

Absence of Sexual Dimorphism in the Symptomatic Responses to Hypoglycemia in Adults With and Without Type 1 Diabetes

JACQUELINE GEDDES, MRCP(UK)¹
 RODERICK E. WARREN, MRCP(UK)¹
 ANDREW J. SOMMERFIELD, MRCP(UK)¹
 VINCENT McAULAY, MD¹

MARK W.J. STRACHAN, MD¹
 KATE V. ALLEN, MRCP(UK)¹
 IAN J. DEARY, PHD²
 BRIAN M. FRIER, MD¹

Insulin-induced hypoglycemia provokes counterregulatory hormonal responses, the magnitude of which is lower in women with and without type 1 diabetes than in their male counterparts (1–5), although the glycemic thresholds at which these responses are triggered are similar in both sexes (6,7). In nondiabetic adults and people with type 1 diabetes, antecedent hypoglycemia and exercise had less effect on the magnitude of the counterregulatory hormonal responses in women than in men (8,9). It has therefore been suggested that exposure to recurrent episodes of hypoglycemia could abolish the difference in counterregulatory responses between the sexes, explaining the absence of a difference in the overall frequency of severe hypoglycemia observed in the Diabetes Control and Complications Trial (10).

Detection of the symptoms of hypoglycemia alerts the person with diabetes to the decline in blood glucose, prompting corrective action to be taken before the effects of neuroglycopenia become disabling. Symptoms of hypoglycemia are generated as part of the established hierarchy of responses (11,12) and are idiosyncratic and age specific (13). Sex differences have not been reported, but in small studies with few subjects, a putative difference may not be discernible (1,14). The most common hypoglycemia symptoms have been classified into subgroups

in physiological studies (15,16) and by statistical methodology (17–20) using factor analysis. The subgroups include autonomic symptoms, such as hunger, pounding heart, sweating, or shaking, arising from central autonomic neural activation via hypothalamic centers (21), predominantly of the sympathetic division; neuroglycopenic symptoms, such as drowsiness, confusion, odd behavior, speech difficulty, or incoordination, caused by the direct effect of glucose deprivation on the brain; and nonspecific symptoms, including headache and malaise. The symptoms of hypoglycemia can be measured using the Edinburgh Hypoglycemia Score (17–19). The symptoms of hypoglycemia are generated independently of the counterregulatory hormonal responses, although falling blood glucose triggers both. To ascertain whether sexual dimorphism occurs in the hypoglycemia symptomatic response, symptom scores were analyzed in 160 subjects in whom controlled hypoglycemia had been induced.

RESEARCH DESIGN AND METHODS

The Edinburgh Hypoglycemia Symptom Scores (19) of 160 adult subjects (age range 18–45 years) were obtained from eight separate studies, six of which have been published (22–27) and were performed in our laboratory. Hypoglycemia was induced in an

identical manner in all studies using a modified hyperinsulinemic glucose clamp technique, with a duration of hypoglycemia of 1 h. All studies achieved a blood glucose nadir of 2.5 mmol/l, with one exception in which the target was 2.6 mmol/l (22). The symptom score recorded at the midpoint of the induced hypoglycemia ($t = 30$ min) in all studies was analyzed. The diabetic subjects ($n = 72$, 31 women) all had type 1 diabetes for at least 1 year (median 6.9 years, range 1.1–30.9), had reasonable glycemic control (mean \pm SD, HbA_{1c} [A1C] $7.9 \pm 2.0\%$), and had normal awareness of hypoglycemia, evaluated using a validated seven-point scale (28) (Table 1). The nondiabetic subjects ($n = 88$, 45 women) were taking no medication other than the contraceptive pill. All adult female participants were of childbearing age, with 42 (55%) using the contraceptive pill; none were postmenopausal (Table 1).

A general linear model of assessment (repeated-measures ANOVA) was used, with order of session (euglycemia-hypoglycemia or hypoglycemia-euglycemia), sex (male or female), and type of subject (nondiabetic volunteer or type 1 diabetic subjects) as between-subject factors and condition (euglycemia or hypoglycemia) as a within-subject factor (repeated measure). All analyses were performed using SPSS version 12.0 for Windows.

RESULTS—No significant order effects were observed. Scores for the autonomic, neuroglycopenic, and nonspecific symptoms were all significantly higher during hypoglycemia than euglycemia ($P < 0.0005$). No statistical differences existed in age, duration of diabetes, or A1C between the sexes in either cohort. The nondiabetic subjects had higher autonomic symptom scores than the type 1 diabetic subjects, and the difference was statistically significant ($P = 0.011$, $F = 0.176$). No significant relationship was demonstrated between diabetes duration and autonomic symptom scores in people

From the ¹Department of Diabetes, The Royal Infirmary of Edinburgh, Edinburgh, U.K., and the ²Department of Psychology, University of Edinburgh, Edinburgh, U.K.

Address correspondence and reprint requests to Professor Brian M. Frier, Consultant Physician and Honorary Professor of Diabetes, Department of Diabetes, The Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, EH16 4SA, U.K. E-mail: brian.frier@luht.scot.nhs.uk.

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

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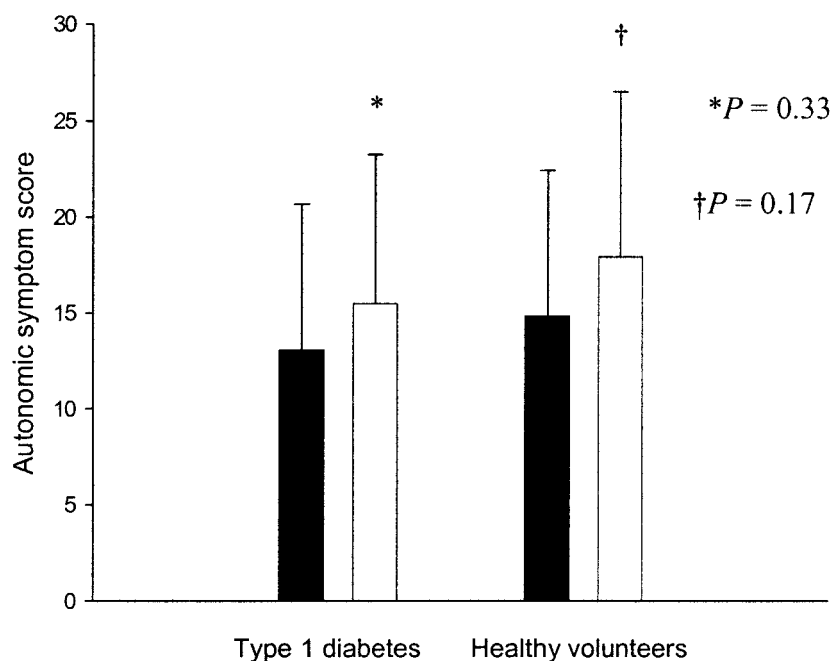


Figure 1—Differences in autonomic symptom scores using the Edinburgh Hypoglycemia Score (19) in people with type 1 diabetes compared with nondiabetic healthy volunteers. ■, men; □, women.

with type 1 diabetes ($r = -0.02$, $P = 0.870$). No differences were observed in the autonomic symptom scores between sexes in either cohort ($P = 0.196$, $F = 1.683$; type 1 diabetes $P = 0.33$, healthy volunteers $P = 0.17$) (Fig. 1). No statistical difference in neuroglycopenic symptom scores was found between the nondiabetic and type 1 diabetic subjects, nor was any effect of sex evident).

CONCLUSIONS— Although sexual dimorphism in counterregulatory responses to hypoglycemia has been demonstrated in several studies (1–5), in the present study, no sex differences were observed in either the autonomic or the neuroglycopenic symptom scores during hypoglycemia, regardless of whether the

subjects had type 1 diabetes. The symptoms of hypoglycemia are generated independently of, and at a lower blood glucose than, counterregulatory hormonal secretion (11,12). Autonomic symptoms arise via sympathetic activation, which provokes neural stimulation of end organs (such as sweat glands). People with tetraplegia, who have a preganglionic sympatheticotomy secondary to cervical cord transection, have neither peripheral autonomic activation nor epinephrine secretion and in response to insulin-induced hypoglycemia do not experience autonomic symptoms (29,30). People who have undergone bilateral adrenalectomy or splanchnicectomy do not secrete epinephrine in response to hypoglycemia, but their autonomic nervous system is

otherwise intact, and they experience a normal autonomic symptomatic response (31,32). This demonstrates that the autonomic symptoms are generated by direct autonomic innervation. The rise in circulating plasma epinephrine following stimulation of the adrenal glands can augment the intensity of a few symptoms, such as “pounding heart” (33), but epinephrine secretion does not generate these symptoms (34). Sweating is a cholinergic sympathetic response (15). Neuroglycopenic symptoms are not generated through the influence of hormonal secretion.

Thus, while there is an apparent sexual dimorphism in the magnitude of counterregulatory hormonal responses to hypoglycemia in humans that is manifested by physiological differences in hemodynamic responses (2,7), this sex difference does not appear to be replicated in the symptomatic response, which is generated separately. This absence of sexual dimorphism in the symptomatology and perception of hypoglycemia may explain the lack of a demonstrable sex difference in the overall rate of severe hypoglycemia in the Diabetes Control and Complications Trial (10). In conclusion, the present study suggests that the symptoms of hypoglycemia do not differ between men and women with and without type 1 diabetes.

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Table 1—Baseline characteristics for diabetic and nondiabetic subjects

	Healthy volunteers			Type 1 diabetic subjects		
	Men	Women	P	Men	Women	P
n	45	43	—	31	40	—
Age (years)	30.49 ± 6.67	28.84 ± 5.19	0.20	28.90 ± 6.21	27.45 ± 6.57	0.34
Duration of diabetes (years)	—	—	—	6.75 ± 5.64	8.56 ± 6.49	0.22
A1C (%)	—	—	—	7.99 ± 1.03	7.53 ± 0.84	0.07
Autonomic symptom scores	17.93 ± 8.58	15.49 ± 7.77	0.17	13.07 ± 7.62	14.84 ± 7.59	0.33
Neuroglycopenic symptom scores	15.12 ± 8.88	13.47 ± 8.80	0.38	13.66 ± 6.97	14.58 ± 7.69	0.60
Nonspecific symptom scores	4.72 ± 4.07	3.98 ± 3.22	0.34	4.95 ± 3.57	5.81 ± 4.26	0.37

Mean ± SD levels for autonomic, neuroglycopenic, and nonspecific symptom scores during experimental hypoglycemia. No significant differences were present between men and women with type 1 diabetes for age, duration of diabetes, or A1C.

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