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The β-cell, autoimmunity, and insulin resistance

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This is the second of three reports on the 35th Annual Meeting of the European Association for the Study of Diabetes (EASD) held in Brussels in September 1999. It covers topics related to the β-cell, the role of antibodies in type 1 diabetes, pancreas and islet transplantation, obesity, and insulin resistance.

The β-Cell

Cosgrove et al. (abstract 231) studied intact islets and single cells isolated from a diet-treated patient with type 2 diabetes who suffered a fatal myocardial infarction (MI). Only 3 of 11 islet cells possessed functional ATP-sensitive K^+ (K_{ATP}) channels, compared with all recordings from 164 control human β-cells. In those cells that possessed K_{ATP} channels, there were no effects of intracellular nucleotides or tolbutamide on channel activity. Only 5 of 10 cells possessed functional voltage-dependent Ca^{2+} channels, compared with all recordings from 67 control cells (n = 67), and the currents in the β-cells in the patient with diabetes were approximately half those in control cells. Thus, type 2 diabetes may be associated with loss of ion channel function and disruption of cytosolic Ca^{2+} signaling events.

Rustenbeck et al. (abstract 480) studied the effect of prolonged stimulation of pancreatic islets by inhibitors of K_{ATP} channels in decreasing in vitro islet insulin secretory responsiveness, showing that K_{ATP} channels remain responsive but that the ability to increase intracellular calcium levels decreases. Similarly, McClenaghan et al. (abstract 479) reported that prolonged exposure to tolbutamide downregulates both K_{ATP}-channel–dependent and –independent insulin-secretory actions of this agent. In a related study, Barnes et al. (abstract 482) showed that the thiazide diuretic hydrochlorothiazide, which can impair glucose tolerance, is an agonist of K_{ATP} channels in β-cells. It inhibits glucose- and tolbutamide-stimulated insulin release, while activating K_{ATP} channels and reversing ATP-induced channel inhibition, again showing that prolonged channel activation acts distal to the channel to impair insulin secretion.

In another report addressing calcium signaling in the islets, Squires et al. (abstract 494) used reverse transcription–polymerase chain reaction to show expression of the parathyroid calcium receptor on α- and β-cells. Incubation with calcium induced a transient increase in intracellular calcium 59% of that seen with tolbutamide, suggesting that the calcium receptor affects insulin secretion independent of sustained change in intracellular calcium levels. Finally, addressing another potential regulatory mechanism, Josefsen et al. (abstract 245) reported that naloxone increased glucose-induced insulin release by rat islets in vitro approximately 2-fold after stimulation at 4.5 and 11 mmol/l glucose, suggesting a tonic inhibitory effect of endogenous opioid peptides. Incubation with dynorphin 1-17, dynorphin 1-13, or Met- or Leu-enkephalin did not have a suppressive effect.

Wily Gepts Memorial Lecture

Daniel Pipeleers, Brussels, Belgium, discussed β-cells in diabetes in a memorial lecture honoring Wily Gepts, who established the pathology of the pancreas in type 1 diabetes more than 3 decades ago. One finding of Pipeleers's work is the presence of new islets developing adjacent to duct cells in patients with onset of diabetes in early childhood. Duct cells are required for expression of islet NO synthase. NO acts as an inflammatory mediator. Duct cells may also be involved in cytokine-mediated HLA expression, suggesting that they may act as antigen-presenting cells.

Pipeleers hypothesizes that some of the heterogeneity of islet loss among different lobes of the pancreas in a given patient may be related to differences in duct cell factors. In patients with older age of onset, there is more evidence of fibrosis, suggesting either that there were inflammatory lesions earlier or that additional processes are involved in islet loss. These patients often have hyperplastic islets, suggesting that "the β-cells should not be considered as passive victims." Instead, they play a role in antigen presentation and modulate the immune system response, and they may also have adaptations aimed at preserving islet function.

Another area of Pipeleers's work has been to assess the mediators of islet cytotoxicity and whether the mechanism of cell death is necrosis or apoptosis. In an in vitro model, oxidant factors cause necrosis and low glucose causes both necrosis and apoptosis, while levels over ~10 mmol/l are protective. This paradoxical finding suggests that the inability to respond to glucose underlies β-cell loss, primarily in Pipeleers's work involving apoptosis. Interleukin-1, interferon-γ, and tumor necrosis factor-α decrease levels of the islet glucose transporter GLUT2, while increasing superoxide dismutase and NO synthase, and there is evidence that the β-cell phenotype can be transformed to one less able to respond to

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Abbreviations: CHD, coronary heart disease; CHF, congestive heart failure; CT, computed tomography; CV, coefficient of variation; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; DPP-IV, dipeptidyl peptidase IV; EASD, European Association for the Study of Diabetes; FFA, free fatty acid; ICA, islet cell antibody; IGT, impaired glucose tolerance; JDF U, Juvenile Diabetes Foundation unit; K_{ATP}, APT-sensitive K^+; MI, myocardial infarction; MRI, magnetic resonance imaging; PC-1, plasma cell membrane glycoprotein-1; QOL, quality of life; TNF, tumor necrosis factor; UAE, urinary albumin excretion; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

glucose and more prone to apoptosis, perhaps an important process in the development of type 1 diabetes.

Discussing the β-cell in type 2 diabetes, Pipeleers pointed out that chronic stimulation in the insulin-resistant setting, perhaps mediated by high glucose and free fatty acid levels, is associated with decreasing β-cell function. This may also be associated with a change in β-cell phenotype to one showing decreased glucose uptake and increased susceptibility to apoptosis. As in type 1 diabetes, there is heterogeneity of distribution of abnormal β-cells in the pancreas of the patient with type 2 diabetes, which can be shown by the distribution of amyloid deposits. Amyloid may require a high fat intake for expression, with a relevant pathological finding being the presence of lipid-storage lysozymal vesicles in β-cells in humans, increasing with age and taking up circulating LDL and VLDL particles.

Two studies presented at the meeting addressed additional abnormalities of the pancreas in type 2 diabetes. Rathmann et al. (abstract 297) found fecal elastase-1 <100 μg/g stool, which suggests pancreatic exocrine insufficiency, in 11.8% of 526 patients with type 2 diabetes and 3.8% of 526 nondiabetic age- and sex-matched control subjects. The presence was associated with a higher HbA_{1c} level, but not with diabetes duration or peripheral neuropathy. In an examination of 122 patients at the time of diagnosis of type 2 diabetes, Katsaros et al. (abstract 298) found levels of the tumor marker CA-19-9 >900 U/ml in 5 patients, who were found to have pancreatic cancer, suggesting a potential screening modality. An additional 5 patients had levels between 80 and 100, with negative computed tomography scans.

Autoimmunity in Type 1 Diabetes

Decochez et al. (abstract 222) followed 172 type 1 diabetic patients <40 years of age for 2 years. C-peptide values decreased to <0.15 μg/l in 88% of patients diagnosed before age 7 years, in 45% diagnosed between ages 7 and 15 years, and in 29% diagnosed after age 15 years. In the latter group, 25 of 70 patients (36%) with islet cell antibody (ICA) titers >12 JDF U developed low C-peptide levels, compared with 5 of 35 (14%) with lower ICA levels. With diabetes onset before age 15 years, a rapid decline in C-peptide was observed in 34 of 49 patients with ICA >50 JDF U at diagnosis versus 3 of 18 with lower ICA titers. Glutamate decarboxylase (GADA) and IA-2 protein antibodies did not predict the fall in C-peptide level. The authors suggested that β-cell–preserving strategies should primarily be tested in the high-ICA subgroup and that this assay measures clinically relevant antibodies that are not detected in the molecular antibody assays using recombinant human islet cell autoantigens as substrate.

Petersen et al. (abstract 22) assessed treatment of female NOD mice with daily subcutaneous insulin injections of 7.2 U/kg, 0.3 U/kg (similar to what is currently being used in human trials), or buffer from age 12 weeks. At age 47 weeks, 8 of 21 treated with the high insulin dose, but 20 of 23 and 18 of 23 treated with the low insulin dose or with buffer developed diabetes, suggesting that the dosage level may be crucial for prevention of type 1 diabetes. Chaillous et al. (abstract 221) randomized 163 patients aged 7 to 40 years who did not have severe ketoacidosis at onset of type 1 diabetes to 0, 2.5 or 7.5 mg oral in addition to subcutaneous insulin treatment. Subcutaneous insulin requirements, HbA_{1c}, and fasting, glucagon-, and meal-stimulated C-peptide were not significantly affected by oral insulin treatment at 6 or 12 months.

In a similar study, Pitocco et al. (abstract 336) treated 78 patients with type 1 diabetes of <4 weeks duration with oral insulin (5 mg daily) or placebo, showing no increase in C-peptide or improvement in glycemic control during the first year after diagnosis. Vidal et al. (abstract 296) treated 34 newly diagnosed patients with type 1 diabetes with intensive insulin with or without oral nicotinamide (700 mg 3 times/day) plus a 72-h intravenous insulin treatment, showing higher maximal stimulated C-peptide and therefore suggesting an effect in preserving β-cell function.

Osterbye et al. (abstract 110) reported that sulfatide (3-sulfogalactosylceramide), which is present in the secretory granules and at the surface of β-cells, binds to the A-chain of insulin. It stabilizes insulin in the crystalline form at pH 5.5, similar to what is seen in β-cell granules, and hastens the dissociation of insulin hexamers and dimers to monomers at pH 7.0. Buschard et al. (abstract 111) from the same group reported that incubation of rat β-cells with serum containing antisulfatide antibodies, which are found in the majority of newly diagnosed type 1 patients and in prediabetic individuals, decreases Ca^{2+}-induced exocytosis by 42%, potentially contributing to the clinical insulin-secretory defect.

Mehta et al. (abstract 294) reported that the presence of either islet-cell or GAD antibodies, which were found in 20% of patients in the UKPDS, was associated with a 10-year mean HbA_{1c} of 8.6%, compared with 7.5% in antibody-negative patients. Schernthaner et al. (abstract 352) reported that GAD antibodies were found in 21% of 204 insulin-treated and 9.7% of 186 non–insulin-treated patients with type 2 diabetes. Cabrera-Rode et al. (abstract 784) addressed the question of whether sulfonylurea treatment would increase β-cell autoantigen expression in 14 patients with latent autoimmune diabetes of adulthood, 8 treated with insulin alone and 6 also receiving glyburide (20 mg daily). After 1 year of treatment, 6 of the former but none of the latter group lost islet-cell antibodies; GAD antibodies were positive in all patients and did not change in either group.

Rosenbauer et al. (abstract 268) compared 767 children who had developed diabetes before 5 years of age with 1,886 control subjects. They showed a 32% lower risk in children breast fed for >21 weeks and similar protection with late exposure to bottle-feeding of cow's milk. Saukkonen et al. (abstract 991) screened 776 children with type 1 diabetes for reticulin antibodies, and they confirmed celiac disease by jejunal biopsy in 18 of these subjects. Only 1 patient had failed to gain weight and height, and that patient responded to a gluten-free diet. The remainder of the group did not show disturbance in growth and actually showed a trend toward increased HbA_{1c} with the diet, suggesting screening for celiac disease to be counterproductive.

Hypoglycemia

Several studies addressed issues related to hypoglycemia. Pampanelli et al. (abstract 248), reporting on blockade of the acute cortisol response to hypoglycemia with metyrapone, and Fanelli et al. (abstract 249), reporting on omission of replacement cortisol in patients with Addison's disease, found similar glycemic responses to insulin but greater catecholamine and glucagon responses and more impairment in cognitive function. Cortisol replacement normalized all responses in both studies. Ellringmann et al. (abstract 820) reported that 6 of 9 patients with type 1 diabetes and blood glucose <40 mg/dl at least once weekly had pathologic results in at least 1 neuropsychological test of memory; there were no pathologic results in 9 age- and education-matched control subjects without diabetes.

Islet and Pancreas Transplantation

Ritzel et al. (abstract 117) compared 7 patients with type 1 diabetes and pancreas-transplantation using portal-venous drainage and 8 patients with the usual systemic-venous drainage of the pancreas graft vein anastomosis to the iliac veins. Basal and stimulated insulin levels were significantly lower after portal-venous drainage, suggesting this procedure to be advantageous. Lohmann et al. (abstract 359) reported that treatment with the immunosuppressive drug tacrolimus, which may lead to development of diabetes, was associated with islet-cell antibodies in 5 of 22 liver-transplant patients, but that cyclosporin A did not produce antibodies in 20 similar patients after liver transplantation. Three of the 5 antibody-positive patients and 2 antibody-negative patients developed diabetes. Use of this drug may not, therefore, be appropriate in patients with type 1 diabetes after pancreas transplantation.

P. Marchetti, Pisa, Italy, discussed animal studies pertaining to islet transplantation. The pancreatic islets comprise 1–2% of the pancreatic mass, with 300,000–1,000,000 islets per pancreas. Islet transplantation is simple, with feasibility of storage and possible in vitro modification of islet immunogenicity. Since the first studies, this research has attracted great attention, but it remains beset by problems (2). Preparation factors involve the chemicals used; the presence of small amounts of endotoxin, which may be particularly damaging to islets; and the storage procedures, with cryopreservation potentially decreasing islet mass and function.

Immunosuppressive treatment offers another potentially toxic factor that may impair islet engraftment. The number of islets transplanted is crucial, with 6,000/kg body wt appearing to be the minimum. The purity of the transplanted islets is a potential problem, but interestingly, islets completely separated from pancreatic parenchyma appear to show increased apoptosis, suggesting the need for trophic factors not produced in the islets themselves. The optimal location for the transplant remains uncertain; the liver is best physiologically, but some studies suggest that subcapsular renal transplants show increased survival. Another potential difficulty is the establishment of islet innervation and revascularization.

Immune factors, not only involving specific immune rejection but with macrophage-mediated "nonspecific" immunity and recurrence of the autoimmune islitis (3), are major issues. It is fascinating that autoimmunity is less of a problem with whole-pancreas than with islet-cell transplantation. The findings that islet autografts in diabetic patients undergoing pancreatectomy have ~7-fold longer survival than allografts and that allografts for patients without type 1 diabetes have ~5-fold longer survival suggests the importance of these factors.

Metabolic factors impairing the function of the transplanted islets include glucotoxicity and lipotoxicity, with elevated glucose and fat levels potentially increasing cytokine levels around the transplanted islets. Potential solutions include new immunosuppressants, including antibodies to CD154 lymphocytes (4); encapsulation of transplanted islets, although this may paradoxically cause local hypoxia and decreased graft function; and eventually, genetic manipulation of xenograft islets.

Antonio Secchi, Milan, Italy, concluded with a review of the current state of clinical human islet transplantation, pointing out the basic problem that so few individuals make arrangements to make organ donations. Only several hundred islet transplants have been performed, somewhat more in Europe than in the U.S. Giessen, Germany (5), and Milan, Italy (6), where 60 and 30 islet transplants have been performed, are the largest centers.

Insulin Resistance

Plasma cell membrane glycoprotein-1 (PC-1) inhibits insulin receptor tyrosine kinase activity and subsequent cellular signaling. Frittitta et al. (abstract 72) reported an association of the PC-1 gene polymorphism K121Q with insulin resistance in 121 healthy subjects and 135 type 2 diabetic patients. Bavenholm et al. (abstract 98) measured hepatic glucose production and glucose requirement during insulin infusion in 29, 10, and 15 men with normal, impaired, or diabetic glucose tolerance. They found that 41% of the variability in glycemic response to glucose was explained by the degree of decrease in hepatic glucose production in response to insulin, 18% by extra-hepatic insulin sensitivity, and 12% by the insulin response, with hepatic sensitivity to insulin being the most important factor both in those with and in those without diabetes.

NO deficiency may play a role in insulin resistance. Monti et al. (abstract 195) treated 6 patients with type 2 diabetes and HbA_{1c} 5.7% with L-arginine, a precursor of NO, 3 g three times daily for 1 month, showing that hepatic glucose production and peripheral insulin sensitivity increased 36% and 61% during a euglycemic hyperinsulinemic clamp.

A number of studies suggest a relationship between insulin resistance and fatty acids. Diraison et al. (abstract 163) measured free fatty acid (FFA) turnover and oxidation rates, total lipid oxidation by indirect calorimetry, and intrahepatic reesterification of [^{13}C]palmitate into triglyceride in 5 normal and 5 insulin-resistant individuals, showing the latter group to have 2-fold higher FFA levels with increased hepatic lipogenesis. Vessby et al. (abstract 168) administered isocaloric diets with 38% of calories as fat to 86 men and 76 women with diets containing 18% and 14% or 10% and 22% of calories as saturated or monounsaturated fatty acids for 3 months. Insulin sensitivity decreased 10% on the high–saturated fatty acid diet, without change in insulin secretion.

Sebokova et al. (abstract 53) reported increased muscle levels of malonyl-CoA and triglycerides and higher serum FFA in the hereditary hypertriglyceridemic rat and in normal rats fed a high-fat diet, supporting the hypothesis that an increase in skeletal muscle cytosolic long-chain fatty acyl coenzyme-A contributes to insulin resistance. Ryysy et al. (abstract 301) measured liver and visceral fat by proton spectroscopy and magnetic resonance imaging (MRI) in 20 patients with type 2 diabetes treated with metformin and NPH at bedtime in dosages between 10 and 176 U/day. Their results showed that the degree of hepatic sensitivity to insulin correlated with fat content of the liver.

Qvigstad et al. (abstract 569) treated 21 patients with type 2 diabetes with acipimox after triglyceride-heparin infusion to increase FFA levels, showing a 48% decrease in FFA in association with a 29% increase in insulin secretion and insulin sensitivity, suggesting that chronic increases in FFA may mediate in part the abnormalities of type 2 diabetes. Rivellese (abstract 777) reported the relationship between insulin sensitivity measured by the frequently sampled intravenous glucose tolerance test and lipids in 162 individuals without diabetes or dyslipidemia, showing LDL size to correlate with both insulin sensitivity and HDL cholesterol level.

Several additional features of insulin resistance syndrome were explored. IJzerman et al. (abstract 219) used data from the

Hoorn Study, a study of glucose tolerance among 1,141 men and 1,324 women aged 50–75 years, to show an association of waist-to-hip ratio and, to a lesser extent, BMI with hematocrit. Lidfeldt et al. (abstract 395) screened 5,000 women (610 with glucose intolerance, 95 with impaired fasting glucose, 399 with impaired glucose tolerance [IGT], and 116 with diabetes), showing wrist bone density to be higher in women with IGT and still higher in women with diabetes than in women with normal glucose tolerance.

Adler et al. (abstract 697) reported no association of insulin sensitivity and β-cell function with risk of macrovascular complications in 4,623 patients treated in the UKPDS. Each 1% decrease in HbA_{1c}, however, was associated with significant 9% and 32% decreases in the risks of MI and lower-extremity amputation in multivariate analysis. The authors suggest that "once diabetes develops, insulin resistance per se no longer increases risk, and that glucose-induced damage predominates."

In a fascinating study of the interaction between insulin resistance and type 1 diabetes, Fernández Castañer et al. (abstract 785) compared 33 patients with versus 109 patients without family history of type 2 diabetes followed for 1 year from diagnosis of type 1 diabetes. Autoimmune markers and glycemic control were similar. LDL cholesterol was 3.2 versus 2.7 and HDL cholesterol was 1.3 versus 1.5 mmol/l, with a trend toward higher glucagon-stimulated C-peptide and blood pressure, suggesting features of the insulin resistance syndrome and a possible increase in risk of macrovascular complications.

Harder et al. (abstract 923) studied 104 children between 1 and 5 years of age whose mothers had insulin-requiring diabetes during pregnancy. The degree of insulin secretion during an oral glucose tolerance test independently showed negative correlation with birth weight, suggesting features of the "small-baby-syndrome," and positive correlation with a measure of insulin resistance at birth, the insulin-to-glucose ratio. Several animal models explored additional features of the small baby syndrome. Merezak et al. (abstract 47) reported increased apoptosis of fetal rat β-cells when the mothers were fed a low-protein diet during pregnancy, and Bréant et al. (abstract 48) reported a similar decrease in β-cell mass with overall maternal undernutrition. The low protein and calorie diets increased susceptibility to apoptosis by NO, with protection by the amino acid taurine in the former study and increased susceptibility to streptozotocin in the latter study. Ozanne et al. (abstract 51) reported that maternal protein restriction in a similar model induced insulin resistance in the offspring, with decreased insulin action on adipocyte glucose transport and suppression of lipolysis, with a postreceptor mechanism of decreased insulin stimulated phosphotyrosine-associated phosphatidylinositol 3-kinase activity.

Obesity

Bognetti et al. (abstract 781) evaluated body mass composition by MRI and dual-energy X-ray absorptiometry, showing similar levels of subcutaneous adipose tissue but 39% lower levels of intra-abdominal adipose tissue in 13 obese women with type 1 diabetes than in 13 obese control subjects. Stolk et al. (abstract 782) used ultrasound to measure the distance between peritoneum and lumbar spine. They reported a Pearson correlation of 0.82 with computed tomography (CT) measurement of abdominal fat assessed in a single slice at L4-L5 by counting the tissue area with Hounsfield units between −150 and −50 inside the peritoneum. The waist-to-hip ratio showed correlation coefficients of 0.71 and 0.57 with ultrasound and CT abdominal fat measurements, suggesting the former to be a reliable method to assess abdominal fat for clinical and epidemiological studies.

A number of genetic abnormalities associated with obesity were reported at the EASD meeting. Shnawa et al. (abstract 286) found that 26% of 70 women with gestational diabetes but 11% of women with normal glucose tolerance had the $Trp^{64}Arg$ missense mutation polymorphism of the β_3-adrenergic receptor, potentially predisposing to obesity. Branchtein et al. (abstract 978) reported that height ≤151 cm was associated with a 60% increase in risk of gestational diabetes independent of age, obesity, family history of diabetes, ethnicity, education, or gestational age.

de Silva et al. (abstract 71) studied 311 males from Nauru with BMI 36 and 483 Australian women with BMI 27 for polymorphism in the tumor necrosis factor (TNF)-α gene. The *Nco*1 polymorphism at position −308 of the TNF-α promoter region that has been associated with increased gene transcription was not seen in the Nauruans, but was seen in 21% of the Australian group. Individuals who were homozygotic for this polymorphism had lower fasting insulin, suggesting increased insulin sensitivity. Wauters et al. (abstract 73) reported on 32 women aged 45–60 years with IGT or diabetes in whom significant associations were found between the $Lys^{109}Arg$ polymorphism of the leptin receptor and fasting insulin and 2-h insulin response during an oral glucose tolerance test. In a report that may have bearing on the risks associated with obesity, Niskanen et al. (abstract 1206) reported that a $Leu^{7}Pro$ polymorphism in the prepro–neuropeptide Y gene, present in 10 and 14% of individuals with and without diabetes, was associated with increased carotid intima-media thickness, independent of age, sex, diabetes, clinical macrovascular disease, smoking, systolic blood pressure, or LDL cholesterol.

Segal et al. (abstract 171) randomized 359 normal, IGT, and diabetic patients to treatment with orlistat (120 mg t.i.d.) and 316 normal, IGT, and diabetic patients to placebo plus hypocaloric diet. Weight loss was 6.9 and 7.2% with orlistat in normal and IGT subjects; 5% in diabetic patients; and 4, 3.4, and 3.8% in the 3 groups given placebo. LDL decreased 9.8, 8.2, and 3.3% in the 3 groups given orlistat; it decreased 1.2 and 2.2% in normal and IGT patients given placebo and increased 7.3% in the diabetic patients given placebo. Changes in triglyceride, HDL, and blood pressure were inconsistent and minimal in all groups.

Wilding (abstract 807) pooled data from 5 multicenter, 2-year, randomized, placebo-controlled trials of orlistat in 1,561 patients and placebo in 1,119 patients with BMI 28–43. Weight loss after 1 year was 9.2 and 5.8%, and after an additional year on a weight maintenance diet, weight loss was 6.7 and 3.7%. The homeostasis model insulin resistance index, calculated as insulin (pmol/l) × glucose (mmol/l) ÷ 22.5, decreased 0.51 from placebo at 1 year and 0.84 from placebo at 2 years.

Rigalleau et al. (abstract 731) addressed the effect of insulin on body weight and body fat measured using body-impedance analysis 3 months after initiation of insulin treatment. In 24 patients with type 1 diabetes, there was a 2.5-kg weight gain without change in body fat, while in 12 patients with type 2 diabetes, there was a 1-kg weight gain with a 0.6-kg increase in body fat. Twelve patients with type 2 diabetes discontinuing insulin showed a 1.3-kg weight loss with a 0.9-kg fall in fat mass after 3 months.

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