

## OBSERVATIONS

## Androgen Therapy Improves Insulin Sensitivity and Decreases Leptin Level in Healthy Adult Men With Low Plasma Total Testosterone

A 3-month randomized placebo-controlled trial

In men, an association between lower plasma total testosterone (PTT) and insulin resistance has been found in cross-sectional studies (1,2) and in one nested case-control study (3) without any possible conclusion in terms of causality or direction of the relationship. Indeed, to obtain such information, randomized controlled trials are needed. Until now, only one clinical trial has suggested that testosterone therapy improves insulin sensitivity in obese men (4). Cross-sectional studies concerning leptin regulation by androgens have provided no definitive conclusions as to whether the negative association between androgens and leptin level is independent (5) or dependent (6). This randomized controlled trial was designed to assess the role of androgens on insulin sensitivity and leptin regulation in healthy adult men.

This study was a randomized, double-blind, unicentric, controlled, clinical trial. Three treatments (testosterone, dihydrotestosterone [DHT], and placebo) were compared in parallel groups during a 3-month period. All of the examinations were performed by only two physicians, using a standardized protocol. Blood was drawn between 8:00 A.M. and 9:30 A.M. after an overnight fast to determine fasting plasma glucose, insulin, leptin, sex hormones, lipids, coagulation and fibrinolysis parameters, hepatic enzymes, and prostate-specific antigen (PSA) and blood cell count. Then, a standard 75-g oral glucose tolerance test and a digital rectal examination were performed. In addition, between days 10 and 20, all of the sub-

jects were monitored to measure sex hormones in order to adapt the treatment dose. The study protocol was approved by the Henri Mondor Hospital Ethics Committee. All of the included subjects gave written informed consent.

Men with low levels of PTT (confirmed by two measurements) were selected from a large occupation-based population. The inclusion criteria were as follows: 1) either PTT  $\leq 3.4$  ng/ml [5th percentile value of PTT distribution in the 1,718 men of the TELECOM Study (7)] from 1985 to 1987 and  $< 4.0$  ng/ml (13th percentile value) from 1992 to 1993 (3) or PTT  $< 4.0$  ng/ml from 1992 to 1993 and  $< 4.0$  ng/ml a few days before inclusion; 2) no history of vascular thrombosis or ischemic heart disease; 3) no treatment by androgens, anti-androgens, and anti-diabetic or antithrombotic drugs; 4) normal values of plasma prolactin, estradiol, and thyroxin; 5) no current prostatic disease and a normal PSA value. A total of 18 healthy men with stable low plasma androgens (Table 1) and a range of PTT from 1.4 to 3.7 ng/ml at baseline were included.

The 18 selected men were randomly assigned to one of three treatment groups: testosterone, DHT, or placebo. The randomization code was known only to the study manager. Treatment was a gel administered every morning by percutaneous route. The daily dose during the first weeks was 125 mg for the testosterone and 35 mg for the DHT treatment groups. The adaptation of treatment doses between days 10 and 20 aimed at obtaining a trough level of PTT between 4 and 10 ng/ml for the testosterone group and a trough level of plasma DHT between 4 and 10 ng/ml for the DHT group. To maintain the double blinding, the study manager also sometimes changed the dose of placebo. The subjects were asked not to change their dietary and physical activity. Compliance to treatment was assessed by interview and by measuring sex hormones and gonadotropins at the end of the trial.

Plasma glucose, total cholesterol, HDL cholesterol, triglycerides, apolipoprotein (apo)-A1, apoB, hepatic enzymes, and blood cell count were assayed on the same day of venipuncture. PSA and fibrinolysis markers were measured within 3 days after venipuncture. For hormone measurements at baseline and at the end of the trial, plasma was separated

by centrifugation immediately after sampling and frozen at  $-20^{\circ}\text{C}$  until the end of the trial, then all of the samples were thawed and the analyses performed in a single batch. All of the analysts were blind to the treatment allocation. Insulin was determined by the immunoradiometric assay method (Medgenix Diagnostics, Fleurus, Belgique), leptin by a commercial radioimmunoassay (RIA) (Linco Research, St. Charles, MO), follicle-stimulating and luteinizing hormone by the Automated Chemiluminescence System 180 (Ciba Corning), and androgens and estradiol by RIA (7). The only missing datum was one 2-h plasma insulin measurement at 3 months in a subject treated by DHT.

The primary end points to assess insulin sensitivity were fasting plasma insulin-to-fasting plasma glucose ratio and homeostasis model assessment (HOMA) index. Plasma leptin, 2-h plasma glucose and insulin, and blood pressure were taken as secondary criteria. Treatment tolerance was assessed by interview, by prostatic examination, and by PSA, as well as by weight, electrocardiogram (ECG), lipid, hemoglobin, hematocrit, fibrinolysis markers, and hepatic enzyme variations.

A sample size of 36 subjects was needed to detect a difference of 5 mg/dl for the decrease of fasting plasma glucose, assuming  $\text{SD} = 5$  mg/dl, using a two-tailed Student's *t* test with  $\alpha = 0.05$  and  $\beta = 0.20$ . However, we could not reach that number, and the recruitment was closed after having included 18 subjects. To evaluate the treatment effect, the difference between the values at entry and at the end of the treatment period was calculated for each subject, and then the Kruskal-Wallis nonparametric test was used. When statistical significance ( $P \leq 0.05$ ) was reached for any overall three-group comparison, two-by-two comparisons were performed using the Bonferroni test to correct for multiple comparisons.

At baseline, the three treatment groups were similar with respect to age, BMI, waist-to-hip ratio (WHR), blood pressure, plasma glucose, lipids, insulin, leptin, androgens, and sex hormone-binding globulin, as well as hemoglobin, hematocrit, coagulation, and fibrinolysis parameters (data not shown). At the end of the trial, a significant difference was shown for the variation of fasting plasma insulin ( $P < 0.05$ ), fasting plasma insu-

Table 1—Baseline characteristics and variations in the three treatment groups (after minus before)

	Testosterone	DHT	Placebo	P
n	6	6	6	
Age (years)	52.8 ± 4.2	51.2 ± 3.9	55.4 ± 3.6	0.80
BMI (kg/m <sup>2</sup> )	29.9 ± 0.9	27.8 ± 0.9	28.0 ± 1.1	0.84
WHR	0.95 ± 0.02	0.96 ± 0.02	0.96 ± 0.03	0.99
Systolic blood pressure (mmHg)	152 ± 5	143 ± 7	126 ± 8	0.08
Diastolic blood pressure (mmHg)	93 ± 4	88 ± 2	80 ± 5	0.17
Fasting plasma glucose (mg/dl)	101 ± 5	97 ± 2	99 ± 4	0.97
Total cholesterol (mg/dl)	212 ± 14	228 ± 11	221 ± 14	0.70
HDL cholesterol (mg/dl)	45 ± 4	44 ± 4	42 ± 6	0.81
Triglycerides (mg/dl)	126 ± 20	142 ± 18	123 ± 18	0.64
Fasting plasma insulin (μU/ml)	14 ± 4	18 ± 4	13 ± 3	0.52
Leptin (ng/ml)	10.1 ± 4.5	6.4 ± 1.3	6.2 ± 1.5	0.81
Plasma total testosterone (ng/ml)	2.4 ± 0.1	2.9 ± 0.3	2.7 ± 0.3	0.20
Plasma bioavailable testosterone (ng/ml)	0.6 ± 0.1	0.8 ± 0.1	0.6 ± 0.1	0.06
Plasma SHBG (nmol/l)	16.5 ± 1.9	16.9 ± 2.6	21.0 ± 3.3	0.32
Δ Fasting plasma glucose (mg/dl)	4 ± 3	-1 ± 3	3 ± 4	0.42
Δ Fasting plasma insulin (μU/ml)	-0.8 ± 2.0	-6.2 ± 2.2	2.7 ± 1.6	0.02*
Δ Fasting plasma insulin/fasting plasma glucose	-0.23 ± 0.32	-1.09 ± 0.29	0.43 ± 0.35	0.003*
Δ HOMA index	-0.09 ± 0.53	-1.54 ± 0.69	0.73 ± 0.39	0.012*
Δ Leptin (ng/ml)	-1.2 ± 1.7	-1.8 ± 0.6	0.4 ± 0.4	0.05†
Δ Total cholesterol (mg/dl)	-7 ± 7	-4 ± 5	-12 ± 5	0.66
Δ HDL cholesterol (mg/dl)	-1 ± 2	-5 ± 1	1 ± 2	0.09
Δ Triglycerides (mg/dl)	6 ± 18	11 ± 12	19 ± 24	0.78
Δ Systolic blood pressure (mmHg)	4 ± 5	-3 ± 5	21 ± 7	0.052†
Δ Diastolic blood pressure (mmHg)	4 ± 5	5 ± 5	14 ± 3	0.22
Δ Weight (kg)	3.3 ± 1.1	1.4 ± 1.0	-0.3 ± 1.0	0.09

Data are means ± SEM. \* $P < 0.01$  for DHT vs. placebo; † $P < 0.05$  for DHT vs. placebo.

lin-to-fasting plasma glucose ratio ( $P < 0.01$ ), and HOMA index ( $P < 0.05$ ), which all decreased under androgens. The two-by-two comparisons showed a significant improvement only for DHT compared with placebo ( $P < 0.01$  for all of these indexes of insulin sensitivity). No significant differences were observed for 2-h plasma glucose and insulin among the three groups (data not shown), whereas plasma leptin significantly decreased under androgen treatment ( $P < 0.05$ ), mainly with DHT ( $P < 0.05$  for DHT vs. placebo). Systolic blood pressure increased in the placebo group ( $P = 0.052$ ) (Table 1).

The only serious event was the discovery of a prostatic nodular hyperplasia, benign at biopsy, in a subject treated by testosterone. A trend for an increase in weight was observed under androgen treatment ( $P = 0.09$ ), mainly with testosterone (Table 1), without any modification of waist circumference and WHR (data not shown). No change was observed on the ECG recordings. No significant difference was shown among the

three groups for lipids (Table 1), PSA, hepatic enzymes, coagulation, and fibrinolysis parameters, but hemoglobin and hematocrit increased under androgens ( $P < 0.05$  and  $P < 0.01$ , respectively), mainly with testosterone (data not shown).

This randomized, controlled, double-blind trial provides evidence that in healthy men, androgen treatment, particularly DHT, improves insulin sensitivity and decreases plasma leptin level without notable side effects. The three treatment groups were quite identical at baseline concerning glucose tolerance status. In the placebo group, one subject was diabetic according to 2-h plasma glucose (227 mg/dl, with fasting plasma glucose at 85 mg/dl), and none had impaired glucose tolerance (IGT) or impaired fasting glucose (IFG). In the DHT group, one subject had IGT, and none had diabetes or IFG. In the testosterone group, all of the subjects had normal glucose tolerance. The primary differences at baseline concerned bioavailable testosterone with a trend for a higher level in the DHT group, which should have blunted (not

increased) the response to DHT treatment and blood pressure, probably explaining the nearly significant improvement of systolic blood pressure under androgens by a regression to the mean phenomenon in the placebo group. On the contrary, the parallel decrease in fasting plasma insulin and leptin and the improvement in insulin sensitivity under androgens appear very consistent. Our study may appear limited because of the sample size (half of that planned), enjoining the use of conservative nonparametric tests, and causing the final statistical analysis to be equivalent to a planned intermediary analysis. Indeed, to have confirmed the a priori hypotheses in these conditions of weak statistical power emphasizes the effect of androgens, mainly DHT, to improve insulin sensitivity and to decrease leptin concentrations in healthy men with low PTT. Very few side effects were observed, including a tendency for weight increase and an increase in hemoglobin and hematocrit, although these were reversible a few months later (data not shown), thus indicating good patient

compliance to the allocated treatment, also confirmed by hormone measurements.

From the literature, we can speculate that the effect of androgens on insulin sensitivity could be caused by changes in body composition and fat mass distribution. Indeed, androgens are known to increase fat-free mass and muscle size and to decrease visceral fat mass (8) by inhibiting lipoprotein lipase activity, therefore inhibiting triglyceride uptake and accelerating triglyceride release from abdominal adipose tissue (9). In turn, a decrease in abdominal fat mass may induce an improvement in insulin sensitivity via a reduction in circulating free fatty acids (10). In our study, no significant variation of waist circumference was found under androgens, but this measurement was probably too imprecise to detect changes. In the only previous controlled clinical trial having compared testosterone, DHT, and placebo gel treatments, 31 abdominally obese subjects with a moderately low PTT level (mean 4.5 ng/ml) were treated during 9 months (4). In that study, the testosterone group had a significant decrease in visceral fat mass seen by computerized tomography, and a marked augmentation of glucose disposal rate was observed with euglycemic-hyperinsulinemic clamp, whereas plasma triglycerides and total cholesterol had decreased. Leptin was not measured. No significant improvement was shown with DHT treatment. This striking contrast with our study concerning the respective effects of testosterone and DHT could be explained by the higher PTT level at baseline and mostly by an undertreatment in the DHT group in the trial by Marin et al. (4). We used larger doses of DHT and adapted the doses of testosterone and DHT after 2 weeks, when necessary, according to the circulating androgen level, whereas in the trial by Marin et al. (4) no monitoring of sex hormones level was performed.

The decrease in plasma leptin concentration is also probably explained by the supposed reduction in adipose tissue mass (11), but the influence of androgens on leptin could also be mediated by a stimulation of the splanchnic  $\beta$ -adrenoceptors (12) or by a direct suppressive effect on *ob* gene expression (13). Nevertheless, our data clearly demonstrate the role of androgens to decrease leptin levels in healthy men, as previously suggested (5).

In conclusion, this clinical trial dem-

onstrates that androgens improve insulin sensitivity and decrease leptin levels in adult men. We recruited healthy subjects ranked in the lowest 10 percentiles of the PTT distribution from a large occupation-based population by systematically measuring PTT. Therefore, these data can most likely be extrapolated to healthy men in the first decile of the PTT distribution. The pathways through which androgens exert their inhibiting effects on insulin and leptin in humans deserve further fundamental research. In parallel, as low levels of testosterone are predictive of the development of insulin resistance and type 2 diabetes (14), and as type 2 diabetic patients are known to have a lower level of PTT than nondiabetic men (15), larger studies on androgen treatment in insulin-resistant nondiabetic subjects and in type 2 diabetic patients are necessary.

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## Lipid Lowering Does Not Improve Endothelial Function in Subjects With Poorly Controlled Diabetes

Cutaneous microangiopathy is suspected to play a role in the pathogenesis of diabetic foot ulcers (1). Because microcirculatory flow is regulated in part by the endothelium and prior studies of the coronary microcirculation showed significant improvement in endothelium-dependent vasodilatory responses with lipid-lowering therapy (2), we examined the effect of lipid lowering on endothelial function in cutaneous microcirculation in patients with type 2 diabetes.

Patients aged 21–80 years with diabetes and LDL cholesterol  $>3.4$  mmol/l were randomized in a double-blind fashion to treatment with either simvastatin 40 mg daily or placebo and followed for 3 months after randomization. All patients received dietary counseling with regard to lowering LDL, but no attempt was made to alter glycemic control. The study was approved by the Institutional Review Board of the Mount Sinai School of Medicine, and informed consent was obtained before enrollment.

Cutaneous microcirculatory flow from the same site of the dorsum of the foot was measured with the Periflux System PF3 (Perimed, Järfälla, Sweden) at every visit in all patients. The flow response to heating was recorded at a skin temperature of 32°C and then at 44°C (the skin temperature at which maximal flow is achieved) (3). Endothelium-dependent and -independent microcirculatory responses were recorded using acetylcholine (ACh) and sodium nitroprusside (SNP) iontophoresis, respectively (Peri-Iont Micropharmacology System PF380; Perimed). All flow measurements were performed with subjects in a fasting state. Normalized values of flow (the ratio of flow in response to ACh or SNP to the flow reaction to heating to 44°C) were used for comparisons between the groups. When appropriate, Mann-Whitney *U* and Wilcoxon tests were used for group comparisons.  $P < 0.05$  was considered significant.

A total of 18 diabetic patients were enrolled in the study. Five patients dropped out for logistical reasons, none because of adverse reactions. Of the 13 patients who completed the study, 7 were randomized to the simvastatin group (all women; 5 African-Americans and 2 Latinos) and 6 to the placebo group (5 women; 5 African-Americans and 1 Latino). The subjects were elderly ( $61 \pm 6$  vs.  $60 \pm 5$  years of age, simvastatin versus placebo, respectively), obese (BMI:  $33 \pm 5$  vs.  $32 \pm 5$  kg/m<sup>2</sup>), and had a relatively long duration of diabetes ( $11 \pm 8.5$  vs.  $6.7 \pm 3.8$  years). Diabetes was poorly controlled (HbA<sub>1c</sub>  $9.3 \pm 1.7$  vs.  $9.1 \pm 2.5\%$ ) and LDL cholesterol levels were elevated ( $4.6 \pm 0.5$  vs.  $4.2 \pm 0.6$  mmol/dl) in both groups. The two groups were not significantly different in any of the above parameters. Endothelium-dependent and -independent responses (ACh:  $0.7 \pm 0.6$  vs.  $0.8 \pm 0.3$ ; SNP:  $1.6 \pm 1.0$  vs.  $1.5 \pm 1.0$ ) were also similar at baseline. LDL cholesterol was significantly reduced at 3 months in the simvastatin group (from  $4.6 \pm 0.5$  to  $2.8 \pm 0.6$  mmol/dl,  $P < 0.01$ ) but not in the placebo group (from  $4.2 \pm 0.6$  to  $3.8 \pm 0.6$  mmol/dl,  $P = \text{NS}$ ). There was no significant change in HbA<sub>1c</sub> over the course of the study. Endothelium-dependent vasodilatation remained unchanged in both the simvastatin and the placebo groups ( $\Delta\text{ACh}$ :  $-0.1 \pm 1$  vs.  $0.3 \pm 1.1$ ,  $P = \text{NS}$ ;  $\Delta\text{SNP}$ :  $-0.6 \pm 1.4$  vs.  $0.2 \pm 1.4$ ,  $P = \text{NS}$ ).

The main result of this study is the lack of beneficial effect of lipid lowering on skin microcirculation vasomotion in this population of poorly controlled diabetic patients. Neither endothelium-dependent nor -independent responses were significantly improved in the treated group, although total and LDL cholesterol were significantly lowered by simvastatin. A similar lack of improvement in endothelial function in a large conduit artery (brachial artery) was recently reported in type 2 diabetic patients treated with simvastatin (4). Our results extend this finding to the microcirculation. This negative result may be explained by several factors. First, a longer follow-up may be necessary to demonstrate significant improvement in cutaneous microcirculation in the population of patients with a long duration of diabetes. Second, glycemic control may be needed to achieve beneficial effects of LDL lowering on endothelial function. This hypothesis is further supported by

the recent finding that glycated LDL from diabetic patients reduces endothelial cell nitric oxide synthesis and bioactivity (5). Therefore, in our study, we speculate that glycated LDL may have interfered with endothelium-dependent vasorelaxation in both groups. Finally, it could not be excluded that the long duration of diabetes may have induced diabetic neuropathy, which may affect flow response to ACh (6). However, this possibility is less likely because we systematically excluded patients with neuropathy on physical examination.

In summary, LDL lowering does not appear to improve endothelial function in the microcirculation without adequate glycemic control. Further studies are needed to assess the benefit of optimal control of diabetes in conjunction with lipid lowering on endothelium-dependent microcirculation vasomotion.

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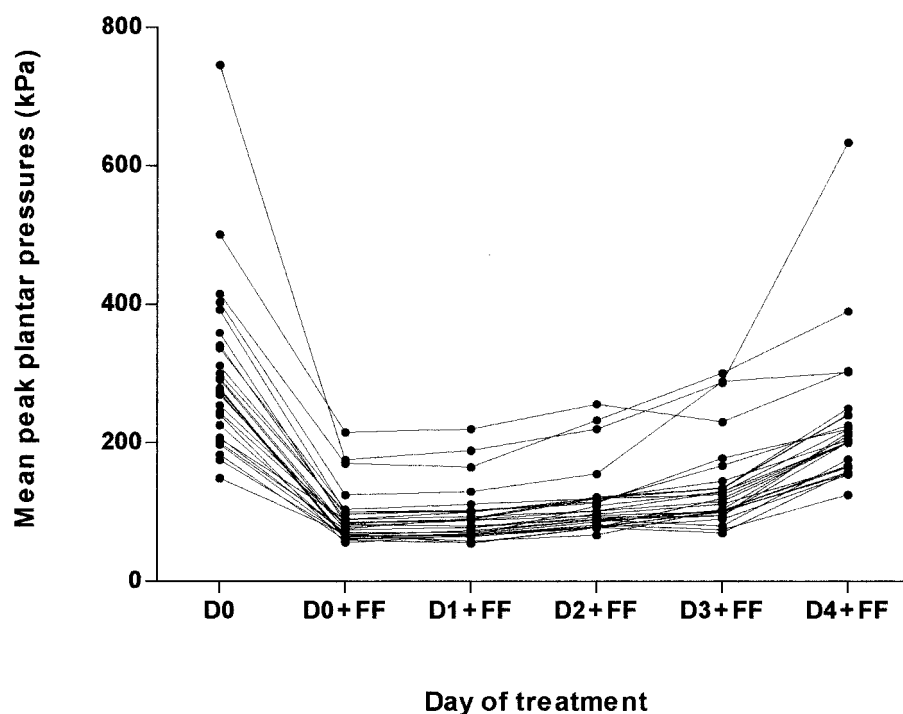
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## Effects of Felted Foam on Plantar Pressures in the Treatment of Neuropathic Diabetic Foot Ulcers

It is generally accepted that (besides infection control and revascularization, when necessary) pressure relief is the most important measure in the treatment of diabetic foot ulcers. The use of felted foam dressings is a promising but not yet well-standardized technique for the treatment of neuropathic diabetic foot ulcers and may have some advantage over total contact casting (1–4). We aimed to assess the effects of felted foam on plantar pressure reduction during the therapy of neuropathic foot ulcers and to define the optimal time course for renewal of the felted foam according to the plantar pressure. Using felted foam dressings, plantar pressure reduction and wound healing was determined in 9 type 1 and 19 type 2 diabetic patients (15 men and 13 women, aged  $61.0 \pm 13.6$  years) with neuropathic foot ulcers up to a Wagner grade 2. Physical examination included the inspection of the foot and the palpation of the peripheral pulses. Peripheral diabetic neuropathy was evaluated by measuring the vibration perception threshold with the calibrated Rydell-Seiffer tuning fork. Pa-



**Figure 1**—Mean peak plantar pressures of 28 diabetic patients with neuropathic foot ulcers up to a Wagner grade 2. D, day; FF, application of felted foam.

tients with neuroischemic or ischemic diabetic foot ulcers were excluded from the study.

The felted foam (i.e., a combination of 0.635-cm thick rubber foam with a 0.158-cm layer of felt adhered, fixed by rubber glue) was measured exactly to fit the plantar aspect of the foot. Using a scalpel, an aperture was cut from the felted foam at the exact location of the ulcer, allowing clear visualization of the ulcer. Gauze was then wrapped around the foot and the felted foam pad to secure the pad. The wound was covered with a saline-soaked sponge, which was cut according to the size of the ulcer and changed every day. The felted foam was kept dry at all times. A compress was placed over the wet sponge and fixed with Peha-haft. The felted foam dressing was exclusively used for plantar ulcerations. Foot pressure was measured using the FastScan system, as described elsewhere (5,6). Recordings of the plantar pressures were first done without any dressings and then with the attached felted foam dressing every day to day 4. The plantar pressures were measured by selecting the area of interest under the foot, within an area of  $25 \times 25$  mm<sup>2</sup> in the center of the ulceration. A

mean of all pressures measured in each walk (three steps per walk and two walks per test) was calculated for each patient. Differences between the plantar pressures at each day were compared by analysis of variance;  $P < 0.05$  was considered significant.

The mean ulcer area in the patients studied was  $159.9 \pm 102.6$  mm<sup>2</sup>. By the application of the felted foam dressing, the mean peak plantar pressures at the ulceration site was significantly reduced, from  $297.3 \pm 120.0$  kPa before to  $90.3 \pm 38.2$  kPa immediately after the application ( $P < 0.0001$ ). In the following period, over at least 4 days with the mounted felted foam dressing, the plantar load in the area of interest significantly increased, from  $93.6 \pm 39.6$  kPa the day after the application to  $222.6 \pm 97.8$  kPa at day 4 ( $P < 0.0001$ , Fig. 1). On days 2 and 3, the plantar pressures at the ulceration site varied, from  $113.8 \pm 47.6$  to  $137.5 \pm 63.9$  kPa, without significant day-to-day changes. However, from day 3 to day 4 there was a clear-cut increase of the plantar pressure in the area of interest, from  $137.5 \pm 63.9$  to  $222.6 \pm 97.8$  kPa ( $P = 0.0001$ ).

Because the relief of the plantar load at the ulceration site is one of the most

important factors in the outcome of neuropathic foot ulcerations, the application of the felted foam appears to be useful to reduce the peak plantar pressures at the site of ulceration. We have shown that the pressure relief from attaching the felted foam dressing at the ulceration site lasts up to 3 days after its application. Taking into account the distinct increase in plantar pressure on the fourth day, we recommend changing the felted foam each 3rd to 4th day. Interestingly, we did not observe the development of callosity at the ulceration site, which underlines the efficacy of the felted foam technique for pressure relief. In contrast to other methods for pressure relief, such as total contact cast, felted foam also enables daily dressing changes and can be used in patients with smaller infections (7,8).

We conclude that in diabetic patients with neuropathic foot ulcerations, the felted foam technique effectively reduces the pressure load at the ulceration site. This pressure relief persists for 3 days, and we therefore recommend renewing the felted foam after each 3–4 days of treatment.

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## Diagnosing Osteomyelitis in Patients With Diabetic Neuropathic Osteoarthropathy

Approximately 15% of diabetic people will develop foot ulcers during their lifetime, and early detection of osteomyelitis is crucial to the management of diabetic foot ulcers (1). Differentiating osteomyelitis from neuropathic osteoarthropathy is clinically difficult, as the symptoms and signs are nonspecific. These patients all present with hot and erythematous feet. At presentation, there is often no change on plain radiographs (2). Many of the imaging findings are also similar, especially in rapidly progressing, noninfected neuro-osteoarthropathy. The most reliable method of establishing infection is to analyze microbiological samples of the lesion. However, this is not always practical and may lead to seeding of the infection or damage to the area biopsied. Magnetic resonance imaging (MRI) is a useful method of tissue localization and is currently the most sensitive method to detect osteomyelitis (3).

Technetium (Tc)-99 m Infecton consists of ciprofloxacin linked to Tc99 m. The antibiotic is taken up and bound specifically by living bacteria, where it inac-

tivates DNA gyrase. As the antibiotic is chelated with 99 Tc, the area of bacterial infection should be identifiable during imaging (4).

A total of 16 diabetic patients with a hot swollen foot were studied prospectively using plain radiographs, MRI, Gallium-67, and Tc99 m Infecton. The MRI and plain radiographs were reported independently, blinded from the radionuclide imaging, and vice versa. The definitive diagnosis was established by findings at surgery, microbiological results, or definitive imaging (e.g., plain radiograph to detect fractures).

In our prospective study, four (25%) patients had osteomyelitis, three (19%) had neuropathic fractures, and nine (56%) had soft tissue swelling. MRI accurately diagnosed all of the four cases with osteomyelitis. Tc99 m Infecton was only able to localize infection to bone in one of the four cases with osteomyelitis. In the rest of the cases, Infecton could not differentiate whether infection was confined to soft tissue or bone. Plain radiographs were able to diagnose two of the four cases with osteomyelitis. MRI correctly diagnosed fractures in all of the three patients who had evidence of fractures on plain radiograph. Infecton and Gallium scans reported bone or soft tissue as infected in all of the three cases. Therefore, the nuclear medicine scans can falsely indicate infection or inflammation in the presence of fractures.

Radionuclide imaging is not reliable to differentiate among infection, inflammation around fractures, or Charcot joint, even when infection is correctly identified. The limited spatial resolution in the forefoot does not allow accurate discrimination between soft tissue infection and osteomyelitis. Plain radiograph was essential in the initial work-up, as hot spots on Infecton scans and Gallium 67 scans can indicate fracture rather than infection. MRI is the imaging of choice to distinguish osteomyelitis from other conditions, such as cellulitis and neuropathic osteoarthropathy in diabetic patients with a hot swollen foot. Infecton scans are helpful when used in conjunction with MRI to localize an infected area before surgery but cannot be used independently as a diagnostic tool in the assessment of a hot swollen diabetic foot.

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## Extreme Subcutaneous Insulin Resistance Successfully Treated by an Implantable Pump

Extreme subcutaneous insulin resistance is a very rare syndrome characterized by severe resistance to subcutaneous insulin together with normal or near normal intravenous insulin sensitivity. The pathophysiology is unknown. An increased insulin-degrading activity has been reported in the subcutaneous adipose tissue fraction (1). The proposed treatments are disappointing. We report such a case that was successfully treated by intraperitoneal insulin.

A 36-year-old male patient was ad-

mitted for acute pancreatitis of unknown etiology associated with diabetes. His mother had type 2 diabetes. The patient's BMI was 31 kg/m<sup>2</sup>. After the onset of acute pancreatitis, the patient discontinued his antidiabetic treatment. Five years later, he was admitted in a hyperosmolar state (fasting blood glucose of 1,000 mg/dl) without ketoacidosis. His BMI was 28 kg/m<sup>2</sup>. Subcutaneous insulin was resumed, using multi-injections, followed by subcutaneous treatment with an insulin pump. Despite a dramatic increase in the insulin dose (up to 1,800 units/day), metabolic control was bad (HbA<sub>1c</sub> 11%; high-performance liquid chromatography <6% [normal]). Intravenous insulin infusion was then attempted through an implanted venous access port. Continuous insulin was given with an external insulin pump through a Port-A-Cath (Braun, Boulogne Billancourt, France), whereby the catheter was connected to a subcutaneous reservoir. After initial success, this treatment was withdrawn because the metabolic state was deteriorated in a septic context (catheter infection). Continuous subcutaneous infusion was resumed with freeze-dried insulin (endopancrine; Organon Eragny/Epte, France), up to 4,000 units/day, and then with lispro insulin (Lilly), up to 420 units/day. Then, a protease inhibitor, aprotinin (Iniprol 8 million units/day for 4 days; Laboratoire Choay, Gentilly, France) was mixed with insulin, but >1,500 units/day insulin was needed to achieve euglycemia. Corticosteroid therapy (dexamethasone [Soludecadron; MSD Chibret, Clermond-Ferrand, France] 40 mg for 3 days, then prednisolone [Solupred, Houde, Paris-Defense, France] 60 mg/day for 3 days) and intravenous immunoglobulin therapy were also ineffective. For 8 years, blood glucose remained very high, between 300 and 400 mg/dl and, consequently, diabetic complications appeared: retinopathy (macular edema), painful neuropathy with neuropathic ulcer, nephropathy, and sepsis. Then, an intraperitoneal insulin infusion with an implantable pump (MIP 2001; Minimed, Sylman, CA) was started. After implantation, the metabolic state dramatically improved; weight increased from 65 to 70 kg (BMI from 21.2 to 22.8 kg/m<sup>2</sup>), insulin requirement decreased to 40 units/day, and HbA<sub>1c</sub> dropped from 10 to 6%. Sixteen months later, the good metabolic state was maintained.

Abdominal tomodensitometry was normal, and there was no alteration of exocrine pancreatic function. There were no islet cell antibodies, GAD autoantibodies, or anti-insulin and anti-insulin-receptor antibodies. Insulin secretion was preserved (basal C-peptide before glucagon: 5 ng/ml; after glucagon: 10 ng/ml). Levels of glucagon, vasoactive intestinal peptide, and somatostatin were normal. The euglycemic clamp study showed a decrease in both sensitivity (ED<sub>50</sub> = 1.13 vs. 0.62 mU · kg<sup>-1</sup> · min<sup>-1</sup> in control subjects) and responsiveness (mean maximal glucose disposal: 10.2 mg · kg<sup>-1</sup> · min<sup>-1</sup>, or 73% of the control subjects) to intravenous insulin.

Insulin binding was normal on the patient's erythrocytes. Insulin receptor number and phosphorylation, studied on skin-cultured fibroblasts, were not altered. We did not find any coding mutation in the insulin receptor or the lamin A/C genes (2). Finally, plasma insulin measurements showed subcutaneous malabsorption of insulin; plasma free insulin was 26 mU/l when 3,600 units/day insulin was subcutaneously infused and 7 mU/l when 30 units/day was intraperitoneally infused.

We have described a case of severe subcutaneous insulin resistance that was treated by intraperitoneal insulin therapy. Such cases have already been described. For some of them, an insulin-degrading activity has been found in muscle or adipose tissue (1,3). Therefore, some patients were successfully treated with a protease inhibitor, aprotinin (1,3–5). Other patients did not respond to this treatment (6). Intramuscular insulin therapy was successfully attempted in some cases (7,8). All of these treatments were ineffective in our patient. Intraperitoneal insulin therapy, through a subcutaneous access device, was proposed in some cases (9–11) with good results. We tried the same route of insulin therapy using an implantable pump (MIP 2001). As a result, glycemic control dramatically improved with good efficiency for 1 year.

Therefore, extreme subcutaneous insulin resistance is a new indication of implantable pump use. The pathophysiology of this syndrome remains unexplained.

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## Association of Rapid-Onset Type 1 Diabetes and Clinical Acute Pancreatitis Positive for Autoantibodies to the Exocrine Pancreas

A 24-year-old woman presented with epigastralgia on day 0. About 2 weeks before day 0, she had a low-grade fever for a few days. On day 3, she consulted a clinic, where hyperamylasemia (2.8 multiples of the upper normal limit) and swelling of the pancreas on ultrasonography were detected. The subject's fasting plasma glucose (FPG) level was 85 mg/dl. Her serum insulin and C-peptide levels, as measured later with the frozen plasma, were 20.5  $\mu$ U/ml and 7.7 ng/ml, respectively. On day 5, the subject's serum amylase was 4.58 multiples of the upper normal limit. On day 6, her FPG level was elevated to 370 mg/dl and her urinary ketone showed +++. After treatment with intravenous administration of glucose, insulin, and ulinastatin (serine protease inhibitor) at the clinic, she was referred and admitted to Ohtsu Red Cross Hospital. The subject had no history of diabetes, pancreatitis, or alcohol consumption. Her BMI was 17.2 kg/m<sup>2</sup>, her serum amylase was 3.22 multiples of the upper normal limit, and her serum elastase 1 was 1,400 ng/dl (range 100–400). The subject's plasma glucose level was 329 mg/dl, and her HbA<sub>1c</sub> was 4.9% (3.0–6.0). The serum C-peptide level was 0.2 ng/ml, the urinary

C-peptide excretion rate was 4  $\mu$ g/day, and the increment of serum C-peptide in response to intravenous administration of 1 mg of glucagon was not detectable, indicating severe impairment of insulin secretion. Islet cell antibody, anti-GAD antibody, and anti-IA-2 (tyrosine phosphatase-like protein) antibody were negative. Dynamic computed tomography showed swelling of the pancreas, with enhancement on the early phase. Magnetic resonance cholangiography and pancreatography examinations were normal. Virus antibodies showing acute infection with cytomegalovirus, Epstein-Barr virus, rubella virus, mumps virus, herpes simplex 1 and 2, herpes zoster virus, coxsackie B viruses, and rotavirus were all negative. The patient possessed HLA DQA1\*0102 and DQB1\*0602, the HLA types resistant to type 1 diabetes in Japanese individuals (1). Other HLA types in this case were A24, A33, B7, B44, Cw7, DRB1\* 0101 and 1501, DQA1\* 0101, and DQB1\* 0501. The bentiromide test value on day 28 was 63.7% (73.1–90.1), showing mild exocrine dysfunction. Even after acute pancreatitis was remedied with ulinastatin, the subject remained insulin-dependent. In this case, it is unlikely that diabetes is secondary to classical pancreatitis, considering the severity of insulin deficiency with only mild exocrine dysfunction. Rather, this patient was diagnosed as an association of type 1B (idiopathic) diabetes and clinical acute pancreatitis. This association suggests a common etiopathogenesis in both exocrine and endocrine dysfunction, although the mechanism remains to be elucidated.

Simultaneous involvement of exocrine and endocrine pancreas has been reported in type 1 diabetic patients (2,3). Recently, a novel subtype of type 1 diabetes, characterized by a rapid onset, an absence of diabetes-related antibodies, and hyperamylasemia with lymphocytic infiltration in the exocrine pancreas, was postulated to be "nonautoimmune" fulminant type 1 diabetes (4). Our case subject showed characteristics, i.e., hyperglycemia with low HbA<sub>1c</sub>, an absence of autoantibodies to the endocrine pancreas, and hyperamylasemia, that seem compatible with this entity. The relatively high levels of serum insulin and C-peptide for normoglycemia on day 3 appear to reflect the ongoing destruction of  $\beta$ -cells.

Serum levels of autoantibodies against human carbonic anhydrase II



(ACA) and autoantibodies against lactoferrin (ALF), which are distributed in the pancreatic duct cells and the acinar cells, respectively, were measured using the solid-phase ELISA method, as previously described (5). ACA and ALF were positive in the present case subject.

It was reported that ACA and ALF were detected in patients with autoimmune pancreatitis, whereas they were not detected in any of the patients with alcoholic or gall stone–related pancreatitis (5). Although our present case was uncharacteristic of autoimmune chronic pancreatitis after completion of imaging studies and the clinical course (6,7), the presence of these antibodies suggests the involvement of autoimmunity against the exocrine pancreas.

We have recently demonstrated the presence of ACA and ALF in type 1 diabetic patients and proposed the concept of autoimmune exocrinopathy and endocrinopathy of the pancreas (8).

In conclusion, we reported the first case of an association of rapid-onset type 1 diabetes and clinical acute pancreatitis that tested positive for autoantibodies to the exocrine pancreas. Although known antibodies against the endocrine pancreas were not detected, autoimmunity, at least against the exocrine pancreas, was suggested.

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## Case of Pseudohypoglycemia

The patient is a 44-year-old white woman with a history of myasthenia gravis, hypothyroidism, epilepsy, and Raynaud's phenomenon. In May 2000, while hospitalized for gastroenteritis, a fingerstick glucose reading reported as "low." Subsequent outpatient testing showed a normal random venous glucose level with concurrent normal C-peptide and insulin levels. The patient obtained a

One Touch glucose meter and continued to monitor her glucose frequently for the next few months. The glucose readings were consistently 30–40 mg/dl. She often reported symptoms of lightheadedness, fatigue, and sweating, but in retrospect, the relationship between these symptoms and the glucose readings was inconsistent.

A second endocrinologist repeated the glucose and C-peptide tests, and these were again normal. A urine screen for sulfonyleurea agents was negative.

The patient was then referred for a prolonged fast. On greeting the patient, her hands were white and cold. Over the subsequent 2 h, using a Freestyle meter (FM) and a Precision QID meter (PM), glucose measurements were obtained from the patient's fingertips and forearms and by venipuncture.

At 9:00 A.M., glucose levels from the fingertips were 53 and 56 (FM) and 49 and 38 (PM) mg/dl, and the forearm level was 83 mg/dl (FM). At 10:00 A.M., glucose levels from the fingertips were 50 (FM) and 48 (PM) mg/dl, and the forearm level was 73 (FM) mg/dl. At 11:00 A.M., glucose levels from the fingertips were 42 (FM) and 53 (PM) mg/dl, and the forearm level was 78 (FM) mg/dl. Also, at 11:00 A.M., a venous blood sample was drawn. This sample was used for a glucose check on each meter and was sent to the clinical laboratory (LAB). The 11:00 A.M. glucose levels from the venous sample were 88 (FM), 93 (PM), and 86 (LAB) mg/dl.

Fingertip capillary glucose levels were consistently lower than simultaneous forearm capillary glucose levels and/or venous glucose levels. We believe the patient's false low fingertip glucose readings were secondary to the circulatory change from Raynaud's phenomenon. Similar pseudohypoglycemia has been reported in patients with altered circulation from shock (1).

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 COMMENTS AND  
 RESPONSES
 

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## Homocysteinemia in Patients With Type 1 Diabetes in Relation to Renal Function

In the study by Pavia et al. (1) and the subsequent commentary by Cotellessa et al. (2), the problem of homocysteine levels in patients with type 1 diabetes was raised. The authors found no differences in plasma total homocysteine (tHcy) concentration between diabetic children and/or adolescents and age-matched control subjects. They also did not observe any association between tHcy levels and either duration or metabolic control of the disease or its complications. The 91 patients analyzed had a duration of type 1 diabetes ranging from 1 to 15 years, and in ~50% of them, the duration of the disease was >5 years. Patients did not have microalbuminuria and had serum creatinine within the normal range.

Pavia et al. (1) pointed out that hyperhomocysteinemia is already present in the early stages of renal failure (3). However, no change in renal function, measured as the serum creatinine concentration, was found in their patients.

In our opinion, there are two points that should be emphasized in this context. First, serum creatinine concentration is not an accurate measure of glomerular filtration rate (GFR), especially in the range of 50–140% of normal. Therefore, mildly disturbed renal function is underestimated when assessed only on the basis of serum creatinine concentration. Although not perfect, the Cockcroft-Gault formula should at least be used to measure creatinine clearance as a surrogate of GFR (4). The second and probably more important point is that renal abnormalities may already be present at very early stages of type 1 diabetes. In-

deed, at the onset of the disease, a state of hypertrophy and hyperfunction (with hyperfiltration) of the kidneys is often observed. GFR may be as much as 40% above normal. The next stage is the appearance of microalbuminuria, a phenomenon that is thought to be an early marker of diabetic nephropathy. This is of special interest because GFR is the strongest independent predictor of plasma tHcy concentration. The study performed by Wollesen et al. (5) clearly showed that in diabetic patients with a normal serum creatinine concentration (<115  $\mu\text{mol/l}$ ) and GFRs in the lower range, the concentration of tHcy was higher than in subjects who had GFRs in the upper range. Hyperfiltration or GFRs above the normal values for their age and sex were found in >80% of patients. The authors found a strong inverse linear correlation between plasma tHcy and GFR in the range of 47–165  $\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ . In this study, GFR determined plasma levels of tHcy independently of age, serum folic acid and B-group vitamin concentrations, serum creatinine concentration, and urine-albumin excretion rate.

Thus, because no patients suffered from overt nephropathy in the population of patients studied by Pavia et al. (1), a relative hyperfiltration is the most plausible cause of their results, which showed low tHcy concentrations in this group of diabetic patients. Although they found a correlation between tHcy and creatinine concentration, measuring only creatinine concentration is not sufficient for assessing GFR (with special regard to hyperfiltration) in this specific population. We agree that hyperhomocysteinemia is not the cause of vascular complications in diabetic patients, at least in those without overt nephropathy.

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## Glitazones, Glycemia, and Global Health Status

The recent study by Raskin et al. (1) failed to emphasize three important points. In the study (1), the mean weight gain was 4.0 and 5.3 kg for the study groups given rosiglitazone 4 and 8 mg/day, respectively. No range of weight change or standard deviation was given, making it impossible to appreciate the maximum and minimum weight changes of this 26-week trial. It would be interesting to see if any factors predicted weight change for combination therapy. Furthermore, the authors failed to comment on the adverse health consequences of further weight gain in these obese study patients. Despite improved glycemia and other potential cardiovascular benefits of thiazolidinediones (2), at some point, weight gain, which is common, significant, and seen with all agents in this drug

class when given with insulin, will probably outweigh any putative positive benefits. Also, because these drugs cause differentiation of preadipocytes into adipocytes (3), it is possible that weight gain may be progressive with time in some patients. We do not consider weight increases of  $\geq 10$  kg unusual when thiazolidinediones with insulin are being used; in two of our patients, we saw weight increases of  $>40$  kg. Intensive dietary intervention may be necessary to preclude this development in patients on insulin treatment concomitantly with a thiazolidinedione.

Edema was noted in 17 of 103 patients on insulin plus 8 mg rosiglitazone. Although edema is not considered to be a serious adverse event, it can be troubling for some patients. Expanded extracellular water is commonly seen with thiazolidinediones. Although echocardiographic studies in humans have failed to detect deleterious effects in the short term, the adverse cardiac effects seen in animal models (4) should give physicians

some pause in their enthusiasm for these drugs. Perhaps exercise testing would be more confirmatory of the cardiovascular safety of these agents in the short term.

Finally, despite a therapeutic effect, the mean achieved HbA<sub>1c</sub> (8.5 and 7.9% for 4 and 8 mg/day rosiglitazone, respectively) is still much greater than the glycemic goals mandated by the American Diabetes Association (5). Although the combination of a thiazolidinedione and insulin is useful for the control of glycemia, it will nonetheless fail to achieve adequate glycemic control in many patients.

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