Taurine Intestinal Absorption and Renal Excretion Test in Diabetic Patients

A pilot study

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There is evidence that diabetes is characterized by taurine deficiency (1–4), which has been linked to diabetic retinopathy, neuropathy, and nephropathy (5–7). Taurine is involved in neuronal modulation, osmoregulation (8), and protection against oxidative stress (9). Its plasma levels are maintained within a normal range through protein intake, and de novo synthesis is limited by the activity of hepatic cysteinesulphinic acid decarboxylase, which is low in humans. Taurine depletion can occur rapidly (10), possibly leading to retinal, cardiac, neural, immune, and hemostatic dysfunction (4,11–14).

The reasons for taurine deficiency in diabetes remain unclear. A decrease in the overall body pool (1,2) and/or internal redistribution between the intra- and extracellular compartments are possibilities. The former can be secondary to decreased oral intake, poor intestinal absorption, renal wasting, or a combination of factors.

In diabetic rats, intestinal absorption of taurine is reduced (K.B., Camille Nassar, unpublished data), while urinary taurine excretion is enhanced (15). Kidney loss in uncontrolled diabetes is aggravated by severe hyperglycemia and ketoacidosis (4). Data are lacking, however, on urinary excretion and pharmacokinetics of taurine absorption in human diabetes with mild-to-moderate hyperglycemia. This pilot study was therefore conducted in patients with moderately impaired glucose control and in matched nondiabetic subjects to evaluate the pharmacokinetics of taurine absorption following an oral load and to elucidate the mechanism of taurine deficiency in diabetes.

RESEARCH DESIGN AND METHODS

— A total of 16 subjects were enrolled in the study: 6 patients with type 2 diabetes, 2 with type 1 diabetes, and 8 healthy subjects; subjects were pair-matched for age, sex, and BMI. The inclusion criteria for the patients were age 18–65 years, BMI 20–35 kg/m^2, and A1C >7%. We excluded patients with chronic kidney disease, cholestatic liver disease, gastroparesis, malabsorption, and severe ophthalmopathy or neuropathy.

After a 10-h fast, blood was drawn for plasma taurine, fasting glucose, creatinine, triglycerides, and A1C. Height, weight, heart rate, and blood pressure were measured. A baseline urine specimen was collected for creatinine, microalbumin, and taurine, followed by six 500-mg tablets of taurine given once orally with water. Blood was then drawn every hour for 6 h, and urine was collected over the study period for taurine analysis.

Biochemical measurements were performed using established methods. The glomerular filtration rate values calculated by the Modification of Diet in Renal Disease Study formula (16) and the creatinine clearances based on 6-h urine collection were similar. Taurine was determined using reverse-phase chromatography (17). For each subject, hourly and peak plasma taurine and the time to achieve peak concentration following the oral taurine load were determined. The area under the curve was calculated, and linear regression analysis was performed on only the descending part of the curve. The rate constant (K_e) and half-life of elimination ($t_{1/2}$) were derived from the slope of the curve (slope $-K_e/2.3$ and $t_{1/2}$ $0.693/K_e$).

The urine taurine excretion rate was expressed in micromoles per hour. Fractional excretion is the ratio of taurine clearance to creatinine clearance, expressed as a percentage. The Mann-Whitney *U* test was used to compare variables between groups, and *P* values ≤0.05 were considered significant (SPSS version 14.0; SPSS, Chicago, IL).

RESULTS

— The baseline characteristics and the plasma and urine parameters of diabetic patients and control subjects are shown in Table 1. Subjects in both groups had normal kidney function.

There was a trend toward a lower baseline plasma taurine concentration in type 2 diabetic patients ($P = 0.056$), whereas the temporal pattern of the rise and decline in plasma taurine concentration was similar in both groups. After the taurine load, peak plasma concentration of taurine was significantly lower in diabetic subjects ($P = 0.007$). The increment in plasma taurine level from baseline to the first hour (hour 1) was lower in diabetic patients. The 1-h plasma taurine concentration was lower in diabetic subjects than in control subjects ($P = 0.015$). Moreover, area under the curve was significantly lower in diabetic subjects ($P = 0.028$). Both groups had comparable basal urine taurine levels. After the taurine load, diabetic patients had a higher urinary taurine excretion rate ($P = 0.028$) and higher taurine clearance ($P < 0.001$). This was reflected in doubling of the frac-

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

Table 1—*Baseline characteristics, plasma, and urine taurine parameters in diabetic patients and control subjects*

	All patients	All control subjects	*P**	Type 2 diabetic patients	Control subjects	*P*†
n	8	8		6	6	
Age (years)	44 ± 18	45 ± 15	0.87	48 ± 18	48 ± 15	0.9
Sex (female/male)	3/5	3/5	—	1/5	1/5	—
Duration of diabetes (years)	8.8 ± 7.8	—	—	9.5 ± 8.7	—	—
Hypertension (*n*)	3/8	1/8	—	3/8	1/8	—
Blood glucose (mg/dl)	209 ± 49	89 ± 12	0.001	187 ± 32	92 ± 13	0.001
A1C (%)	8.2 ± 1.4	5.5 ± 0.5	<0.001	8.6 ± 1.2	5.5 ± 0.5	0.001
BMI (kg/m^2)	27.2 ± 2.6	28 ± 4.0	0.32	28.3 ± 1.94	30.2 ± 2.8	0.217
Systolic blood pressure (mmHg)	135 ± 12	113 ± 10	0.007	137 ± 14	117 ± 5.3	0.008
Diastolic blood pressure (mmHg)	80 ± 9	70 ± 13	0.105	82.5 ± 8.8	69.5 ± 15	0.105
Baseline creatinine (mg/dl)	0.77 ± 0.18	0.77 ± 0.15	0.95	0.8 ± 0.2	0.7 ± 0.2	0.744
GFR MDRD (ml/min per 1.73 m^2)	111 ± 19	105 ± 32	0.16	111 ± 20	110 ± 36	0.985
Baseline plasma taurine (μmol/l)	53.5 ± 11	68.1 ± 20	0.195	51.3 ± 11	72.2 ± 21	0.056
Plasma concentration at 1 h (μmol/l)	351 ± 120	621 ± 255	0.017	335 ± 134	654 ± 291	0.035
Plasma concentration at peak (μmol/l)	568 ± 68	742 ± 162	0.007	552 ± 67	772 ± 179	0.019
AUC (μmol · h^{-1} · l^{-1})	1,499.5 ± 266	2,119 ± 642	0.028	1,485 ± 312	2,173 ± 729	0.059
Time to peak (h)	1.8 ± 0.3	1.8 ± 1.1	0.6	1.8 ± 0.4	1.8 ± 1.3	1.0
$t_{1/2}$ (h)	2.3 ± 0.7	2 ± 0.61	0.5	2.5 ± 0.8	1.9 ± 0.5	0.241
Urine taurine excretion rate (μmol/h)	1,225 ± 206	932 ± 245	0.028	1,266 ± 221	938 ± 279	0.048
Urinary taurine clearance (l/h)	4.2 ± 0.9	2.4 ± 0.5	<0.001	4.5 ± 0.8	2.4 ± 0.57	0.001
Urinary fractional excretion (%)	0.6 ± 0.1	0.34 ± 0.13	0.002	0.58 ± 0.1	0.37 ± 0.1	0.008

Data are means ± SD unless otherwise indicated. *$P < 0.05$ for all patients vs. all control subjects and $P < 0.05$ for all type 2 diabetic patients vs. control subjects. (Mann-Whitney *U* test). Glomerular filtration rate was estimated by the Modification of Diet in Renal Disease Study formula. The study was approved by the institutional review board at the American University of Beirut. $t_{1/2}$, half-life. AUC, area under the curve; GFR, glomeruler filtration rate; MDRD, Modification of Diet in Renal Disease Study.

tional excretion of taurine in the diabetic group.

CONCLUSIONS — Our results indicate a difference in the pharmacokinetics of taurine in patients with diabetes compared with nondiabetic matched control subjects. After an oral taurine load, diabetic patients have a significantly lower plasma taurine concentration at peak. This might be due, in part, to impaired renal reabsorption with enhanced urinary clearance and fractional excretion. The lower plasma taurine concentration of the diabetic group in the first hour suggests that there may also be a component of decreased net intestinal absorption in diabetes. There was also a trend (although not significant) for a lower baseline plasma taurine level, consistent with previous reports. Ingested taurine is absorbed in the small intestine via its receptor (TAUT [taurine transporter]) (18) and is then distributed by active uptake to many organs against a concentration gradient (18,19).

Taurine is then conjugated in the liver to bile salts or excreted by the kidneys. The final outcome of taurine homeostasis is through fecal excretion after deconjugation by the bacterial flora or renal excretion as intact molecules (19,21–23). In this study at similar half-life in both groups, the urinary excretion rate of taurine was higher in diabetic subjects. Because the kidneys regulate the body taurine pool, a high-taurine diet induces hypertaurinuria and reduces renal tubular uptake (24), and the opposite happens on a low-taurine diet. At a comparable glomerular filtration rate but lower plasma taurine concentration at each hour of assessment, the filtered load of taurine in diabetic subjects is lower than that of control subjects. The higher taurine excretion rate suggests that renal tubular reabsorption is decreased in diabetes. The latter finding may be confounded to some extent by hyperglycemia in the diabetic group (209 ± 49 mg/dl) inducing osmotic diuresis or, alternatively, may theoretically involve a decrease in the activity of the brush-border taurine transport protein in the proximal tubule of the kidney.

In experimental diabetes, taurine supplementation may improve metabolic control (25), restore the endothelium-dependent vascular relaxation (26), improve insulin sensitivity, attenuate hypertension, prevent diabetic cardiomyopathy (27), reverse neuropathy (28), and reduce mortality (29). Such beneficial effects may be mediated through binding of taurine to the insulin receptor (4), decreasing glucose absorption (30), and/or directly modulating hepatic glucose metabolism (31). Human studies on taurine supplementation are thus far inconclusive (32,33).

This is the first study to demonstrate that, after a taurine load, diabetic patients waste taurine more extensively in urine than matched control subjects and probably have a lower rate of net intestinal absorption. The pathogenesis of the renal findings is most likely through decreased tubular reabsorption, whereas the gastrointestinal effect is likely through decreased intestinal transfer, as further supported by animal studies. It is tempting to postulate that diminution in the activity of the brush-border taurine transport protein in the proximal tubule and in the luminal cell membrane of the small intestine can account for both the enhanced renal excretion and the impaired intestinal taurine absorption. Further studies are required to test this postulate and to assess other parameters such as fecal excretion, liver utilization, and tissue distribution.

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References

1. Franconi F, Bennardini F, Mattana A, Miceli M, Ciuti M, Mian M, Gironi A, Anichini R, Seghieri G: Plasma and platelet taurine are reduced in subjects with insulin-dependent diabetes mellitus: effects of taurine supplementation. *Am J Clin Nutr* 61:1115–1119, 1995
2. De Luca G, Calpona PR, Caponetti A, Romano G, Di Benedetto A, Cucinotta D, Di Giorgio RM: Taurine and osmoregulation: platelet taurine content, uptake, and release in type 2 diabetic patients. *Metabolism* 50:60–64, 2001
3. Goodman HO, Shihabi ZK: Supplemental taurine in diabetic rats: effects on plasma glucose and triglycerides. *Biochem Med Metab Biol* 43:1–9, 1990
4. Hansen SH: The role of taurine in diabetes and the development of diabetic complications. *Diabete Metab Res Rev* 17:330–346, 2001
5. Pop-Busui R, Sullivan KA, Van Huysen C, Bayer L, Cao X, Towns R, Stevens MJ: Depletion of taurine in experimental diabetic neuropathy: implications for nerve metabolic, vascular, and functional deficits. *Exp Neurol* 168:259–272, 2001
6. Ha H, Yu MR, Kim KH: Melatonin and taurine reduce early glomerulopathy in diabetic rats. *Free Radic Biol Med* 26:944–950, 1999
7. Vilchis C, Salceda R: Effect of diabetes on levels and uptake of putative amino acid neurotransmitters in rat retina and retinal pigment epithelium. *Neurochem Res* 21: 1167–1171, 1996
8. Ziyadeh FN, Feldman GM, Booz GW, Kleinzeller A: Taurine and cell volume maintenance in the shark rectal gland: cellular fluxes and kinetics. *Biochim Biophys Acta* 943:43–52, 1988
9. Milei J, Ferreira R, Llesuy S, Forcada P, Covarrubias J, Boveris A: Reduction of reperfusion injury with preoperative rapid intravenous infusion of taurine during myocardial revascularization. *Am Heart J* 123:339–345, 1992
10. Paauw JD, Davis AT: Taurine supplementation at three different dosages and its effect on trauma patients. *Am J Clin Nutr* 60:203–206, 1994
11. Martensson J, Hermansson G: Sulfur amino acid metabolism in juvenile-onset nonketotic and ketotic diabetic patients. *Metabolism* 33:425–428, 1984
12. Vinton NE, Laidlaw SA, Ament ME, Kopple JD: Taurine concentrations in plasma, blood cells, and urine of children undergoing long-term total parenteral nutrition. *Pediatr Res* 21:399–403, 1987
13. Hayes KC, Carey RE, Schmidt SY: Retinal degeneration associated with taurine deficiency in the cat. *Science* 188:949–951, 1975
14. Geggel HS, Ament ME, Heckenlively JR, Martin DA, Kopple JD: Nutritional requirement for taurine in patients receiving long-term parenteral nutrition. *N Engl J Med* 312:142–146, 1985
15. Lee YM, Choi MJ, Chang KJ: The effect of dietary taurine supplementation on plasma and urine free amino acid concentrations in diabetic rats. *Adv Exp Med Biol* 526:75–82, 2003
16. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D, Modification of Diet in Renal Disease Study Group: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 130: 461–470, 1999
17. Godel H, Graser T, Foldi P, Pfaender P, Furst P: Measurement of free amino acids in human biological fluids by high-performance liquid chromatography. *J Chromatogr* 297:49–61, 1984
18. Han X, Patters AB, Jones DP, Zelikovic I, Chesney RW: The taurine transporter: mechanisms of regulation. *Acta Physiol (Oxf)* 187:61–73, 2006
19. Ruessheim CM: Taurine: a compilation [Internet], 2000. Available from http://www.serve.com/BatonRouge/taurine_chmr.htm. Accessed March 2007
20. Shimizu M, Satsu H: Physiological significance of taurine and the taurine transporter in intestinal epithelial cells. *Amino Acids* 19:605–614, 2000
21. Hickman MA, Morris JG, Rogers QR: Intestinal taurine and the enterohepatic circulation of taurocholic acid in the cat. *Adv Exp Med Biol* 315:45–54, 1992
22. Hepner GW, Sturman JA, Hofmann AF, Thomas PJ: Metabolism of steroid and amino acid moieties of conjugated bile acids in man. 3. Cholyltaurine (taurocholic acid). *J Clin Invest* 52:433–440, 1973
23. Rakotoambinina B, Marks L, Badran AM, Igliki F, Thuillier F, Crenn P, Messing B, Darmaun D: Taurine kinetics assessed using [1,2–13C2]taurine in healthy adult humans. *Am J Physiol Endocrinol Metab* 287:E255–E262, 2004
24. Chesney RW, Zelikovic I, Friedman AL, Dabbagh S, Lippincott S, Gusowski N, Stjeskal-Lorenz E: Renal taurine transport: recent developments. *Adv Exp Med Biol* 217:49–59, 1987
25. You JS, Chang KJ: Effects of taurine supplementation on lipid peroxidation, blood glucose and blood lipid metabolism in streptozotocin-induced diabetic rats. *Adv Exp Med Biol* 442:163–168, 1998
26. Kamata K, Sugiura M, Kojima S, Kasuya Y: Restoration of endothelium-dependent relaxation in both hypercholesterolemia and diabetes by chronic taurine. *Eur J Pharmacol* 303:47–53, 1996
27. Li C, Cao L, Zeng Q, Liu X, Zhang Y, Dai T, Hu D, Huang K, Wang Y, Wang X, Li D, Chen Z, Zhang J, Li Y, Sharma R: Taurine may prevent diabetic rats from developing cardiomyopathy also by downregulating angiotensin II type 2 receptor expression. *Cardiovasc Drugs Ther* 19: 105–112, 2005
28. Li F, Abatan OI, Kim H, Burnett D, Larkin D, Obrosova IG, Stevens MJ: Taurine reverses neurological and neurovascular deficits in Zucker diabetic fatty rats. *Neurobiol Dis* 22:669–676, 2006
29. Di Leo MA, Santini SA, Silveri NG, Giardina B, Franconi F, Ghirlanda G: Long-term taurine supplementation reduces mortality rate in streptozotocin-induced diabetic rats. *Amino Acids* 27:187–191, 2004
30. Kim HW, Lee AJ, You S, Park T, Lee DH: Characterization of taurine as inhibitor of sodium glucose transporter. *Adv Exp Med Biol* 583:137–145, 2006
31. Franconi F, Di Leo MA, Bennardini F, Ghirlanda G: Is taurine beneficial in reducing risk factors for diabetes mellitus? *Neurochem Res* 29:143–150, 2004
32. Chauncey KB, Tenner TE Jr, Lombardini JB, Jones BG, Brooks ML, Warner RD, Davis RL, Ragain RM: The effect of taurine supplementation on patients with type 2 diabetes mellitus. *Adv Exp Med Biol* 526: 91–96, 2003
33. Brons C, Spohr C, Storgaard H, Dyerberg J, Vaag A: Effect of taurine treatment on insulin secretion and action, and on serum lipid in overweight men with a genetic predisposition for type II diabetes mellitus. *Eur J Clin Nutr* 58:1239–1247, 2004