Microdialysis assessment of local adipose tissue lipolysis during β-adrenergic stimulation in upper-body-obese subjects with type II diabetes

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ABSTRACT

The present study was designed to investigate indicators of abdominal adipose tissue lipolysis (microdialysis), and subcutaneous adipose tissue blood flow and whole-body lipolysis, in obesity-associated type II diabetes during overnight-fasted conditions (baseline) and during intravenous infusion of the non-selective β-agonist isoprenaline. Basal subcutaneous adipose tissue blood flow and isoprenaline-induced increases in adipose tissue blood flow were not significantly different between subjects with type II diabetes and non-obese, non-diabetic controls. Adipose tissue interstitial glycerol concentrations were significantly higher in subjects with type II diabetes compared with controls ($P<0.01$), and during isoprenaline infusion there was a decrease in interstitial glycerol in both groups ($P<0.001$). Arterial glycerol concentrations were higher in subjects with type II diabetes compared with controls ($P<0.05$), whereas the increases in arterial glycerol concentration in response to isoprenaline infusion were of a similar magnitude in the two groups. Estimated subcutaneous adipose tissue glycerol release was not significantly different between the groups (controls and subjects with type II diabetes: baseline, $-129 \pm 32$ and $-97 \pm 72 \mu\text{mol}\cdot\text{min}^{-1}\cdot\text{100 g}^{-1}$ adipose tissue respectively; isoprenaline, $-231 \pm 76$ and $-286 \pm 98 \mu\text{mol}\cdot\text{min}^{-1}\cdot\text{100 g}^{-1}$ respectively). Values for fat oxidation were not significantly different between groups, whereas the isoprenaline-induced increase in fat oxidation tended to be less pronounced in subjects with type II diabetes compared with controls ($0.022 \pm 0.008$ and $0.038 \pm 0.003\text{ g/min}$ respectively; $P=0.058$). Thus estimated basal subcutaneous adipose tissue glycerol release, expressed per unit of fat mass, is not different in controls and in subjects with type II diabetes. Additionally, the isoprenaline-induced increases in indicators of local abdominal subcutaneous adipose tissue, systemic lipolysis and abdominal adipose tissue blood flow responses were comparable in obese subjects with type II diabetes and in controls. The last two findings contrast with previous data from obese subjects, indicating that the regulation of lipolysis may differ in obesity and obesity-associated type II diabetes.

INTRODUCTION

Abdominal obesity plays a central role in the development of insulin resistance and type II diabetes [1]. Several pathogenic mechanisms responsible for the development of impaired glucose metabolism and insulin resistance can be linked to fat metabolism. First, blunted catecholamine-induced lipolysis has been reported in vitro in subcutaneous adipocytes from abdominally obese males with insulin resistance or type II diabetes [2],
and \textit{in vivo} in upper-body-obese subjects before and after weight reduction [3–5]. A factor possibly involved in the defect in lipid mobilization in abdominal obesity is adipose tissue blood flow, which was shown to be blunted in obese subjects during catecholamine stimulation [6,7]. Secondly, diminished catecholamine-induced oxidation of fat has been reported in obese subjects [4,5,8,9] and in obese subjects with type II diabetes [10], which is most probably a consequence of impaired muscle uptake of non-esterified fatty acids (NEFA) [4,5]. The diminished sympathetically mediated mobilization and oxidation of fat under conditions whereby the energy demands of the body are increased may favour the maintenance of large fat stores, and consequently may promote obesity and insulin resistance. It has been suggested that the diminished NEFA uptake in muscle may increase the supply of NEFA to the liver, thereby promoting increased hepatic insulin resistance and increased production of very-low-density lipoproteins [11].

Thirdly, increased basal adipose tissue lipolysis and increased circulating NEFA concentrations have been linked to peripheral insulin resistance [12,13]. Moreover, increased glycerol release and accelerated glycerol turnover may provide carbon skeletons for gluconeogenesis in the liver, thereby stimulating hepatic glucose output [14].

The present study intended to investigate whether the defects in \(\beta\)-adrenocceptor-mediated lipolysis in obese males previously observed in our laboratory [4,5] are also present in obese males with type II diabetes, by comparing them with a non-obese control group. Indicators of local abdominal subcutaneous lipolysis and blood flow and whole-body lipolysis were studied during rest and during \(\beta\)-adrenergic stimulation by the non-selective \(\beta\)-agonist isoprenaline.

\textbf{METHODS}

\textbf{Subjects}

Subjects were eight healthy lean males (controls) and eight obese subjects with type II diabetes of average duration 2 years and 2 months (range 0.5–8 years). The diabetic subjects were treated by dietary intervention alone \((n = 2)\) or together with sulphonylurea \((n = 6)\). All diabetic subjects had reasonable blood glucose control \([\text{HbA}_1c, \text{glycosylated haemoglobin}] 6.4 \pm 0.3\% \); range 5.6–7.8\%; normal values 4.2–6.2\%\]. Besides sulphonylureas, no other medication was used. Medication was stopped 2 days before the experiment. No subject had serious health problems apart from their diabetes. A normal resting ECG and normal blood pressure (diastolic pressure \(< 95\text{ mmHg}\) ) were prerequisites for participation in the study. Subject characteristics are listed in Table 1. All subjects participated in sports for no more than 3 h per week, and none had a physically demanding job.

The study protocol was reviewed and approved by the Medical Ethical Review Committee of Maastricht University, and all subjects provided written consent.

\textbf{Body composition}

Body composition was determined by hydrostatic weighing with simultaneous lung volume measurement (Volugraph 2000, Mijnhardt, The Netherlands). Body composition was calculated according to the formula reported by Siri [15].

\textbf{Experimental design}

The subjects arrived in the laboratory at 8.00 hours, after an overnight fast. They all came to the laboratory by car or bus. All subjects were studied while resting supine on a comfortable bed in a room kept at 23–25 °C. At the beginning of the experiment two catheters were inserted: one in the radial artery of the forearm (under local anaesthetic), and the other in an antecubital vein for the infusion of the non-selective \(\beta\)-agonist isoprenaline. A microdialysis probe (see below) was placed subcutaneously under sterile conditions 5–8 cm left from the umbilicus using a 17 G intravenous catheter as a guide. The experiment was started 1 h after the insertion of the cannulae and microdialysis probe. Intermediary metabolites, arterial and extracellular microdialysate glycerol concentrations, adipose tissue blood flow (see below) and whole-body energy expenditure and substrate utilization were studied at rest (1 h period) and during a 1 h infusion of isoprenaline at a dose of 20 ng·min\(^{-1}\)·kg\(^{-1}\) fat-free mass. The dose is related to isoprenaline sulphate, 69\% of which corresponds to isoprenaline free base. Microdialysate was collected in 15 min fractions throughout the 2 h experimental period. Arterial blood was sampled in the middle of the microdialysis sampling periods, at 22.5, 37.5 and 52.5 min during both the baseline and the isoprenaline-treatment

\begin{table}
\centering
\caption{Baseline characteristics of the subjects}
\begin{tabular}{l l l}
\hline
 & Control subjects & Subjects with type II diabetes \\
\hline
Age (years) & 50.6 ± 2.4 & 51.8 ± 2.4 \\
Weight (kg) & 73.7 ± 2.6 & 103.6 ± 5.5 \\
Height (cm) & 178 ± 2 & 177 ± 2 \\
Body mass index (kg/m\(^2\)) & 23.6 ± 0.7 & 32.6 ± 1.4 \\
Body fat (%) & 16.9 ± 1.8 & 33.8 ± 2.1 \\
Waist/hip ratio & 0.94 ± 0.02 & 1.06 ± 0.03 \\
HbA\(_1c\) (%) & 5.1 ± 0.1 & 6.4 ± 0.3 \\
\hline
\end{tabular}
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periods. Energy expenditure and substrate utilization were measured by means of indirect calorimetry throughout the entire experiment using an open-circuit ventilated hood system.

**Abdominal subcutaneous microdialysis**

The subcutaneous microdialysis probes were constructed of cuprophane fibres (inner diam. 240 μm; wall thickness 50 μm; molecular mass cut-off 20 000 Da), obtained from an artificial kidney (Hospal B.V., Uden, The Netherlands), as described previously by de Boer and co-workers [16]. One single fibre (20 mm exposed) was glued with polyurethane glue (Morton International G.m.b.H., Bremen, Germany) into polyethylene tubing (Portex Ltd., Hythe, Kent, U.K.; 0.80 mm outer diam. and 0.40 mm inner diam.). A pair of twisted stainless steel wires (0.06 mm diam.) in the fibre prevented collapse. The probes were sterilized with ethylene oxide. The wires (0.06 mm diam.) in the fibre prevented collapse. The probe was placed subcutaneously under sterile conditions 5–8 cm left from the umbilicus using a 17 G intravenous catheter as a guide. The polyethylene tubing was perfused continuously with standard Ringer solution. The probe membranes were coated with glycerol. For this reason, the probe was perfused at a high flow rate of 50 μl/min (Harvard microinfusion pump; Plato b.v., Diemen, The Netherlands) for the first 1 h after placement, in order to wash out all the membrane glycerol, after which time the real experiment was started. In separate pilot experiments, a volume of 2 ml of Ringer solution appeared to be sufficient to remove the glycerol coating. Following this initial period, the experiment was started at a perfusion flow rate of 5 μl/min. Microdialysate was collected in fractions corresponding to 15 min.

The relative *in vivo* recovery of glycerol in the microdialysate was determined individually in an additional experiment by means of the equilibrium technique described by Lönnroth and co-workers [17]. After an overnight fast, the microdialysis probe was placed subcutaneously under sterile conditions, as described above. Four different concentrations of glycerol (0, 75, 150 and 300 μM) were added in turn to the perfusion fluid (each concentration for 1 h). The net changes in dialysate glycerol were determined. Regression analysis of the net change in dialysate glycerol against the ingoing glycerol concentration showed a good linear correlation during the calibration period (all experiments: r > 0.85). The glycerol concentration that resulted in no net change in dialysate glycerol was assumed to correspond to the actual extracellular glycerol concentration.

**Measurement of adipose tissue blood flow**

**¹³¹Xe-washout method**

Subcutaneous adipose tissue blood flow was measured using the **¹³¹Xe-washout method** on the abdomen a little distal and lateral to the umbilicus (near the microdialysis probe), as described previously [6,18]. From the regression of count rate against time, the rate of disappearance of **¹³¹Xe** (injected dose 5.5 MBq, dissolved in saline) was determined over the last 30 min of the resting period and during an early (from 10 to 30 min) and late phase (from 30 to 60 min) of the isoprenaline infusion.

**Tissue–blood partition coefficient**

Adipose tissue blood flow can be calculated by multiplying the disappearance constant for xenon by the partition coefficient for the distribution of xenon between the adipose tissue and blood. Thus, for the calculation of quantitative values of adipose tissue blood flow (per 100 g of tissue), the relative solubility of xenon between tissue and blood, i.e. the partition coefficient, must be known. We calculated the tissue–blood partition coefficient on an individual basis, taking into account the lipid content of adipose tissue, the haematocrit, and the solubility of xenon in blood, red blood cells, adipose tissue, lipid and plasma [19,20], as described in detail previously [6].

**Biochemical analyses**

For the determination of arterial concentrations of glycerol, NEFA, glucose and insulin, blood was taken into syringes containing EDTA. Plasma NEFA, glucose and glycerol were measured using standard enzymic techniques automated on a Cobas Farah centrifugal analyser at 340 nm (NEFA, NEFA c, Wako Chemicals, Neuss, Germany; glucose, Roche Diagnostics, Hoffmann-La Roche, Basel, Switzerland; glycerol, Boehringer, Mannheim, Germany). Microdialysate glycerol was determined fluorimetrically on the Cobas Farah with the same standard enzymic assay, but with adapted concentrations of NAD⁺, enzymes and buffer to achieve accurate fluorimetric detection. The detection limit of this assay was 10 μM. Plasma insulin was measured by a specific double-antibody radioimmunoassay for human insulin (Kabi Pharmacia Diagnostics, Uppsala, Sweden). Urine was collected overnight and at the end of the experiment for the determination of urinary nitrogen, in order to calculate the non-protein respiratory exchange ratio, as well as carbohydrate and fat oxidation (see below).

**Calculations**

**Glycerol release**

Glycerol release across adipose tissue (μmol min⁻¹ 100 g⁻¹ adipose tissue) was calculated according to Fick’s equation, as described previously [21,22]:

\[
\text{Glycerol release} = \frac{(A - V)}{100 \times \text{ATBF} \times (1 - \text{Ht}/100)}
\]

where \( A \) is the arterial plasma glycerol concentration (μmol/l), \( V \) is the capillary venous plasma glycerol
concentration (μmol/l), Ht is the haematocrit, and ATBF is adipose tissue blood flow (ml·min⁻¹·100 g⁻¹ adipose tissue). Conversion of interstitial into capillary venous plasma substrate concentration was performed using the equation:

\[ V = (I - A) \times (1 - e^{-PS/\Delta}) + A \]

where \( V \) is the capillary venous substrate concentration, \( I \) is the interstitial substrate concentration, \( A \) is the arterial substrate concentration, \( PS \) is permeability surface product area for glycerol (±5 ml·min⁻¹·100 g⁻¹) [22–24] and \( Q \) is adipose tissue plasma flow rate.

Gas exchange monitoring
The metabolic rate was calculated from \( O_{2} \) consumption (\( VO_{2} \)) and \( CO_{2} \) production (\( VCO_{2} \)) according to the equation of Weir [25]. Carbohydrate and fat oxidation rates were calculated from \( VO_{2} \) and \( VCO_{2} \) and urinary nitrogen excretion. The amount of protein oxidized was estimated from total nitrogen excretion, since most urinary nitrogen (> 80%) is in the form of urea, with 1 g of nitrogen arising from approx. 6.25 g of protein. Rates of carbohydrate and fat oxidation were calculated using values for gas exchange from the table reported by Frayn [26].

Statistical analysis
Results are presented as means ± S.E.M. To compare responses between and within groups, a two-factor repeated-measures analysis of variance (ANOVA) was performed. A \( P \) value of < 0.05 was regarded as statistically significant.

RESULTS

Interstitial and arterial glycerol concentrations
As described in the Methods section, adipose tissue extracellular glycerol concentrations were calculated by determining the ingoing glycerol concentration that resulted in no net change in dialysate glycerol concentration. The resting adipose tissue extracellular concentrations were 170 ± 11 μmol/l in control subjects and 279 ± 34 μmol/l in subjects with type II diabetes (\( P < 0.01 \)). The \( in vivo \) recovery of the microdialysis probes was 18 ± 3% in control subjects and 17 ± 4% in subjects with type II diabetes. In both groups there was a decrease in the interstitial glycerol concentration as result of isoprenaline infusion (repeated measures, \( P < 0.001 \); Figure 1). Interstitial glycerol levels remained higher throughout the experiment in subjects with type II diabetes compared with controls (group effect, \( P < 0.01 \)). Arterial glycerol concentrations were higher in subjects with type II diabetes than in controls, both during rest and during isoprenaline infusion (group effect, \( P < 0.05 \)), whereas the increases in arterial glycerol concentration as a result of isoprenaline infusion (group effect, \( P < 0.001 \)) were of a similar magnitude in the two groups (Figure 1).

The arterial–interstitial concentration difference tended to be higher in subjects with type II diabetes than in control subjects (\( P = 0.0507 \)), and this difference decreased in both groups during isoprenaline infusion (repeated measures, \( P < 0.001 \)).

Adipose tissue blood flow
On the basis of a previously described equation [6], the partition coefficient for xenon between adipose tissue and blood was calculated, and this amounted to 6.1 ± 0.2 in control subjects and 8.2 ± 0.2 in subjects with type II diabetes. Basal blood flow values (0.77 ± 0.48 and 2.04 ± 0.37 ml·min⁻¹·100 g⁻¹ respectively) and isoprenaline-induced increases in blood flow (repeated measures, \( P < 0.01 \)) were not significantly different between the groups (Figure 1). The estimated subcutaneous adipose tissue glycerol release was not significantly different between groups, both during baseline conditions and during isoprenaline treatment (Figure 2). Isoprenaline infusion increased glycerol release in both groups (repeated measures, \( P < 0.05 \)).

Arterial insulin, glucose and NEFA concentrations
Figure 3 shows values for arterial insulin, glucose and NEFA concentrations throughout the experiment. The basal insulin concentration and the isoprenaline-induced increase in insulin concentration were higher in subjects with type II diabetes compared with controls (group effect, \( P < 0.01 \); interaction: group × repeated measures, \( P < 0.02 \)). Glucose concentrations were higher in subjects with type II diabetes than in control subjects throughout the experiment (group effect, \( P < 0.01 \)), whereas the glucose concentration decreased significantly during isoprenaline treatment in subjects with type II diabetes, but remained stable in control subjects (interaction: group × repeated measures, \( P < 0.05 \)). Basal NEFA concentrations were comparable in both groups, whereas the isoprenaline-induced increase in NEFA concentration tended to be blunted in subjects with type II diabetes (Figure 3; interaction: group × repeated measures, \( P = 0.10 \)).

Energy expenditure and substrate utilization
Figure 4 shows values for energy expenditure, carbohydrate oxidation and fat oxidation, expressed per kg fat-free mass, in both groups. After 10 min of isoprenaline infusion, a steady state for energy expenditure was reached, i.e. values at 5 min did not change significantly.
until the end of the infusion. For the respiratory exchange ratio, carbohydrate oxidation and fat oxidation, a steady state was reached after 20 min of isoprenaline infusion. The final 30 min of the isoprenaline infusion period were taken as being representative of the responses for both energy expenditure and substrate utilization. Absolute basal values for energy expenditure were significantly higher in subjects with type II diabetes compared with control subjects (5.9 ± 0.3 and 5.1 ± 0.2 kJ/min respectively; \( P < 0.05 \)). Basal energy expenditure expressed per kg fat-free mass or corrected for fat-free mass by means of analysis of covariance was not significantly different between groups. Isoprenaline-induced thermogenesis was comparable in the two groups, irrespective of whether it was expressed as increase per kg fat-free mass (Figure 4) or as percentage increase above baseline (type II diabetes, 14.0 ± 1.8%; controls, 15.9 ± 2.2%). Values for fat oxidation were not significantly different between the two groups. The isoprenaline-induced increase in fat oxidation (absolute or per kg fat-free mass; \( P < 0.01 \)) was less pronounced in subjects with type II diabetes than in control subjects (Figure 4; interaction: group \( \times \) repeated measures, \( P = 0.05 \)), resulting in similar values for fat oxidation in the two groups during isoprenaline infusion.

Values for carbohydrate oxidation (absolute or expressed per kg fat-free mass) were not significantly different between the two groups (group effect, \( P = 0.11 \)). The decrease in carbohydrate oxidation as a result
Figure 3 Arterial insulin, glucose and NEFA concentrations during 60 min of intravenous isoprenaline infusion in obese subjects with type II diabetes and in non-obese controls

Controls; ◦, ○, subjects with type II diabetes. Results of ANOVA are indicated in the text.

DISCUSSION

Previous studies have found impaired lipolysis and fat oxidation during stimulation by catecholamines in obese males [4,5,8,9]. The impaired lipolysis was accompanied by a lowered blood flow response during stimulation of the \(\beta\)-adrenoceptors, indicating that blood flow may be of importance in the regulation of fat mobilization [6]. These disturbances may be important in the development of a positive fat balance (i.e. fat intake exceeds fat utilization), obesity and insulin resistance [11]. The present study was intended to investigate whether similar mechanisms are operative in obese subjects with type II diabetes. The major finding of the present study is that \(\beta\)-adrenergically mediated lipolysis, as reflected by arterial glycerol concentrations and estimated local abdominal subcutaneous glycerol release, is normal in obesity-associated type II diabetes.
Methodological considerations

First, a comparison of glycerol release values estimated from microdialysis and the arteriovenous technique yielded on average 40% lower values with the former compared with the latter technique. This may be partly caused by the assumptions for the permeability surface product that are made in calculating venous plasma values from interstitial glycerol values. Additionally, microdialysis may reflect intracellular lipolysis rather than intravascular lipolysis [27]. Thus it must be stressed that quantitative values for local glycerol release have to be interpreted with caution.

Secondly, for calculating quantitative blood flow values from the $^{133}$Xe-washout curves, the adipose-tissue–blood partition coefficient must be known. The highest solubility coefficients for Xe are found for lipids and haemoglobin, which implies that the lipid content of adipose tissue and the haematocrit of the blood perfusing it will be major determinants of the partition coefficient. For this reason, we calculated the tissue–blood partition coefficient on an individual basis, taking into account the lipid content of adipose tissue, the haematocrit and the solubility of Xe in blood, red blood cells, adipose tissue, lipid and plasma [19,20], as described in detail previously [6]. Notably, the use of similar values for the partition coefficient in the two groups would not alter the conclusions of the present study with respect to the rate of glycerol release.

Indicators of lipolysis and blood flow

Both estimated local subcutaneous abdominal lipolysis, as studied by microdialysis, and the circulating arterial glycerol concentration showed increases of similar magnitude during isoprenaline infusion in subjects with type II diabetes and controls, indicating normal isoprenaline-induced lipolysis in obesity-associated type II diabetes. This was accompanied by a normal isoprenaline-induced increase in adipose tissue blood flow. The above findings are in contrast with previous data from our laboratory obtained with obese subjects [4–6], studied under comparable experimental conditions, where isoprenaline-induced lipolysis and blood flow responses appeared to be blunted [obese subjects in previous study compared with obese type II diabetic subjects in the present study: change in arterial glycerol, $18 \pm 12$ and $53 \pm 9 \mu$mol/l respectively ($P < 0.05$); change in blood flow response, $2.7 \pm 0.9$ and $6.1 \pm 1.1 \text{mmol/l}$ respectively ($P < 0.05$)]. Thus these findings indicate that the relative importance of processes involved in lipid mobilization may differ in obesity and obesity-associated type II diabetes.

The finding of normal glycerol release in abdominal subcutaneous adipose tissue of subjects with type II diabetes seems to contrast with the observations of Reynisdottir and co-workers [2], which showed a resistance of lipolysis to stimulation by catecholamines (defect in $\beta_2$-adrenoceptor mRNA expression) [2,28] in subcutaneous adipocytes from upper-body-obese males with insulin resistance or type II diabetes. Possible explanations for this apparent discrepancy may lie in the fact that the latter data were obtained from in vivo experiments, and cannot be extrapolated to lipolysis in vitro (i.e. the importance of blood flow in the regulation of lipid mobilization), or may lie in differences in the characteristics of the subjects: our subjects had no other health complications apart from their type II diabetes, whereas the subjects in the study of Reynisdottir et al. [2] had other health complications characteristic of the insulin resistance syndrome. Further (in vivo) research is necessary in order to elucidate the factors involved in deviations in lipid mobilization in conditions such as obesity, insulin resistance and obesity-associated type II diabetes.

Fat oxidation

During increased $\beta$-adrenergic stimulation the obese diabetic subjects tended to have a blunted increase in fat oxidation, as reported previously in abdominally obese subjects [8,9] and in obese subjects with type II diabetes [10]. These data suggest that obese subjects with type II diabetes have a diminished ability to increase the utilization of fat as a fuel under conditions where the energy demands of the body are increased. The diminished capacity to increase fat oxidation may possibly contribute to the development of a positive fat balance, and consequently provide a link between obesity and type II diabetes by promoting (abdominal) obesity and insulin resistance.

Estimated basal lipolysis

Increased glycerol release from adipose tissue in the resting state has been indicated as a risk factor in the aetiology of hyperglycaemia, by providing carbon skeletons for gluconeogenesis to the liver, thereby stimulating hepatic gluconeogenesis and hepatic glucose output [14]. The present study shows that, although systemic arterial glycerol concentrations are increased in type II diabetes, indicating greater whole-body lipolysis, estimated glycerol release from subcutaneous adipose tissue, expressed per unit fat mass, is not significantly different from that in control subjects. These findings correspond with results from Jansson and co-workers, who previously reported a normal lipolytic response per unit fat mass in obese subjects [21] and in obese subjects with type II diabetes [22].

Thermogenesis

As discussed elsewhere [10], the thermogenic response in subjects with type II diabetes was comparable with that in control subjects, in agreement with previous data in obese subjects, indicating that a diminished $\beta$-
adrenoceptor-mediated thermogenic response is not involved in the maintenance and/or aetiology of obesity in type II diabetes.

**Conclusion**

In conclusion, \( \beta \)-adrenoergically mediated blood flow responses and indicators of lipolysis are normal in obese subjects with type II diabetes, which contrasts with previous data obtained using obese non-diabetic subjects. This indicates that processes involved in lipid mobilization may differ in obesity and obesity-associated type II diabetes.

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