Insulin & C-Peptide Levels in Sulfonylurea-Induced Hypoglycemia: A Systematic Review

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ABSTRACT

Objectives: We will describe insulin and C-peptide levels observed in sulfonylurea-induced hypoglycemia and determine whether these levels differed if obtained before or after hypoglycemic therapy.

Methods: We performed a systematic review of the English literature to identify Medline articles containing “sets” (glucose < 60 mg/dL with insulin and C-peptide levels). These “sets” were categorized as being obtained BEFORE, AFTER, or UNKNOWN with respect to hypoglycemic therapy.

Results: 22 articles, 76 patients, and 97 “sets” were included. Mean glucose (mg/dL), insulin (μ IU/mL), and C-peptide (ng/mL) for all “sets” were 28.6 ($\pm$ 12.6; 26.1 to 31.2), 54.4 ($\pm$ 126.3; 28.3 to 80.5), 7.2 ($\pm$ 6.2; 5.9 to 8.5).

- The BEFORE measures were 24.3 ($\pm$ 7.3; 18.7 to 30.0), 36.6 ($\pm$ 26.2; 16.5 to 56.7), 5.4 ($\pm$ 4.6; 1.5 to 9.2).
- The AFTER measures were 33.1 ($\pm$ 9.8; 28.2 to 38.0), 126.7 ($\pm$ 278.1; 0 to 265.0), 10.3 ($\pm$ 10.5; 5.1 to 15.4).
- The UNKNOWN measures were 28.0 ($\pm$ 13.5; 24.7 to 31.3), 37.1 ($\pm$ 21.8; 31.7 to 42.5), 6.5 ($\pm$ 4.3; 5.4 to 7.6).
- Only one “set” (glucose 49 mg/dL) had insulin < 3.9 μ IU/mL and C-peptide < 1.4 ng/mL.

Conclusions: Insulin $\geq$ 3.9 μ IU/mL, C-peptide $\geq$ 1.4 ng/mL, and glucose < 49 mg/dL are consistent with sulfonylurea-induced hypoglycemia. BEFORE levels were lower, but they were consistent with sulfonylurea-induced hypoglycemia.

INTRODUCTION

Measurement of insulin and C-peptide levels may be employed in the investigation of an unknown cause of hypoglycemia. When insulin is secreted, equimolar amounts of insulin and

C-peptide (the peptide fragment cleaved from proinsulin) are released into circulation [1]. Increased endogenous insulin secretion is associated with increased C-peptide secretion, whereas insulin levels are high and C-peptide levels low with exogenous insulin administration [2,1]. Thus, serum insulin and C-peptide

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measurements may be exploited to differentiate between endogenous (insulinoma or medications that stimulate insulin secretion) and exogenous (insulin administration) insulin sources. Because sulfonylurea medications stimulate the secretion of insulin, and necessarily C-peptide, sulfonylurea-induced hypoglycemia may mimic hypoglycemia caused by an insulinoma [2–6].

Many medical texts and published algorithms tell us sulfonylurea-induced hypoglycemia yields insulin and C-peptide levels that are “high” or “elevated,” but the texts and published algorithms fail to provide details; such as the magnitude of the effect and the effect of hypoglycemic treatment on expected values [3,7–9]. Other authors provide suggested cut-off values for insulin and C-peptide without reference to values actually observed [4–6,10,11]. The primary purpose of this study was to describe the range of observed values for these variables in sulfonylurea-induced hypoglycemia and determine whether these variables differed if levels were obtained before or after hypoglycemic therapy was administered. We accomplished this aim by performing a systematic review of the English literature to identify cases that report measured serum glucose, insulin, and C-peptide levels associated with sulfonylurea-induced hypoglycemia.

METHODS

We performed a systematic review of the English literature from 1970 (C-peptide assay first described) through March 2004 [12]. The Ovid search engine (Ovid Technologies™, 2000–2003) was used to search the Medline database. Our Medical Subject Headings (MeSH) included the following: “hypoglycemia” AND “sulfonylurea compounds” OR “C-peptide” OR “insulin,” OR the text words “hypoglycemi\$” AND “sulfonylurea\$,” OR “C-peptide,” OR “insulin” for human exposures. A broad search was used because articles identified before the search was initiated had variable MeSH headings. But nearly all were categorized under “hypoglycemia” and/or “sulfonylurea compounds,” “C-peptide,” or “insulin.” The search criteria identified eleven thousand forty-two articles.

The primary author reviewed the titles and/or abstracts of all articles retrieved by the search. We included articles if hypoglycemia was due to sulfonylureas (confirmed by history or laboratory analysis) and if insulin and C-peptide levels were obtained at the time of documented hypoglycemia (blood glucose of <60 mg/dL (3.3 mmol/L) via bedside glucometer or venous sampling). We excluded articles if cases involved another hypoglycemic agent in addition to a sulfonylurea, as well as patients with hepatic or renal failure because insulin is mainly cleared by the liver and C-peptide by the kidney [9,13,14]. The primary author reviewed, in full, the articles that were unable to be included or excluded based on title or abstract.

All authors reviewed articles that met the inclusion criteria to confirm inclusion criteria and to classify patients into groups; (1) those who had “sets” obtained BEFORE hypoglycemic therapy, or (2) those who had “sets” AFTER hypoglycemic therapy. A “set” was defined as blood glucose (<60 mg/dL; 3.3 mmol/L), insulin, and C-peptide levels that were obtained at the same time.

Hypoglycemic therapy included administration of oral or intravenous glucose, glucagon, octreotide, or diazoxide. If it was unknown or unclear when hypoglycemic therapy was administered compared to when “sets” were obtained, they were included in a third UNKNOWN group. The algorithm for article acquisition is shown in *Figure 1*.

Levels reported in SI units were converted to conventional units using the following conversions; glucose: mmol/L = 0.0555 mg/dL; insulin: pmol/L = 6.945 μ IU/mL; nmol/L = 0.333 ng/mL.

Statistical Analysis: All analyses were done using GraphPad Instat version 3.06 (© 1992–2003 GraphPad Software, Inc.). For all articles meeting inclusion criteria, we performed descriptive statistics using all patients and all “sets” of levels. Additionally, descriptive statistics were performed on each group, (BEFORE therapy, AFTER therapy, and UNKNOWN). However, the articles did not provide the ages and sex of many patients. Additionally, several glucose, insulin, and C-peptide levels were reported as non-exact levels (such as values reported as < or >). These levels are not included in mean or median calculations, but they are included in range descriptions.

RESULTS

Through the Ovid search, we identified 19 articles that met the inclusion criteria. Reference lists of these 19 articles were hand-searched, and 4 additional articles meeting inclusion criteria were found: this yielded 23 articles. One article by Hussain et al. was excluded by group consensus because we were unable to determine which blood glucose measurements corresponded to reported insulin and C-peptide levels [16]. This yielded a total of 22 articles. The articles provided cases of 76 patients with 97 “sets” of levels that met inclusion criteria. All authors agreed on the classification of each case into the BEFORE, AFTER or UNKNOWN groups. Information for all included articles and cases is shown in *Table 1*.

A single C-peptide value (in the BEFORE therapy group) was reported as 12,100 ng/mL [20]. This level was 270 times higher than the next highest level, and considered erroneous by the authors. It was excluded from all calculations, but it is shown in *Table 1* for completeness. Finally, the article by Hampton et al. reported only mean glucose, insulin, and C-peptide levels of 3 patients. These levels are not included in descriptive statistics, but they are included in *Table 1*.

Table 2 shows the descriptive statistics of all articles that met inclusion criteria, and *Table 3* shows the statistics of the BEFORE, AFTER, and UNKNOWN groups. There is a wide variation in reported insulin and C-peptide levels in sulfonylurea-induced hypoglycemia. Although glucose, insulin, and C-peptide levels tended to be higher in the AFTER therapy group, there was wide overlap with results in the BEFORE therapy group.

DISCUSSION

Although the medical literature tells us insulin and C-peptide levels are elevated in sulfonylurea-induced hypoglycemia, there is a

Figure 1: Algorithm for article acquisition.

lack of information regarding levels that are actually observed [3,7,8]. However, we must first understand what actually constitutes an "elevated" insulin or C-peptide level in a hypoglycemic setting. It is not that levels are above normal fasting ranges, but they are relatively greater than what would be expected at a given blood glucose level. Normal fasting ranges do not apply to hypoglycemic patients [10,11]. As blood glucose levels fall around 45–60 mg/dL, insulin and C-peptide secretion nearly ceases [3,17,38]. Failure to

suppress insulin and C-peptide secretion, in the setting of hypoglycemia, indicates inappropriate endogenous insulin secretion.

We must also realize that laboratories utilize different assay techniques. Older polyclonal insulin assays cross-react with proinsulin and insulin precursors, yielding insulin levels higher than the newer monoclonal assays [4,9,14]. However, there is still a large amount of variability in the sensitivity and cross-reactivity of monoclonal assays, and universally accepted levels for the

Table 1: Articles meeting inclusion criteria

Article	Age/sex	Glucose (mg/dL)	Insulin (mIU/mL)	C-peptide (ng/mL)	Assay for Insulin and C-peptide	Sulfonylurea involved	Circumstances
<i>Articles with levels drawn BEFORE hypoglycemic therapy administered</i>							
Cryer[17]	64/M	36	15	1.5	Not provided	Glipizide	Accidentally dispensed instead of nifedipine
Krentz[18]	36/M	18	41	4.6	"Double-antibody RIAs"	Tolbutamide	Intentional ingestion in non-diabetic
Labib[19]	90/F	13	3.9	2.5	"competitive double antibody radio-immuno-assay"	Glyburide	Presumably inadvertent administration by husband
Ludman[20]	65/F	20	85.8	12100†	Not provided	Chlorpropamide	Accidentally dispensed instead of acetazolamide
Manning[21]	47/F	34	15.1	3.2	Not provided	Glyburide	Presumably intentional administration by husband
Owen[22]	0.5/M	23	61.6	16.2	Not provided	Specific sulfonylurea not identified, but sulfonylurea screen positive	Munchausen by proxy
Sener[23]	23/M	23	52.1	6.3	Not provided	Glipizide	Presumably inadvertent administration by girlfriend
Shima[15]	23/F	25	25	3.5	"plasma immuno-reactive insulin (IRI) and C-peptide immuno-reactivity (CPR)"	Tolbutamide	Not identified
	Comments: Levels were drawn during a 100 g oral glucose tolerance test after an overnight fast. The first "set" of levels was obtained at the same time glucose was given, and thus considered BEFORE therapy. Subsequent levels were obtained every 30 minutes thereafter and are included in the AFTER therapy group.						
Sledge[24]	72/M	27	30	5.4	Not provided	Acetohexamide	Accidentally dispensed instead of acetazolamide
<i>Articles with levels drawn AFTER hypoglycemic therapy administered</i>							
Christesen[25]	Newborn/M	23	49	6.2	"DELFA analysis (two-site two-step time resolved immuno-fluorometric assay)"	Tolbutamide	Mother taking tolbutamide for gestational diabetes when patient was born
	Comments: Born with hypoglycemia. Levels drawn 3 hours after birth while receiving glucose and octreotide infusions. Three additional complete "sets" were drawn, but excluded because glucose $\geq$ 60 mg/dL. Five incomplete "sets" excluded (no insulin level obtained).						
Earle[26]	82/F	33	72	44.1	Not provided	Glimepiride	Inadvertently administered by husband
	Comments: 10% dextrose infusion was held for "a short time." The patient then became symptomatic and these levels were drawn.						
Goudie[27]	56/M	52	50	11.4	Not provided	Glyburide	Adulterant in herbal medication
	Comments: Received 1 mg IM glucagon 1 hour before levels drawn, and was eating "sugary" foods when levels drawn.						
Shenfield[28]	85/F	43	14.6	5.4	Not provided	Chlorpropamide	Thought due to a dispensing error
	Comments: Receiving "continuous dextrose infusion" when levels drawn.						
Teale[29]	40/F	32	17.9	3.8	Not provided	Glyburide	Not identified
	Comments: Receiving "continuous intravenous glucose infusion" when levels drawn.						

Table 1: (Continued)

Article	Age/sex	Glucose (mg/dL)	Insulin (mIU/mL)	C-peptide (ng/mL)	Assay for Insulin and C-peptide	Sulfonylurea involved	Circumstances
Thoma[30]	50/M	22	42	4.3	Not provided	Glyburide	Intentional overdose
		29	49	8.2			
		27	1115	28.2			
		29	577	19.4			
		25	34	5.8			
		31	77	7.5			
	Comments: Received 25 g IV glucose boluses, glucose infusions (up to 10%), and oral glucose throughout course. Also, 5 mg IV glucagon given approximately 1 hour after 2nd set of levels drawn (approx 1.5 hours before 3rd set drawn). Glucagon was given for presumed beta-blocker ingestion.						
Shima[15]	See same patient in BEFORE therapy group above	45	34	6.3	See same article in BEFORE therapy group above	See same article in BEFORE therapy group above	See same article in BEFORE therapy group above
		30	28	5.9			
		50	40	7.7			
		35	30	6.6			
		45	20	5.9			
		20	16	4.4			
		25	15	3.4			
	Comments: These levels were drawn at 30 minute intervals after oral glucose administered.						
Articles where it is UNKNOWN when levels drawn with respect to hypoglycemic therapy							
Ahlquist[31]	70/F	40	102	10.2	Not provided	Tolazamide	Accidentally dispensed instead of tolmetin
	Comments: May have been receiving glucose infusion when levels drawn, but unclear.						
Hampton[32]	3 patients with unknown ages and sex.	29 ± 4*	24.9 ± 18*	2.9 ± 1.2*	Assumed to be radio-immuno-assay, as this was used to detect proinsulin, but does not specifically state	Chlorpropamide in 1 patient, Glyburide in 2 patients	Not provided
	Comments: Unknown if patients received therapy before levels drawn. Exact levels for each patient are unknown.						
Klonoff[33]	38/F	43	39.4	6.6	Not provided	Glyburide	Presumably confused with friends' furosemide tablets
	Comments: Unknown if patient received therapy before levels drawn.						
Kwong [34]	Exact ages unknown but ranged from >21 to >91 yrs. Sex unknown for all patients.	13	26.2	5.7	"Insulin was measured by an established in-house double-antibody competitive RIA . . ."	Glyburide in 7 patients	Ten cases of suspected or proven factitious drug ingestion: 1 with intentional ingestion, 1 'accidentally' took wife's medication, 2 with Munchausen's, 6 others suspected, but not proven.
	Comments: Levels are not included in article, but were provided by author. (Kwong PY, personal communication March 23, 2004)						
		27	16.3	2.2	"C-peptide was measured by a competitive RIA kit . . ."		

Table 1: (Continued)

Article	Age/sex	Glucose (mg/dL)	Insulin (mIU/mL)	C-peptide (ng/mL)	Assay for Insulin and C-peptide	Sulfonylurea involved	Circumstances
Kwong [34] <i>continued</i>		11	34.6	4.4		Glicazide in 3 patients	One mentally ill patient living in a residential home took another patient's medications, but intent unclear.
		31	72.6	5.7			
	Comments: Five additional complete "sets" were drawn, but excluded because glucose $\geq$ 60 mg/dL. Two incomplete "sets" excluded (no insulin level obtained).						
		27	11.4	1.8		Tolbutamide in 1 patient	Three elderly patients took their spouse's medication, but intent unclear.
		11	42.3	7.4			
		18	25.5	4.6		Glipizide in 1 patient	Ten patients had non-insulin dependent diabetes and were taking sulfonylurea medications at the time of hypoglycemia, but intent unclear.
		13	39.9	5.5			
		20	58.5	22		Chlorpropamide in 1 patient	Remainder not provided
		25	5.3	1.7			
		40	42	7.9		Others not provided	
		34	27.4	13.1			
		23	15.8	5.4			
		40	22.5	7.8			
		32	30	11.7			
		25	19.3	9.2			
		25	61.2	4.8			
		32	40.6	4.3			
		43	25.1	3.6			
		4	57.3	7.5			
		2	41.8	5.8			
		11	81.1	14.3			
		49	48.4	5.4			
		13	12.5	3.6			
		13	58.6	7			
		54	22.5	6			
		45	51.4	9.2			
		23	60	4			
		32	10.9	3.9			

Table 1: (Continued)

Article	Age/sex	Glucose (mg/dL)	Insulin (mIU/mL)	C-peptide (ng/mL)	Assay for Insulin and C-peptide	Sulfonylurea involved	Circumstances
Kwong [34] <i>continued</i>		51	84.4	6.5	These two “sets” are from the same patient.		
		58	79.3	6.3			
			34	40.2	>9.4*	These two “sets” are from the same patient.	
		34	73.2	>9.4*			
		31	4.3	1.4	These three “sets” are from the same patient.		
		43	14.5	2.8			
		49	<3.6*	<0.3*			
Marks[35]	85/M	25	5.3	1.7	Not provided	Glyburide in 1 patient	Intent not provided for cases. Four patients had diabetes (one patient on glyburide). Three patients took their wife’s medication. Two patients given wrong medication. One patient living with a diabetic. Remainder unclear.
	72/F	29	11.4	1.8			
	67/M	23	15.8	5.4		Others not identified	
	91/F	27	16.3	2.2			
	86/M	34	19.2	4.7			
	73/F	25	19.3	9.2			
	50/M	40	22.5	7.8			
	54/M	43	25.1	3.6			
	84/M	18	25.5	4.6			
	88/M	13	26.2	5.7			
	76/M	34	27.4	13.1			
	68/M	32	29.9	11.7			
	70/M	11	34.6	4.4			
	82/M	13	39.9	5.5			
	35/F	2	41.8	5.8			
	69/M	34	42	9.3			
	82/M	11	42.3	7.4			
	28/M	49	48.3	5.4			
	83/M	4	57.3	7.5			
	78/M	20	58.5	22			
	34/M	25	61.2	4.8			
	45/M	11	81.1	14.3			
	Comments: Unknown if patients received therapy before levels were drawn. Five additional patients listed in article, but 1 was excluded because of no accompanying insulin level, one excluded because of renal failure, and 3 excluded because of glucose ≥ 60 mg/dL.						
McDermott[36]	67/F	30	22	12	Not provided	Glyburide	Inadvertently dispensed instead of metoprolol
	Comments: Unknown if patient received therapy before levels were drawn.						
Ziegler[37]		34	25	2.6	Not provided	Glyburide	Intentional ingestion in non-diabetic
		37	16	1.6			
		19	40	2.4			
		36	26	2.8			

Table 1: (Continued)

Article	Age/sex	Glucose (mg/dL)	Insulin (mIU/mL)	C-peptide (ng/mL)	Assay for Insulin and C-peptide	Sulfonylurea involved	Circumstances
Ziegler[37]		37	29	4			
<i>continued</i>		43	40	6.4			
Comments: Unknown if patient received therapy before levels were drawn. Levels obtained on 6 separate admissions for hypoglycemia.							

* Non-exact levels, thus excluded from group comparisons.
† This C-peptide level was excluded from all calculations. See text.
‡ Glucose, insulin, and C-peptide levels reported as means only and excluded from calculations, but included in range descriptions.

Table 2: Descriptive statistics for all articles meeting inclusion criteria

	Number of reported values/ total patients described*	Range	Median	Mean (± SD)
Age (years)	41/76 (54%)	3 hours to >91	67	59 (25)
Sex	41/76 (54%); 63% male	NA	NA	NA
	Number of exact levels/ total levels reported†	Range	Median	Mean (± SD; 95% CI)
Glucose (mg/dL)	94/97 (97%)	Feb-58	29	28.6 (12.6; 26.1 to 31.2)
Insulin (μIU/mL)	93/97 (96%)	<3.6 to 1115	34	54.4 (126.3; 28.3 to 80.5)
C-peptide (ng/mL)	90/97 (93%)	<0.3 to 44.1‡	5.7‡	7.2 (6.2; 5.9 to 8.5)‡

NA = not applicable
* Seventy-six total patients are described in the articles, but age and sex were not reported for all patients.
† Ninety-seven total "sets" of levels are reported from 76 patients. Some levels were reported as non-exact levels (ie. reported as a mean or < or >) and are not included in mean or median calculations.
‡ A C-peptide level of 12,100 ng/mL was excluded from all calculations. See text.

diagnosis of hyperinsulinism in a hypoglycemic setting have not been established [14].

Author opinions and assay methods vary when it comes to suggested insulin and C-peptide cut-off levels needed to diagnose endogenous insulin hypersecretion. And it should be noted that these opinions fail to provide reference to actual values obtained in sulfonylurea-induced hypoglycemia. Service recommends using insulin levels $\geq 6 \mu\text{IU/mL}$ (41.7 pmol/L) using a double-antibody radioimmunoassay (or $\geq 3 \mu\text{IU/mL}$ (20.8 pmol/L) using a immunochemiluminometric assay and C-peptide levels of $\geq 0.6 \text{ ng/mL}$ (0.2 nmol/L) in the hypoglycemic setting (blood glucose $\leq 45 \text{ mg/dL}$ and patient symptomatic) [5,10,11]. Marks and Teale do not provide assay specifics, but Marks and Teale recommend a cut-off of $>5 \mu\text{IU/mL}$ (34.7 pmol/L) for insulin, $>0.9 \text{ ng/mL}$ (0.3 nmol/L) for C-peptide, and blood glucose $<54 \text{ mg/dL}$ [4].

We found a wide range of insulin and C-peptide levels in reported cases of sulfonylurea-induced hypoglycemia. If we apply the extremes of the above thresholds (insulin ≥ 6 or $\geq 3 \mu\text{IU/mL}$; C-peptide ≥ 0.9 or 0.6 ng/mL) to the values obtained in our study, 5 insulin levels fall below $6 \mu\text{IU/mL}$; 1 insulin level ($<3.6 \mu\text{IU/mL}$) was possibly below $3 \mu\text{IU/mL}$; and 1 C-peptide level was below both 0.9 and 0.6 ng/mL . Table 4 shows the details of these cases.

All "sets" with blood glucose $<49 \text{ mg/dL}$ (2.7 mmol/L) had insulin levels $\geq 3 \mu\text{IU/mL}$ (lowest $3.9 \mu\text{IU/mL}$; 1.3 nmol/L) and C-peptide levels $>0.9 \text{ ng/mL}$ and $\geq 0.6 \text{ ng/mL}$ (lowest 1.4 ng/mL ; 0.5 nmol/L). Only 4 "sets" with blood glucose $<49 \text{ mg/dL}$ had insulin levels $<6 \mu\text{IU/mL}$. These 4 "sets" are also shown in Table 4. In "sets" with glucose $\geq 49 \text{ mg/dL}$, insulin was $\geq 22.5 \mu\text{IU/mL}$ and C-peptide was $\geq 5.4 \text{ ng/mL}$ in all but 1 "set". Table 5 provides details of all "sets" with blood glucose $\geq 49 \text{ mg/dL}$. Because

Table 3: Comparison between BEFORE therapy, AFTER therapy, and UNKNOWN groups

	BEFORE therapy	AFTER therapy	UNKNOWN
Age (years)			
mean ($\pm$ SD; 95% CI)	49.7 $\pm$ 29.0	52.2 $\pm$ 31.2	65.4 $\pm$ 20.0
range	0.5–90	3 hrs–85	>21–>91
Number of patients with ages reported/ number of patients in group	8/9*	6/7*	26/61
Sex (% male)			
63		50	69
Number of patients with sex reported/ number of patients in group	8/9*	6/7*	26/61
Glucose (mg/dL)			
mean ($\pm$ SD; 95% CI)	24.3 ($\pm$ 7.3; 18.7 to 30.0)	33.1 ($\pm$ 9.8; 28.2 to 38.0)	28.0 ($\pm$ 13.5; 24.7 to 31.3)
median	23	30.5	29
range	13/36	20/52	2 to 58
Number of exact glucose measurements provided and used in calculations/ total number of glucose levels reported in group	9 of 9	18/18	67/70
Insulin (μIU/mL)			
mean ($\pm$ SD; 95% CI)	36.6 ($\pm$ 26.2; 16.5 to 56.7)	126.7 ($\pm$ 278.1; 0 to 265.0)	37.1 ($\pm$ 21.8; 31.7 to 42.5)
median	30	37	32.3
range	3.9–85.8	14.6–1115	<3.6–102
Number of exact insulin measurements provided and used in calculations / total number of insulin levels reported in group	9 of 9	18/18	66/67
C-peptide (ng/mL)[†]			
mean ($\pm$ SD; 95% CI)	5.4 ($\pm$ 4.6; 1.5 to 9.2)	10.3 ($\pm$ 10.5; 5.1 to 15.4)	6.5 ($\pm$ 4.3; 5.4 to 7.6)
median	4.1	6.3	5.6
range	1.5–16.2	3.4–44.1	<0.3–22
Number of exact C-peptide measurements provided and used in calculations/ total number of C-peptide levels reported in group	8/9 [†]	18/18	64/70

* Because the patient in the article by Shima et al. [15] had “sets” of levels included in both the BEFORE and AFTER therapy groups, this patient was excluded from age and sex calculations.

[†] A C-peptide level of 12,100 ng/mL was excluded from the BEFORE therapy group. See text.

hypoglycemic symptoms may begin at glucose levels of <60 mg/dL[10], clinicians initially faced with a hypoglycemic patient may not have the luxury of confirming that glucose is <49 mg/dL before levels are obtained.

Before blood is obtained to measure insulin and C-peptide levels or before the diagnosis of hyperinsulinemia is entertained, patients may receive hypoglycemic therapy. However, even patients in the AFTER therapy group had elevated insulin and C-peptide levels, and they overlapped with insulin and C-peptide levels in

the BEFORE therapy group. Most patients in the AFTER therapy group received intravenous glucose, but oral glucose, octreotide, and glucagon were also administered. Because there were only 7 patients in the AFTER therapy group, comparisons between these different hypoglycemic therapies was not possible. Interestingly, the patient in the article by Thoma had the 2 highest insulin levels, and the patient had the second highest C-peptide level of all the groups [30]. This may be related to the administration of 5 mg of intravenous glucagon [39,40]. Glucagon stimulates insulin

Table 4: Details for all “sets” with levels below threshold values of 6 μ IU/mL (41.7 pmol/L) for insulin or 0.9 ng/mL (0.3 nmol/L) for C-peptide

Article	Age/sex	Glucose (mg/dL)	Insulin (μ IU/mL)	C-peptide (ng/mL)	Sulfonylurea involved	Comments
<i>Levels drawn BEFORE hypoglycemic therapy administered</i>						
Labib[19]	90/F	13	3.9	2.5	Glyburide	
<i>Levels where it is UNKNOWN when levels drawn with respect to hypoglycemic therapy</i>						
Kwong[34]	Unknown	25	5.3	1.7	Unknown	These 2 “sets” are from the same patient
		31	4.3	1.4		
		49	<3.6	<0.3		
Marks[35]	85/F	25	5.3	1.7	Unknown	

Table 5: Details for all “sets” with glucose levels $\geq$ 49 mg/dl (2.7 mmol/l)

Article	Age/sex	Glucose (mg/dL)	Insulin (μ IU/mL)	C-peptide (ng/mL)	Sulfonylurea involved	Comments
<i>Levels drawn AFTER hypoglycemic therapy administered</i>						
Goudie[27]	56/M	52	50	11.4	Glyburide	
Shima[15]	23/F	50	40	7.7	Tolbutamide	
<i>Levels where it is UNKNOWN when levels drawn with respect to hypoglycemic therapy</i>						
Kwong[34]	Unknown	49	48.4	5.4	Unknown	These 2 “sets” are from the same patient
		54	22.5	6		
		51	84.4	6.5		
		58	79.3	6.3		
		49	<3.6	<0.3		This “set” is also in Table 4
Marks[35]	28/M	49	48.3	5.4	Unknown	

secretion, and intravenous glucagon administration may exaggerate insulin secretion in patients who are already hypersecreting insulin [39,42]. This same dramatic response was not seen in the other patient who received glucagon, and the response, perhaps, is related to a smaller dose or route of administration [27].

Some could argue that measuring insulin and C-peptide levels in hypoglycemia of uncertain cause is unnecessary when sulfonylurea screens are employed as part of the diagnostic work-up. However, not all sulfonylureas are detected by screens, and negative screens do not rule out sulfonylurea-induced hypoglycemia [21,26,30,36,43]. Additionally, quinine, non-sulfonylurea diabetic medications such as repaglinide, and nateglinide can produce hypoglycemia with elevated insulin and C-peptide levels, but these medications do not appear on sulfonylurea screens [43–45].

As with all article reviews there are limitations to this study. Our search was limited to Medline and articles written in English. The non-English literature may include other medications that would produce different results. However, our review

included all sulfonylurea medications available in the US, all but one of those available in Canada (gliclazide), and almost half of those available in other countries [46]. A second limitation includes the values reported in the articles and that insulin and C-peptide levels were measured in several laboratories using different assays. It is possible that there were unreported insulin and C-peptide values that were below that individual laboratory detection limits. A third limitation is the small number of patients available for before and after therapy comparisons. Inclusion of additional levels might alter group comparisons. But given the large overlap between groups, we consider this unlikely. A fourth limitation is that we were limited to the medical details provided in the reports. It is possible some patients had unreported hepatic or renal failure that affected insulin and C-peptide levels. We cannot predict how these unrecognized conditions might alter our results. Finally, all patients did not have confirmatory studies to detect the presence of sulfonylureas. Although unlikely, given the history and laboratory findings, it is

possible that some of these patients did not have sulfonylurea-induced hypoglycemia.

CONCLUSIONS

There is a lack of information regarding insulin and C-peptide levels observed in sulfonylurea-induced hypoglycemia: so what constitutes “elevated” levels? Based on our study, with the exception of 1 insulin and 1 C-peptide level (both from the same “set” with an associated blood glucose level of 49 mg/dL), all insulin levels, based on our study, were ≥ 3.9 μ IU/mL (27.1 pmol/L), and all C-peptide levels were ≥ 1.4 ng/mL (0.5 nmol/L). Therefore, serum insulin ≥ 3.9 μ IU/mL and C-peptide ≥ 1.4 ng/mL in a patient with a blood glucose < 49 mg/dl are consistent with sulfonylurea-induced hypoglycemia. Except for the one aforementioned “set,” this relationship also held true for “sets” with blood glucose from ≥ 49 to < 60 mg/dl.

Glucose, insulin, and C-peptide levels tended to be higher if obtained after hypoglycemic therapy, but there is a large amount of overlap with levels obtained before therapy. Obtaining levels before or after hypoglycemic therapy did not affect interpretation of those levels because all “sets” in the BEFORE and AFTER therapy groups had insulin and C-peptide levels ≥ 3.9 μ IU/mL and ≥ 1.4 ng/mL respectively.

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