Diabetes During Diarrhea-Associated Hemolytic Uremic Syndrome

A systematic review and meta-analysis

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OBJECTIVE — To quantify the incidence of diabetes during the acute phase of diarrhea-associated hemolytic uremic syndrome (D+HUS) and to identify features associated with its development.

RESEARCH DESIGN AND METHODS — A systematic review and meta-analysis of articles assessing diabetes during D+HUS was conducted. Relevant citations were identified from Medline, Embase, and Institute for Scientific Information Citation Index databases. Bibliographies of relevant articles were hand searched. All articles were independently reviewed for inclusion and data abstraction by two authors.

RESULTS — Twenty-one studies from six countries were included. Only 2 studies reported a standard definition of diabetes; 14 defined diabetes as hyperglycemia requiring insulin. The incidence of diabetes during the acute phase of D+HUS could be quantified in a subset of 1,139 children from 13 studies (1966–1998, age 0.2–16 years) and ranged from 0 to 15%, with a pooled incidence of 3.2% (95% CI 1.3–5.1, random-effects model, significant heterogeneity among studies, $P = 0.007$). Children who developed diabetes were more likely to have severe disease (e.g., presence of coma or seizures, need for dialysis) and had higher mortality than those without diabetes. Twenty-three percent of those who developed diabetes acutely died, and 38% of survivors required long-term insulin (median follow-up 12 months). Recurrence of diabetes was possible up to 60 months after initial recovery.

CONCLUSIONS — Children with D+HUS should be observed for diabetes during their acute illness. Consideration should be given to long-term screening of D+HUS survivors for diabetes.

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Hemolytic uremic syndrome (HUS) is characterized by acute hemolytic anemia, thrombocytopenia, and renal failure (1). The incidence of HUS is estimated at 1 per 50,000 person-years for children <18 years of age (2). Over 90% of childhood cases are associated with diarrhea and gastroenteritis due to Shiga toxin–producing *Escherichia coli* O157:H7 (3). Also known as "typical" or "primary" HUS, diarrhea-associated HUS (D+HUS) causes toxin-mediated endothelial cell damage, resulting in thrombotic microangiopathy and intraluminal thrombosis of small vessels, with subsequent tissue ischemia and necrosis (4). Although renal and central nervous system involvement predominate, the pancreas can be affected, causing acute diabetes. Autopsy studies have demonstrated thrombosis of vessels supplying the islets of Langerhans with preservation of the exocrine pancreas (5,6). Although renal complications of HUS have received much attention (7), little is known about the incidence and management of diabetes during D+HUS. Using techniques described by Stroup et al. (8), this systematic review was conducted to better understand diabetes associated with D+HUS.

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Abbreviations: D+HUS, diarrhea-associated hemolytic uremic syndrome; HUS, hemolytic uremic syndrome.

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

RESEARCH DESIGN AND METHODS

Research questions

The primary research questions were as follows. *1*) What is the incidence of diabetes during acute D+HUS? *2*) Is diabetes during acute D+HUS associated with more severe D+HUS, as defined by the presence of coma or seizures, requirement for dialysis, or death? and *3*) What is the long-term prognosis of those who develop diabetes during acute D+HUS? Specifically, what proportion of children recover, have permanent diabetes, and relapse after initial recovery?

Finding relevant studies

All language case series, cohort studies, and randomized trials that described patients with D+HUS (idiopathic, diarrhea, or *E. coli* O157:H7 associated) and examined patients for hyperglycemia or diabetes were included. Two reviewers independently evaluated eligibility of all studies. A third reviewer resolved disagreements.

Citations were retrieved from Medline, Embase, and the Institute for Scientific Information from 1966 to 28 February 2005. The search strategy was pilot tested and modified with known relevant articles in an iterative process and included the terms hemolytic uremic syndrome, thrombotic thrombocytopenic

Table 1—*Methodological assessment of included articles*

Criterion	Number of cohort studies meeting criterion (n = 13)	Number of case reports meeting criterion (n = 8)
Was the study prospective?	2 (15)	NA
Was the study sample representative of the institution's population of D+HUS patients? (i.e., Were all patients with D+HUS within a specified time period included, or was a random sample of these patients included?)	13 (100)	NA
Were clear diagnostic criteria for HUS specified?	5 (38)	6 (75)
Were there clear methods for confirming that the HUS was primary?	11 (85)	8 (100)
Were baseline characteristics (e.g., age, sex, diarrhea, etc.) described for all patients?	8 (62)	6 (75)
Were administered treatments (e.g., dialysis, insulin) described for all patients?	4 (31)	6 (75)
Was a clear definition for diabetes or glucose intolerance specified?	9 (69)	7 (88)
Were all patients with D+HUS tested for diabetes or glucose intolerance?	0 (0)	NA
Were pancreatic autoantibodies measured in all those who developed diabetes?	1 (8)	8 (100)
Were long-term outcomes for patients with diabetes reported?	8 (62)	4 (50)
Was the total mortality reported?	9 (69)	8 (100)
Was the incidence of end-stage renal disease reported?	6 (46)	3 (38)
Was the incidence of long-term central nervous system sequelae reported?	5 (38)	0 (0)
Was the mean follow-up >6 months?	8 (62)	4 (50)
If yes, was the loss to follow-up <10%?	4 (31)	NA

Data are *n* (%). NA, not applicable.

purpura, diabetes mellitus, glucose intolerance, hyperglycemia, glucose, insulin, pancreas, pancreatic diseases, pancreatic necrosis, extrarenal, and nonrenal. Reference lists of included articles were hand searched, and articles citing included articles in the Institute for Scientific Information index were reviewed.

Data abstraction

To summarize the characteristics of the included studies, two investigators developed a methodological assessment tool based on criteria of internal and external validity, as previously described for studies of prognosis (9) (Table 1). Using standardized forms, two investigators independently rated each article on these criteria, as well as abstracted data on study, patient, and outcome characteristics. Disagreements were resolved by consensus.

Statistical analysis

The mean age, proportion of patients with various characteristics, and long-term outcomes are described for all children with diabetes and D+HUS. CIs for single proportions were obtained using the Wilson score method (10).

Those studies that described incidence of diabetes were included in the meta-analysis. Data from these studies are presented in tabular form. χ^2 Tests were used to assess between-study heterogeneity. The I^2 statistic, which describes the percentage of total variation across studies due to heterogeneity rather than chance, was calculated (11). Due to significant heterogeneity among studies, an approach based on generalized estimating equations, which accounted for within- and between-study variability (random-effects modeling), was used to derive pooled estimates and their variances (12). Overall, each study contributed a weight of between 3.7 and 11.7%. Estimates were computed using R2.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

For studies included in the meta-analysis, the odds of having diabetes with severe D+HUS (i.e., central nervous system symptoms, need for dialysis) was compared with the odds of having diabetes without severe D+HUS; the odds of dying with diabetes was compared with the odds of dying without diabetes. As between-study heterogeneity was not significant for the individual odds ratios (ORs), the Mantel-Haenszel method was used to calculate fixed-effects pooled ORs for each of these three factors (13). All analyses were performed with complete data, and P values <0.05 were considered statistically significant.

RESULTS

Finding and selecting studies

Three hundred eighty-four citations in six languages were screened from all sources, and 93 full-text articles were retrieved for detailed review. Twenty-one articles met inclusion criteria (5,14–33). Seven articles seemed to describe patients already included in this review (34–40). Any additional data from these studies were combined with included studies. The agreement beyond chance between two independent reviewers for article inclusion was good (κ = 0.74).

Methodological assessment of included articles

Interrater reliability in the assessment of methodological criteria was good (overall κ = 0.65 [range 0.39–1.0]) (Table 1). No study met all criteria. Cohort studies met 3–11 of 15 criteria, while case series met 3–9 of 11 criteria.

Definition of diabetes

Patients were classified as having diabetes based on the primary author's assessment or if it was evident that the patient was treated with insulin. In one study (23), it was unclear whether the patients were treated with insulin, as the article just stated diabetes was present. Three stated "insulin-dependent diabetes" was present (5,21,26), and one stated "diabetic ketoacidosis" was present (22). Of the remaining 16 studies, 15 referred to patients with hyperglycemia with or without ketoacidosis treated with insulin (14–20,24, 27–33); the glucose cut points defining hyperglycemia were specified in only one study (glucose >360 mg/dl [20 mmol/l] on 3 consecutive days) (24). One study defined diabetes according to standard international criteria (25).

Table 2—*Summary of cohort studies* reporting diabetes during acute D+HUS, 1966 to present*

Author (ref.)	Location of study	Year of HUS	Outbreak or sporadic	Mean or median follow-up (range) (months)	HUS (*n*)
Andreoli and Bergstein (14,34)†	Indiana	~1980	Sporadic	<3	20
Bernard et al. (15)	Paris, France	1985–1992	Sporadic	<3	37
Brandt et al. (16)	Seattle, WA	1996	Sporadic	<3	17
Brandt and colleauges (17,38,40)†	Seattle, WA	1992–1993	Outbreak	27	37
Crawford et al. (18)	Camperdown, Australia	1966–1989	Sporadic	12	80
de la Hunt et al. (19)	Newcastle, U.K.	1982–1989	Sporadic	<3	78
Elliott et al. (20) and Henning et al. (39)†	Australian subcontinent	1994–1998	Both	12	84
Guyot et al. (21)	Nantes, France	1980–1985	Sporadic	24	37
Hughes et al. (22)	Glasgow, Scotland	1972–1988	Sporadic	47.4 (3–170)	79
Milford et al. (23)	British Isles, U.K.	1985–1988	Sporadic	13 (4–40)	273
Robitaille et al. (24)	Montreal, Canada	1976–1996	Sporadic	<3	241
Robson and colleagues (25,35–37)†	Calgary, Canada	1980–1992	Sporadic	<3	121
Taylor et al. (26)	West Midlands, U.K.	1982–1983	Both	NR	35

*Studies in this table were included in the meta-analysis. †Multiple references indicate data from several studies describing same cohort were combined. ‡This study used 1995 World Health Organization criteria to define hyperglycemia. IDDM, as defined by original study authors. CNS, central nervous system; DKA, diabetic ketoacidosis; ESRD, end-stage renal disease requiring permanent renal replacement therapy; HRI, hyperglycemia requiring insulin; NR, not reported (see text for details).

Meta-analysis of diabetes incidence with D+HUS

Point estimates of the incidence of diabetes with D+HUS were reported in 13 of 21 studies (14–26); these were pooled using meta-analysis (Table 2). These 13 studies described 1,189 children aged 0.2–16 years, from five different countries, over the period 1966–1998. There were no adult studies meeting inclusion criteria. One study described an outbreak of D+HUS from meat contaminated with Shiga toxin–producing *E. coli* (17), 10 of 13 studies described sporadic D+HUS (14–16,18,19,21–25), and 2 studies described both outbreak and sporadic D+HUS (20,26). Follow-up was restricted to the acute phase of D+HUS (<3 months) in 6 of 13 studies (14–16,19,24,25) and to 12–48 months in 7 of 13 studies (17,18,20–23,26).

The incidence of diabetes in the individual studies ranged from 0 to 15% (Fig. 1). The variability among studies was larger than would be expected by chance (significant heterogeneity, $P = 0.007$), with $I^2 = 61\%$. Given the high between-study variability, the results pooled using the random-effects model should be interpreted with caution. The pooled estimate of diabetes was 3.2% (random-effects model, 95% CI 1.3–5.1%). We recalculated the pooled estimates after excluding studies that were outliers or qualitatively different. The pooled estimates were similar when studies that did not define diabetes (23) or had some patients with secondary HUS (21,22,24) were excluded (3.4% [95% CI 1.4–5.5] and 3.9% [1.5–6.2], respectively). Two small studies (14,17) had the highest point estimates (8.1 and 15%); the pooled estimate was 2.3% (1.1–3.4) when these two studies were excluded.

Disease severity and diabetes during acute D+HUS

The presence of diabetes was associated with more severe disease. Patients with central nervous system symptoms were more likely to develop diabetes than those without (OR 12.0 [95% CI 4.2–34.2], $P < 0.00001$, $n = 471$ patients in seven studies), as were patients who required acute dialysis versus those who did not (5.4 [1.6–18.4], $P = 0.008$, $n = 355$ patients in five studies). Patients with diabetes were also more likely to die than those without diabetes (15.0 [5.8–38.9], $P < 0.00001$, $n = 712$ patients in eight studies).

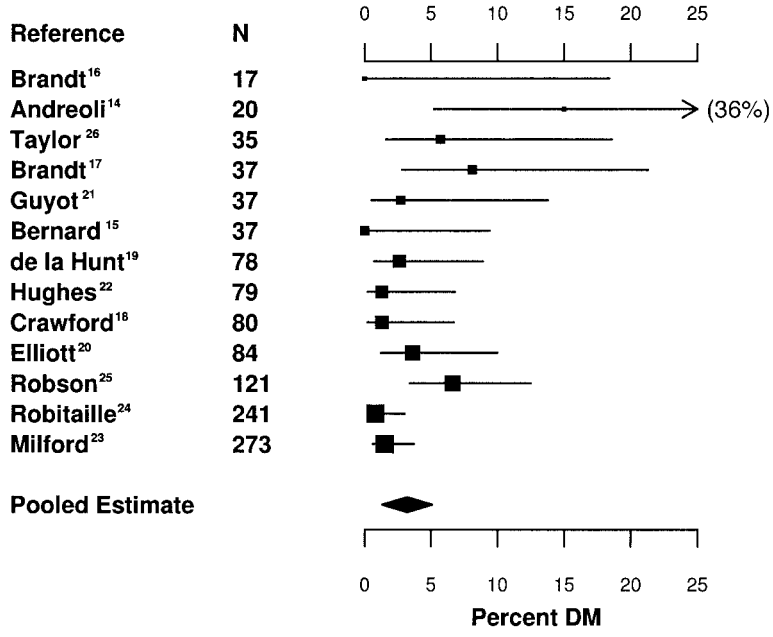

Figure 1—*Incidence of diabetes (DM) during acute D+HUS in 13 cohort studies. Point estimates for each study are presented with 95% CIs. The size of each square is proportional to the number of patients in each study. The random-effects pooled estimate was 3.2% (95% CI 1.3–5.1) (see text).*

Table 2—*Continued*

Male (%)	Mean or median age (range) (months)	Diarrhea (%)	E.coli O157: H7 (%)	CNS symptoms (%)	Acute dialysis (%)	Mortality (%)	Lost to follow-up (%)	Diabetes (%)	Definition of diabetes
NR	NR	NR	NR	NR	NR	NR	0	15.0	HRI
41	25	84	0	19	NR	NR	0	0.0	HRI
59	49.7	100	100	0	59	0.0	0	0.0	HRI
53	60	95	86	16	57	8.1	16.2	8.1	HRI
NR	NR	NR	NR	NR	NR	NR	0	1.3	HRI
42	NR	100	NR	10	9	1.3	0	2.6	HRI
NR	31 (18–99)	100	12	20	63	3.6	22.6	3.6	HRI
46	3	92	NR	32	59	8.1	5.4	2.7	IDDM
47	33 (2–164)	90	NR	41	75	11.4	16.5	1.3	DKA
47	56 (0–180)	100	21	19	58	5.1	7.7	1.5	NR
NR	NR	88	NR	NR	56	3.3	0	0.8	HRI
52	42 (1–192)	100	42	21	50	4.1	0	5.8	HRI‡
37	58 (8–168)	100	9	34	69	8.6	NR	5.7	IDDM

Features and long-term prognosis of children who develop diabetes with D+HUS

The 21 included studies described 49 children who developed diabetes during acute D+HUS (Table 3). All children except one developed diabetes within 14 days of presentation to hospital (mean 8 days [range 1–60]). Insulin was used in 86% of patients ($n = 44$), and ketoacidosis developed in 64% ($n = 11$). In at least one patient, hyperglycemia was noted before the initiation of peritoneal dialysis (18). Pancreatic autoantibodies, including islet cell, insulin, GAD, and insulinoma-associated protein 2 antibodies, were measured in five patients and found to be negative in all; methods used to measure these antibodies were not described (14,29–31,33). These five patients, as well as two additional subjects, were reported to have some measure of impaired insulin secretion (low endogenous insulin levels [14,25,28,31], low basal C-peptide levels [29], impaired response to Sustacal challenge [30], or abnormal first-phase insulin response to intravenous glucose [33]).

Long-term outcome was reported for 44 of 49 children. Of these 44, 23% died acutely (95% CI 13–37). In the 34 survivors, the mean follow-up was 32 months (range 0–180). Thirty-eight percent (95% CI 24–55) of survivors were left with persistent diabetes requiring insulin; 11 of 34 had persistent diabetes from the outset, while 2 of 34 redeveloped diabetes 3 and 60 months after initial apparent recovery. The remaining 21 children (62% [95% CI 45–76]) were reported to have complete recovery from diabetes, having required insulin for 19–120 days. However, follow-up was <12 months or not reported for 48% of these children.

CONCLUSIONS — Based on the available evidence, the incidence of diabetes (hyperglycemia requiring insulin) during acute D+HUS in children <16 years of age ranged from 0 to 15%, with pooled incidence estimated at 3.2% (95% CI 1.3–5.1). This is in contrast to the reported general population incidence of childhood type 1 diabetes of 0.013–0.040% (41–43). The development of diabetes was associated with severe disease, marked by central nervous system symptoms, the need for acute dialysis, and mortality. However, whether diabetes develops in the setting of milder disease is unknown, as all patients were not tested.

These findings would suggest frequent monitoring of blood glucose during acute D+HUS, especially for patients on peritoneal dialysis with glucose solutions.

Table 3—*Characteristics of 49 children with diabetes during acute D+HUS reported in the literature, 1966 to present*

Characteristic	Median or no. with characteristic (range)	Percent with characteristic
Age (years)	2.5 (1.5–9)	—
Female	15 of 24	63
Diarrhea	40 of 40	100
Bloody diarrhea	12 of 13	92
Ketoacidosis	7 of 11	64
CNS symptoms	21 of 25	84
Acute dialysis	31 of 31	100
Peritoneal dialysis	21 of 27	78
Diazoxide	3 of 19	16
Steroids	0 of 14	0
Insulin	38 of 44	86
Death	10 of 44	23
Follow-up (months)	12 (2–180)	—
Persistent diabetes requiring insulin*	11 of 34	32
Relapse after initial recovery*	2 of 34	6
Complete recovery*	21 of 34	62
ESRD*	4 of 19	21
Other renal sequelae*	6 of 13	46
Exocrine pancreatic disease†	7 of 20	35

*In survivors. †Defined as increased amylase or lipase, absent fecal chymotrypsin with increased fecal fat and pancreatic calcifications, and need for pancreatic enzyme replacement. CNS, central nervous system; ESRD, end-stage renal disease requiring permanent renal replacement therapy (see text for details).

Early aggressive treatment of hyperglycemia will not only prevent ketoacidosis but may improve acute outcomes, as has been shown in other critically ill patients (44,45).

Potential pathophysiology of diabetes during acute D+HUS

The pathophysiology of hyperglycemia during D+HUS is not known. Some have proposed that it is related to the initiation of peritoneal dialysis with glucose solutions or to the use of medications such as glucocorticoids or diazoxide. This is unlikely, as the hyperglycemic effects of diazoxide are transient (46); some patients never received glucocorticoids (18,19,25,26,28,30,31), diazoxide (18,19,25,26,29–31,33), or peritoneal dialysis (20,30); and one patient developed diabetes before peritoneal dialysis was instituted (18). It is possible that the children may have had "stress hyperglycemia" rather than true diabetes (47). However, stress hyperglycemia is usually transient (48), while here 38% of survivors required insulin at 12 months. Rather, the hyperglycemia may be due to insulin deficiency, as suggested by impaired insulin secretion in all eight patients who were tested (14,25,28–31,33).

The mechanism of insulin deficiency does not appear to be immune, as pancreatic autoantibodies were negative in all five patients studied (14,29–31,33). A viral etiology producing both diabetes and D+HUS is also unlikely, as viral studies were negative in one patient (31), viral particles were absent at autopsy in two patients (27,28), and the pathogenesis of D+HUS is not viral but related to Shiga toxin–producing bacteria (3). Given that absolute insulin deficiency is not silent, it is unlikely that diabetes predated D+HUS in all patients. The mechanism may instead be the direct result of HUS with thrombotic microangiopathy of the pancreatic microvasculature. Pancreatic necrosis was present in four of five children with diabetes who had autopsies (25,27,28); two of these children demonstrated extensive thrombosis of pancreatic arterides (25,28). That several patients had concomitant exocrine pancreatic dysfunction also suggests a vascular mechanism.

The reasons for predilection of the pancreas to toxin-mediated damage are unclear. Gb3 receptors, associated with toxin binding in the kidney (49), do exist in the pancreas, although not in high density (50). During acute D+HUS, these receptors may be upregulated, and islet cells may be more susceptible to hypoxic ischemic injury due to decreased ability to clear free radicals (51). There are likely other factors involved in the pathophysiology, as one patient with diabetes was described as having no detectable pancreatic injury at autopsy (14).

Long-term outcomes

Of children who developed diabetes during D+HUS and survived, over one-third had permanent diabetes requiring insulin 6 months to 15 years after the acute phase, whereas approximately two-thirds were reported to recover. Given that relapse can occur up to 5 years after the acute illness (32) and that almost 50% of recovering children were not followed for >1 year, the rate of permanent diabetes may in fact be higher than reported.

The mechanism of relapse may be continued loss of islet cells, or alternatively, decreased islet reserve in the face of a predisposition to type 2 diabetes. If this is the case, then even those who were not identified to have hyperglycemia during the acute phase of D+HUS may be at long-term risk of diabetes due to subclinical islet cell injury. Further studies are needed to determine the long-term risk of diabetes in survivors of D+HUS. Until then, consideration should be given to screening all survivors of D+HUS for diabetes with an oral glucose tolerance test at least 1 and 2 years' postillness.

Limitations of this review

The quality of a review is dependent on the quality of the original studies. Although all included studies used a cohort representative of patients with D+HUS at their institutions, the majority were retrospective, few reported a specific definition for D+HUS or diabetes, and long-term follow-up was variable. We only included articles mentioning diabetes, predisposing to potential selection of positive studies and overestimation of the true incidence. To ascertain the impact of such a publication bias, we determined that at least 90 studies, with 50 patients per study, would have to report no cases of diabetes in order to change the pooled incidence from 3.2 to <0.5%. Alternatively, this review may have underestimated the true incidence of diabetes, given that diabetes was not systematically assessed in any of the 13 studies.

Finally, it could be argued that a meta-analysis should not have been performed due to the substantial heterogeneity among studies, potentially resulting in an erroneous estimate of the true incidence of diabetes with D+HUS. The random-effects pooled estimate represents an approximation of the mean incidence, accounting for the variable precisions of the individual estimates of incidence and their pattern of variation. The precision of the pooled estimate takes into account the uncertainty in the estimates from the included studies, as well as the additional between-study variation observed. In keeping with this point, the pooled estimates calculated after excluding outliers fell within the 95% CI of the pooled estimate calculated using all included studies. Thus, the overall pooled estimate with 95% CIs allows us to succinctly summarize existing evidence. Ideally, we would have liked to perform metaregression to explore reasons for heterogeneity but were limited by inadequate statistical power. Potential reasons for the variability include differences in surveillance for diabetes (given that none of the included studies' main purpose was to evaluate incidence of diabetes) and differing severity of D+HUS.

Despite its limitations, this review summarizes the best available evidence on the important but infrequently recognized complication of diabetes associated with D+HUS and highlights the need for further research.

Diabetes is an important complication of D+HUS. Early identification and aggressive treatment of hyperglycemia during D+HUS may improve outcomes acutely. Future studies that prospectively evaluate the incidence of this complication both during the acute phase of D+HUS and after long-term follow-up are needed. Meanwhile, children who present with D+HUS should have aggressive surveillance and treatment of hyperglycemia. Consideration should also be given to long-term screening of all survivors of D+HUS for diabetes.

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