>
<td>15.1</td>
<td>95.7</td>
<td>94.4</td>
<td>63.5</td>
<td>41.8</td>
<td>18.6</td>
<td>14.8</td>
<td>1.0</td>
<td>38.2</td>
<td>191.2</td>
</tr>
<tr>
<td>SEM</td>
<td>±5.0</td>
<td>±5.5</td>
<td>±3.2</td>
<td>±3.5</td>
<td>±17.7</td>
<td>±21.1</td>
<td>±12.3</td>
<td>±7.6</td>
<td>±1.7</td>
<td>±1.6</td>
<td>±2.4</td>
<td>±21.7</td>
<td>±50.3</td>
</tr>
<tr>
<td>Mean blood sugar (mg/100 ml)</td>
<td>85.2</td>
<td>123.5</td>
<td>119.9</td>
<td>101.0</td>
<td>98.2</td>
<td>81.6</td>
<td>86.6</td>
<td>92.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>±2.0</td>
<td>±5.9</td>
<td>±5.3</td>
<td>±2.8</td>
<td>±6.7</td>
<td>±5.0</td>
<td>±3.1</td>
<td>±2.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>88.5</td>
<td>74.1</td>
<td>14.4</td>
<td>9</td>
<td>54</td>
<td>70</td>
<td>85</td>
<td>32</td>
<td>18</td>
<td>0</td>
<td>10</td>
<td>85</td>
<td>269</td>
</tr>
<tr>
<td>Blood sugar (mg/100 ml)</td>
<td>90</td>
<td>142</td>
<td>144</td>
<td>136</td>
<td>110</td>
<td>98</td>
<td>98</td>
<td>98</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 2</td>
<td>69.0</td>
<td>38.6</td>
<td>30.7</td>
<td>12</td>
<td>124</td>
<td>125</td>
<td>250</td>
<td>56</td>
<td>16</td>
<td>38</td>
<td>250</td>
<td>849</td>
<td></td>
</tr>
<tr>
<td>Blood sugar (mg/100 ml)</td>
<td>84</td>
<td>144</td>
<td>170</td>
<td>210</td>
<td>130</td>
<td>76</td>
<td>52</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Fat-free body.
† Total body fat.
‡ No. of subjects.
Table 2. Thinned, Obese Subjects: Plasma Insulin Concentration in Response to Oral Glucose

<table>
<thead>
<tr>
<th></th>
<th>Immediately Postweight Reduction</th>
<th>Late Studies (6–12 Mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B.W.* (kg)</td>
<td>F.F.B.† (kg)</td>
</tr>
<tr>
<td>Mean§</td>
<td>86.4</td>
<td>70.0</td>
</tr>
<tr>
<td>SEM</td>
<td>5.2</td>
<td>5.2</td>
</tr>
</tbody>
</table>

* B.W., body weight.
† F.F.B., fat-free body.
‡ T.B.F., total body fat.
§ No significant difference between corresponding means (p = N.S., n = 8 in each instance).
significantly different from that observed in the obese nondiabetics or in the obese, chemical diabetics.

The mean total plasma insulin level of $1215.0 \pm 222.5 \mu U/ml$ in the obese diabetics was markedly higher than that observed in the normal volunteers and in the obese nondiabetics ($p<0.001$, $p<0.05$, respectively). The mean total plasma insulin level in the obese, overt diabetics was not statistically different from that observed in the chemical diabetic subjects.

The mean total plasma insulin level of $1215.0 \pm 222.5 \mu U/ml$ in the obese diabetics was markedly higher than that observed in the normal volunteers and in the obese nondiabetics ($p<0.001$, $p<0.05$, respectively). The mean total plasma insulin level in the obese, overt diabetics was not statistically different from that observed in the chemical diabetic subjects.

Thinned Obese: After weight reduction, fasting plasma insulin levels fell in all subjects. Total weight loss varied from 12 to 70 kg, with an average of 50.1 kg. Seven subjects were returned to normal body composition. Eight of the 12 subjects studied after weight reduction were diabetic while obese. Six of these subjects had a normal glucose tolerance at the end of the weight reduction period, while an abnormal glucose tolerance persisted in two.

The mean fasting plasma insulin level in all the thinned obese with a normal glucose tolerance was not statistically different from that observed in the normal volunteers but was significantly less than that observed in the obese nondiabetics ($p<0.05$). The mean peak plasma insulin level irrespective of time in the thinned obese with normal glucose tolerance was comparable to the mean peak observed in the normal volunteers.

The mean total plasma insulin level in the thinned obese subjects was not different from that observed in the normal volunteers but was significantly less than that observed in both the obese nondiabetics and the obese diabetics ($p<0.001$ in both instances).

Fasting plasma insulin levels decreased in the two subjects who had an abnormal glucose tolerance after thinning. Both continued to show a delay in insulin release, since the peak level was not achieved until 2 hr after the glucose load. Total measurable insulin decreased in the patient who had returned to normal body composition. The second patient, who was still obese despite a 47 kg weight loss, had a total measurable insulin of $849.0 \mu U/ml$, which was higher than that observed before thinning, $490.0 \mu U/ml$. In this patient, fat constituted 45% of the total body weight after thinning, compared to 53% before weight reduction.

Thinned Obese: Late Studies: The mean fasting plasma insulin level was not different from that recorded in the normal volunteers or in the same subjects immediately after weight reduction and remained significantly less than that observed in the same subjects while obese ($p<0.02$) (Table 2). Six of the eight subjects studied gained weight with a concomitant increase in total body fat. Weight gain varied from 1.8 to 25 kg. Two subjects lost between 5 and 6 kg body weight. Changes in peak and total plasma insulin corresponded to changes in total body fat, such that the mean peak and mean total plasma insulin levels in the eight subjects were higher than those observed in the same subjects immediately after weight reduction. The difference, however, was not significant in either instance. The mean peak plasma insulin level was not different from the normal volunteers and was significantly less than the mean peak recorded in the same subjects while obese ($p<0.05$). The mean total plasma insulin level was significantly higher
Fasting Plasma Insulin Levels and Body Composition

Fasting plasma insulin levels correlated significantly with body weight and total body fat when all the nondiabetic subjects, i.e., volunteers, obese, and thinned obese, are

Fig. 1. Correlation of fasting plasma insulin and body composition: obese nondiabetics.

than the normal volunteers (p<0.01). These patients were also significantly fatter than the normal volunteers, as judged by the difference in total body fat between the two groups (p<0.02). The mean total plasma insulin level was less than that observed in the same subjects while obese, but the difference between the means was not significant. However, each subject had a total plasma insulin response to glucose during this late part of the study that was less than that recorded in the same patient prior to weight reduction, and the data were significantly different when considered as matched pairs (p<0.01).

Plasma Insulin Levels and Body Composition

Fasting Plasma Insulin Levels and Body Composition: Fasting plasma insulin levels correlated significantly with body weight and total body fat when all the nondiabetic subjects, i.e., volunteers, obese, and thinned obese, are
INSULIN SECRETION AND BODY COMPOSITION

Fasting plasma insulin levels correlated with body weight and total body fat in the obese and the thinned obese with normal glucose tolerance (Fig. 1). In each instance, the correlation between fasting plasma insulin levels and total body fat was greater than that observed with total body weight. There was no correlation between fasting plasma insulin levels and the fat-free body in the nondiabetics as a whole group, \( r = 0.134, n = 16 \).

Fasting plasma insulin levels did not correlate with either body weight, total body fat, or fat-free body in the diabetics as a group, \( r = 0.191, r = 0.246, r = 0.282 \), respectively; \( n = 13 \). There was, however, significant correlation between fasting plasma insulin levels and total body fat in the obese and thinned, obese chemical diabetics (Fig. 2). In contrast, there was no correlation between fasting plasma insulin levels and body fat in the overt diabetics, \( r = -0.855, n = 5 \).

Peak Plasma Insulin Levels and Body Composition: There was a strong correlation between peak plasma insulin levels and total body fat in all subjects with normal glucose tolerance, \( r = 0.804, n = 26 \) (p < 0.001). A significant correlation was also observed in the obese and thinned, obese nondiabetics (Fig. 3). There was no correlation between peak plasma insulin levels and total body fat in the diabetics \( r = 0.147, n = 13 \).

Total Plasma Insulin and Body Composition: Total plasma insulin correlated with body weight and total body fat in all subjects with normal glucose tolerance, \( r = 0.702, r = 0.861 \), respectively, \( n = 26 \) (p < 0.001 in both instances). A similar correlation was observed between total plasma insulin
and body weight and total body fat in the obese and thinned obese with normal glucose tolerance. (Fig. 4). There was no correlation between total plasma insulin and fat-free body in the obese and thinned obese with normal glucose tolerance, \( r=0.000, n=16 \).

There was no correlation between total plasma insulin and body weight, total body fat, or fat-free body in the obese diabetics as a group, \( r=0.200, r=0.219, r=0.111 \), respectively, \( n=13 \).

**DISCUSSION**

Despite many studies of the biodynamics of plasma immunoreactive insulin in obesity, the relationship between obesity and diabetes mellitus is not completely understood. The fasting hyperinsulinemia and exaggerated elevation of plasma insulin levels in response to glucose in both the diabetic and nondiabetic obese have been attributed to increased, peripheral insulin resistance,^{3,4} hyperaminoacidemia,^{17} and excessive carbohydrate intake.^{18} Several explanations have been given for the increased insulin resistance associated with obesity, which include intrinsic insulin insensitivity of skeletal muscles,^{8,19} increased adipose cell size,^{9} and increased total body fat.^{3} It has been postulated that the hyperinsulinemia is a compensatory response to the increased peripheral insulin resistance. Failure of this compensatory mechanism, due to an impaired insulin secretory reserve, has been implicated as the cause of diabetes of obesity.^{3,20}

Fasting hyperinsulinemia in both nondiabetic and diabetic obese subjects and an exaggerated insulin response to oral glucose in the nondiabetic obese were demonstrated in our subjects. The insulin secretory response of the
Fig. 4. Correlation of body total plasma insulin and body composition: Obese nondiabetics.
obese diabetic was delayed consistent with previous reports.\textsuperscript{21,22} Furthermore, in the obese diabetics, the increase in insulin response to glucose was less than that observed in the nondiabetic obese. This is indicated by the lack of correlation between either peak or total plasma insulin level and body weight or total body fat in the obese diabetic group.

Bagdade, et al. demonstrated significant correlation between fasting plasma insulin levels and obesity, expressed as percentage overweight.\textsuperscript{23} More recently, Bjorntorp, et al. showed that both fasting and total plasma insulin levels correlated with fat cell diameter and further indicated that there was a correlation between fat cell diameter and total body fat.\textsuperscript{24} Schultz and Parra, on the other hand, could not establish a correlation between total body fat and fasting plasma insulin levels in obese adolescents and attributed this to the low fasting plasma insulin levels observed in the late onset obese group of their study projects.\textsuperscript{25}

Our data demonstrate significant correlation between fasting plasma insulin and both total body weight and total body fat, when the subjects are considered as one population group. This relationship between plasma insulin levels and total body fat extends to the insulin response to an oral glucose stimulus, as indicated by the correlation between total, measurable plasma insulin levels following a glucose load and body weight, total body fat, and surface area. Table 3 shows the matrix of correlation coefficients $r$, together with multiple correlation coefficients $R$. The statistical significance of $R$ is such that it measures the closeness with which the regression fits the observed points.\textsuperscript{26} This means, for example, that $R_1$ measures a 64.6\% combined correlation of body weight, total body fat, fat-free body, and surface area with total plasma insulin during a glucose tolerance test. All multiple correlations shown in Table 3 are significant ($p<0.001$), which indicates that each of the above variables is mutually dependent on all others.\textsuperscript{27}

These data also indicate that all the variations in total plasma insulin cannot be explained by changes in body composition. This is particularly pertinent in view of several recent publications. Bjorntorp et al. have demonstrated that physical training induces a decrease in serum insulin, despite a slight increase

| Table 3. Matrix of Correlation Coefficients Plasma Insulin and Body Composition |
|-----------------|-----------------|-----------------|-----------------|
|                 | Total insulin   | T.B.F.$^*$      | F.F.B.$^\dagger$ | Body Weight     |
| T.B.F.          | $r=0.617$       | $p<0.001$       | $r=0.466$       | $r=0.793$       |
| F.F.B.          | $r=0.306$       | $r=0.908$       | $p<0.001$       | $p<0.001$       |
| Body weight     | $r=0.569$       | $r=0.777$       | $r=0.885$       | $r=0.953$       |
| Surface area    | $r=0.532$       | $p<0.001$       | $p<0.001$       | $p<0.001$       |
| Multiple correlation $R_1=0.646$ | $R_2=0.999$ | $R_3=0.998$ | $R_4=0.999$ |
| $p<0.001$       | $p<0.001$       | $p<0.001$       | $p<0.001$       |

$^*$ Total body fat.
$^\dagger$ Fat-free body.
$^\dagger n=39.$
in body fat, and concluded that changes in muscle metabolism are an important determinant for insulin sensitivity in obesity.\textsuperscript{19} Grey and Kipnis have reported that restriction of dietary carbohydrate will reduce the hyperinsulinemia of obesity and suggested that the excessive carbohydrate intake, which is characteristic of the obese, stimulates beta cell responsiveness and induces an increase in beta cell mass.\textsuperscript{18}

In the present study, the quantitative relationship between insulin and total body fat becomes more significant when one examines the data as representative of two population groups, namely diabetics and nondiabetics, irrespective of the state of obesity. The nondiabetics consistently maintained a correlation between the various insulin parameters and body weight and total body fat. The correlations with total body fat were consistently more statistically significant than were the correlations with body weight. The chemical diabetics, on the other hand, maintained a correlation between plasma insulin levels and total body fat in the fasting state but failed to maintain this correlation when challenged by a glucose load. There was no correlation between plasma insulin and body weight or total body fat in either the fasting state or in response to the glycemic stimulus in the overt diabetics.

These data indicate that total body fat plays an important role in determining plasma insulin homeostasis, both in the basal state and in response to a glucose load. It is conceivable that the hyperinsulinemia of obesity is an adaptive mechanism to meet the metabolic requirements, not defined here, that have resulted from increased body fat and may also be a factor in perpetuating the state of obesity. Carbohydrate intolerance would develop only in those subjects with an inadequate pancreatic insulin reserve. The improvement in glucose tolerance in the diabetic subjects and the reduction in plasma insulin levels in the fasting state and in response to a glycemic stimulus following fat loss support this hypothesis.\textsuperscript{5,6,9,28} Six of the eight obese diabetics in the present study, when restudied after weight reduction, had normal glucose tolerance. Fasting plasma insulin levels fell markedly in all subjects after weight reduction. The mean peak and the mean total plasma insulin levels in the thinned obese with normal glucose tolerance were comparable to those observed in the normal volunteers.

It could be argued that the reduction in basal insulin levels and total plasma insulin in the thinned obese subjects was due to the prolonged interval of hypocaloric feeding and/or restricted carbohydrate intake during the weight reduction period.\textsuperscript{18,29,30,31} The fact that ten of the 12 subjects studied following weight reduction had normal glucose tolerance curves that were not different from the curves recorded in the nondiabetic subjects studied prior to weight reduction or the normal volunteers indicates that the thinned obese were adequately repleted with carbohydrate prior to retesting.\textsuperscript{32,33} Furthermore, there was no change in either the insulin response or glucose tolerance in one of the thinned obese diabetic subjects who was studied after an additional 9 days of carbohydrate repletion.

The follow-up studies reported on eight thinned, obese subjects after more than 6 mo of unrestricted diet and physical activity showed no significant change in the mean fasting, mean peak, and mean total plasma insulin levels
from those observed in the same individuals in the immediate, postweight-reduction period. These parameters remained markedly less than those recorded in the same subjects prior to weight reduction. The observed increase in mean peak and mean total plasma insulin levels was statistically insignificant when compared to the immediate, postweight-reduction values and corresponded with a similar per cent increase in total body fat (Table 2). These data further support the concept that changes in plasma insulin levels observed in the thinned, obese subjects parallel the changes in body composition. However, it is not known whether changes in dietary habits and carbohydrate intake in these subjects following weight reduction might have contributed to the changes observed in plasma insulin levels.

In conclusion, these data lend support to the observation that obesity is associated with a true hyperinsulinemia. The degree of this hyperinsulinemia is directly related to the quantity of total body fat, which determines the degree of obesity, and not the presence or absence of diabetes. Glucose intolerance occurs in those individuals with a limited insulin secretory reserve, which fails to compensate for the increased total body fat. Reduction in total body fat results in a decrease in insulin requirements and hence an improvement in glucose tolerance.

ACKNOWLEDGMENT

We acknowledge with appreciation the technical assistance of Mrs. B. Stein and Mrs. C. Aldige.

REFERENCES


