(2). In a study about contraception and other reproductive issues in consecutively chosen women with type I diabetes (age 16–46 years) on intensified insulin therapy, we had the opportunity to evaluate the use of IUDs among a large group of young diabetic women (n = 808; age 31 ± 7 years; duration of diabetes 14 ± 5 years; mean ± SD [4]).

Through a multiple-choice questionnaire, the women were asked about current and previous contraception, satisfaction with their contraceptive method, and duration of use. If they were using or had previously used an IUD, the women were asked if they had pain, increased menstrual or additional bleeding, accidental pregnancies, or a PID. There were 94 current users (age 32 [20–45] years, 70% nullipara, HbA_{1c} 8.0 ± 1.7%) who had used the IUD for 5 (0.1–20) years, a cumulated use of 466 person-years. Of those, there were nine who indicated less than full satisfaction because of pain and/or bleeding. There were 33 ex-users who had used the IUD for 6 (0.5–16) years, a cumulated use of 146 person-years. Among those, there were two accidental pregnancies, three cases of PID, and twelve cases of bleeding and/or pain. If we combine users and ex-users, one can evaluate 612 person-years in 127 type I diabetic women. The rate of accidental pregnancies per 100 person-years is 0.3 (Pearl index), the rate of PID per 100 person-years is 0.5, and the rate of pain and/or bleeding per 100 person-years is 3.4. These results are well within the corresponding rates seen in large prospective studies of the use of modern copper IUDs in nondiabetic women (5).

We are aware of the problems with self-reported and retrospective data; however, in our questionnaire, the answers were rather complete. We do not think that the diabetic women had any reason not to report or to have forgotten accidental pregnancies and PIDs associated with the use of an IUD. Thus, we believe that our data support the results of previous prospective studies showing that modern copper IUDs are as safe, effective, and well-tolerated in well-controlled diabetic women as in nondiabetic women.

RENATE KIMMERLE, MD
LUTZ HEINEMANN, PHD
MICHAEL BERGER, MD

From the Department of Metabolic Diseases and Nutrition, World Health Organization Collaborating Center for Diabetes, Heinrich-Heine-University, Düsseldorf, Germany.

Address correspondence to Renate Kimmerle, MD, Department of Metabolic Diseases and Nutrition, Heinrich-Heine-University, Moorenstr. 5, 40225 Düsseldorf, Germany.

References

1. Skouby SO, Molsted-Pedersen L, Kosonen A: Consequences of intrauterine contraception in diabetic women. *Fertil Steril* 42: 568–572, 1984
2. Kimmerle R, Weiss R, Berger M, Kurz KH: Effectiveness, safety and acceptability of a copper intrauterine device (CUSafe 300) in type I diabetic women. *Diabetes Care* 16: 1227–1230, 1993
3. Selby PL, Oakley CE: Women's problems and diabetes. *Diabetic Med* 7:290–293, 1991
4. Kimmerle R, Schmitt G, Berger M: Contraception in type I diabetic women: a survey of 808 women of fertile age. *Geburtsh Frauenheilk* 54:691–696, 1994
5. World Health Organization, Special Program of Research, Development and Research Training in Human Reproduction: Task force on the safety and efficacy of fertility regulating methods: the TCU 380A, TCU 220C, Multiload 250, and Nova T IUDs at 3, 5, 7 years of use: results from three randomized multicenter trials. *Contraception* 42:141–158, 1990

Insulin and Proinsulin Secretion in Subjects With Abnormal Glucose Tolerance and a Mitochondrial $tRNA^{Leu(UUR)}$ Mutation

Recent work has linked the mitochondrial $tRNA^{Leu(UUR)}$ mutation at position 3243 with the development of maternally inherited diabetes and a cluster of neurological abnormalities (1,2). The mechanisms leading to the development of diabetes remain unclear, although decreased insulin secretion has been reported by several groups (2,3). We examined, therefore, the relationship between proinsulin and insulin secretory profiles in subjects with the $tRNA^{Leu(UUR)}$ mutation and abnormal glucose tolerance.

Five subjects with $tRNA^{Leu(UUR)}$ mutation and abnormal glucose tolerance (four with impaired glucose tolerance and one with islet cell antibody–negative/C-peptide–positive diabetes) were studied. All had sensorineural deafness, and two had encephalopathy but were otherwise fully mobile. For each affected subject, two control subjects with no family history of diabetes or neurological deficit were pair-matched for age, sex, and body mass index (BMI).

Glucose tolerance was assessed by standard oral glucose tolerance test (OGTT). First-phase insulin secretion (FPIS) and proinsulin secretion (FPPS) (determined as Δ0–10 min hormone area/Δ0–10 min glucose area) were assessed after an intravenous glucose tolerance test (IVGTT) (0.3 g/kg). Whole-body insulin sensitivity was calculated as K_g (index of glucose tolerance) divided by Δ0–40 min insulin area (4), which has been validated against the euglycemic-

Table 1—*Subject characteristics*

	Subjects with the mutation	Control subjects	*P* value
Anthropometric data			
Sex (M/F)	2/3	4/6	—
Age (years)	42 ± 3	42 ± 3	NS
Body weight (kg)	63 ± 8	66 ± 4	NS
BMI (kg/m^2)	22.8 ± 1.3	23.3 ± 0.7	NS
OGTT data			
Fasting plasma glucose (mmol/l)	5.8 ± 0.6	5.1 ± 0.1	NS
2-h plasma glucose (mmol/l)	10.1 ± 0.7	5.9 ± 0.3	<0.01
IVGTT data			
Fasting insulin (pmol/l)	64 (26–96)	56 (20–80)	NS
Fasting proinsulin (pmol/l)	3.6 (1.3–17.0)	2.1 (0.5–8.9)	NS
FPIS (pmol/mmol)	9 (2–25)	30 (24–60)	<0.02
FPPS (pmol/mmol)	0.03 (0.01–0.32)	0.04 (0.01–0.16)	NS
K_g (%/min)	1.06 ± 0.14	1.41 ± 0.08	<0.05
Insulin sensitivity (% · min^{-1} · pmol^{-1} · l^{-1} · min · 10^{-3})	0.27 ± 0.06	0.24 ± 0.02	NS

Data are means ± SE or geometric mean (range). Statistical comparisons by Mann-Whitney *U* test.

hyperinsulinemic clamp. Serum insulin (5) and proinsulin (6) concentrations were measured by specific two-site enzyme-linked immunosorbent assays, and the tRNA$^{Leu(UUR)}$ mutation was identified by amplification of leucocyte and muscle DNA around the 3243 site, followed by restriction digest analysis (1).

The subjects with the mutation and the control subjects were closely matched for age, sex, and BMI (Table 1). Fasting serum proinsulin and insulin concentrations were comparable, although FPIS was significantly lower in the subjects with the mutation ($P < 0.02$). However, there was no difference in FPPS between the groups. K_g was significantly lower in the subjects with the mutation ($P < 0.05$), reflecting the abnormal glucose tolerance, although there was no significant difference between the groups for whole-body insulin sensitivity.

Our principal finding, therefore, was of decreased insulin but normal proinsulin secretion after intravenous glucose administration in subjects with the tRNA$^{Leu(UUR)}$ mutation and abnormal glucose tolerance. This differential secretory response has been described in patients with type II diabetes (7) and is most marked during the first 10 min of the IVGTT. However, the biochemical defect of the β-cell in type II diabetes remains to be identified. The tRNA$^{Leu(UUR)}$ mutation results in a decrease in mitochondrial respiratory chain function (8), while the process of insulin secretion requires a high intracellular ATP-to-ADP ratio (9).

The difference in insulin secretion between the groups was not related to a difference in whole-body insulin sensitivity, which was normal in the subjects with the mutation, as previously reported (10). In conclusion, therefore, subjects with the tRNA$^{Leu(UUR)}$ mutation and abnormal glucose tolerance have impaired FPIS but normal FPPS after intravenous glucose administration.

MARK WALKER, MD
ROBERT W. TAYLOR, PHD
MURRAY W. STEWART, MRCP
LAURIE A. BINDOFF, MD
PATRICIA A. SHEARING, IMLT
VICTOR ANYAOKU, PHD
MARGARET J. JACKSON, MD
DAVID B. HUMPHRISS, MRCP
DESMOND G. JOHNSTON, PHD
K. GEORGE M.M. ALBERTI, PHD
DOUGLASS M. TURNBULL, PHD

From the Departments of Medicine (M.W., R.W.T., M.W.S., P.A.S., D.B.H., K.G.M.M.A.) and Clinical Neurosciences (L.A.B., M.J.J., D.M.T.), University of Newcastle upon Tyne, Newcastle upon Tyne; and the Unit of Metabolic Medicine (V.A., D.G.J.), St Mary's Hospital Medical School, London, U.K.

Address correspondence to Mark Walker, MD, Department of Medicine, The Medical School, Framlington Place, Newcastle upon Tyne NE2 4HH, U.K.

References

1. van den Ouweland JMW, Lemkes HHPJ, Ruitenbeek W, Sandkuijl LA, de Vijlder MF, Struyvenberg PAA, van den Kamp JJP, Maassen JA: Mutation in mitochondrial tRNA$^{Leu(UUR)}$ gene in a large pedigree with maternally transmitted type II diabetes mellitus and deafness. *Nature Genet* 1:368–371, 1992
2. Kadowaki T, Kadowaki H, Mori Y, Tobe Y, Sakuta R, Suzuki Y, Tanabe Y, Sakura H, Awata T, Goto Y-I, Hayakawa T, Matsuoka K, Kawamori R, Kamada T, Horai S, Nonaka I, Hagura R, Akanuma Y, Yazaki Y: A subtype of diabetes mellitus associated with a mutation of mitochondrial DNA. *N Engl J Med* 330:962–968, 1994
3. Katagiri H, Asano T, Ishihara H, Inukai K, Anai M, Yamanouchi T, Tsukuda K, Kikuchi K, Kitaoka H, Ohsawa N, Yazaki Y, Oka Y: Mitochondrial diabetes mellitus: prevalence and clinical characterization of diabetes due to mitochondrial tRNA$^{Leu(UUR)}$ gene mutation in Japanese patients. *Diabetologia* 37:504–510, 1994

4. Galvin P, Ward G, Walters J, Pestell R, Koschmann M, Vaag A, Martin I, Best JD, Alford F: A simple method for quantitation of insulin sensitivity and insulin release from an intravenous glucose tolerance test. *Diabetic Med* 9:921–928, 1993
5. Anderson L, Dinesen B, Jorgenson PN, Poulsen F, Roder ME: Enzyme immunoassay for intact human insulin in serum or plasma. *Clin Chem* 39:578–582, 1993
6. Anyaoku VN, Pavlou R, Rush P, Tan K, Johnston DG: An enzyme-linked immunosorbent assay for measuring intact human proinsulin. *Endocrinol Metab* 2:111–118, 1995
7. Davis SN, Piatti PM, Monti L, Brown MD, Branch W, Hales CN, Alberti KGMM: Proinsulin and insulin concentrations following intravenous glucose in normal, obese, and non-insulin-dependent diabetic subjects. *Metabolism* 42:30–35, 1993
8. Ciafaloni E, Ricci E, Shanske S, Moraes CT, Silvestri G, Hirano M, Simonetti S, Angelini C, Donati MA, Garcia C, Martinuzzi A, Mosewich R, Servidei S, Zammarchi E, Bonilla E, DeVivo DC, Rowland LP, Schon EA, DiMauro S: MELAS: clinical features, biochemistry and molecular genetics. *Ann Neurol* 31:391–398, 1992
9. Cook DL, Hales CN: Intracellular ATP directly blocks K^+ channels in pancreatic B-cells. *Nature* 311:271–273, 1984
10. Walker M, Taylor RW, Stewart MW, Bindoff LA, Jackson MJ, Alberti KGMM, Turnbull DM: Insulin sensitivity and mitochondrial gene mutation. *Diabetes Care* 18:273–274, 1995