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CASE REPORT

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Symptomatic hypoglycemia in a nondiabetic adult female recovering from mild COVID-19 infection: A case report

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Abstract

A 38-year-old lady, recently recovered from SARS-CoV-2 infection and taking grape seed extract, suffered multiple episodes of severe postprandial hyperinsulinemic hypoglycemia. A careful evaluation ruled out the common etiologies of hypoglycemia and identified grape seed extract consumption as a possible cause. She recovered after stopping the nutritional supplements. In her, hypoglycemia could have resulted from transient beta cell dysfunction associated with SARS-CoV-2 infection or proanthocyanidins in the grape seed extract.

KEYWORDS

grapes, homeostasis, insulin, islet cells, seizure

1 | INTRODUCTION

Hypoglycemia is an uncommon presentation in individuals without diabetes or those requiring critical care. The incidence is estimated to be 36 per 10,000 hospital admissions.[1] The incidence of outpatient hypoglycemia is rarer, and very little data are available on its prevalence. The incidence of unexplained hypoglycemia is approximately 9.8% of the total episodes. These patients generally do not have a recurrence of hypoglycemia episodes after complete evaluation and discharge.[1]

Grape seed extracts have active components that are postulated to have anti-oxidant effects.[2] Several patients consume over-the-counter dietary supplements to hasten the process of recovery from SARS-CoV-2 infection. The results of the dietary supplements on the metabolic profile in health and disease are not well studied.

All patients with hypoglycemia need a thorough evaluation to identify the underlying etiology. Occasionally, multiple factors may be associated with the underlying mechanism leading to hypoglycemia. This case brings such an association to light.

2 | CASE REPORT

A 38-year-old lady was brought to the emergency department by her husband in a confused state. Approximately 30 min back at 0300 h, she had an episode of stiffening of her limbs followed by jerky body movements. She had a tongue bite and had passed water in her clothes. There was no history of any aura or focal neurological deficit. The capillary blood glucose was 28 mg/dl. After taking the biochemistry and hormone analysis samples, she was administered 50 ml of 50% dextrose. She had consumed food at approximately 2300 h the previous day. There was no history of consumption of any oral or injectable medications. The mother had a family history of diabetes and was on oral antidiabetic drugs but was not staying with her. There was no family history of hypoglycemia. She

had recovered from a mild SARS-CoV-2 infection about 1 week back which was managed with home quarantine. She took grape seed extract tablets as a dietary supplement to aid her recovery.

She had entirely recovered by the next evening; however, she had a second episode of loss of consciousness at 0100 h on the next day with plasma glucose of 34 mg/dl. She was managed conservatively with bolus glucose and 10% dextrose infusion @ 75 ml/h.

2.1 | Investigations

The hematological, renal and liver profiles, electrocardiogram, chest-X ray, and imaging studies of the brain were essentially normal (Table 1). The sample taken during the episode of hypoglycemia revealed raised insulin levels, 324.9 and 412.8 uIU/ml. There were no ketones in the plasma sample (Table 2). Serum cortisol was 920 nmol/L. Her sulfonyl urea screen was negative, and serum proinsulin levels were not done at admission due to nonavailability. Insulin antibodies were not detected. An abdomen ultrasound revealed a grade I fatty liver. Evaluation for chronic liver disease, including serum ceruloplasmin, ferritin, ceruloplasmin, transferrin saturation, and autoantibody profile, was all within assay limits.

2.2 | Differential diagnosis

Looking at the cause of severe hypoglycemia with high insulin levels, we considered the following differentials: intake of insulin or sulfonyl urea, reactive hypoglycemia, Hirata syndrome, an insulinoma, or noninsulinoma pancreatogenous hypoglycemia syndrome.

There was no history of insulin or sulfonyl urea intake. The sulfonyl urea screen was negative. There was a recurrence of hypoglycemia in the ward under strict observation after 24 h; therefore, exogenous insulin intake was an unlikely possibility. The autoimmune panel for insulin antibodies was negative; consequently, we could not establish Hirata's syndrome as the cause.

Given her thin and lean body habitus and being a marathon runner, we expected her to have high insulin sensitivity. SARS-CoV-2 infection may cause beta cell dysfunction and erratic insulin secretion. Though this has not been reported, it still remains a possibility. The grape seed extract may also have contributed to excessive insulin secretion by the beta cells. Thus, we postulate multiple factors that would have led to the hypoglycemic episodes.

TABLE 1 Baseline laboratory parameters of a 38-year-old female who was treated for hyperinsulinaemic reactive hypoglycemia

Parameter	Value	Normal range
Hemoglobin (g/dl)	11.2	12–15
White blood cell count (/mm^3)	10,200	4000–11,000
Platelets (/mm^3)	320,000	150,000–450,000
Urea/creatinine (mg/dl)	22/0.76	10–50/0.7–1.3
Total protein/albumin (g/dl)	6.4/3.1	6.4–8.2/3.4–5
Calcium/phosphorus (mg/dl)	8.5/4.3	8.5–10.1/2.6–4.7
Electrocardiogram	Normal sinus rhythm	
Fasting/postprandial plasma glucose (mg/dl)	92/81	<100/<140
HbA1c (%)	5.9	<5.7
Na/K (mEq/L)	140/4.8	136–145/3.5–5.1
Total cholesterol (mg/dl)	150	<200
Alkaline phosphatase (IU/L)	66	46–116
Lactate dehydrogenase (IU/L)	144	85–227

2.3 | Treatment given

During the episodes of hypoglycemia, she was managed with an intravenous dextrose infusion. Post-recovery after 48 h, there were no episodes of hypoglycemia. This was confirmed by ambulatory blood glucose monitoring. A mixed-meal test revealed a small postprandial drop in plasma glucose levels at 2 h but no hypoglycemia. A 72-h fasting test did not show any fresh episodes of hypoglycemia (Table 3). Computed tomography imaging of the chest and abdomen was unremarkable. She was subsequently started on Acarbose 25 mg thrice daily to be taken before meals. She was also advised to avoid simple sugars and take high-starch meals.

At 1-month follow-up review after discharge, she had no fresh episodes of hypoglycemia, and acarbose was stopped. There were no episodes of hypoglycemia at 3 and 6 months on the continuous glucose monitoring system (CGMS). A repeat 72-h fasting and mixed-meal test at 6 months was normal.

3 | DISCUSSION

This 36-year-old lady presented with classical features of hypoglycemia as described by Whipple's triad. The incidence of hypoglycemia in individuals without diabetes or in noncritical care settings is infrequent.[1] Evaluation of hypoglycemia is recommended for all patients presenting with classical Whipple's triad.[3] On further evaluation, she was found to have raised insulin levels during hypoglycemic episodes. Hyperinsulinemic hypoglycemia is associated with dysregulated secretion of insulin that

TABLE 2 Critical sample evaluation during two episodes of hyperinsulinaemic reactive hypoglycemia in a 38-year-old female

Parameter	Episode 1	Episode 2	Normal range
Plasma glucose (mg/dl)	21	24	NA
Serum insulin (uIU/ml)	324.9	412.8	2.1–22
C-peptide (mg/ml)	15.2	14.8	0.8–3.85
Serum cortisol (nmol/L)	920	1021	140–690
Serum ketone (nmol/L)	0.03	Not detected	NA
Insulin auto-antibodies	Negative		
Serum pro-insulin	Not done		
Sulfonylurea screen	Negative		

TABLE 3 Follow up evaluation of a 38-year-old female who recovered from hyperinsulinaemic reactive hypoglycaemia

Test	Values
Mixed-meal test	Basal plasma glucose: 88 mg/dl 1-h plasma glucose: 72 mg/dl 2-h plasma glucose: 64 mg/dl 3-h plasma glucose: 82 mg/dl
72-h fasting	No hypoglycaemia
14 days continuous glucose monitoring system (1 month after recovery)	No evidence of hypoglycaemia (plasma glucose in the range of 80–150 mg/dl)

persists despite low plasma glucose.[4,5] When iatrogenic or surreptitious insulin secretagogues or insulin intake has been ruled out, the most common cause is insulinoma in adults. However, insulinoma was ruled out, given the absence of hypoglycemia during the 72-h fast.

SARS-CoV-2 infection is known to cause pathogenic derangement in the islet cells of the pancreas.[6] The involvement of pancreatic islets causes beta cell dysfunction and destruction. SARS-CoV-2 is associated with persistent insulin resistance, new onset hyperglycemia, and beta cell dysfunction.[7] Reactive or postprandial hypoglycemia may be a manifestation of these metabolic derangements. The mixed-meal test revealed a fall in the postprandial glucose, revealing beta cell dysfunction. SARS-CoV-2 infection is associated with an increase in insulin resistance.[8] With the resolution of the inflammatory state and accompanying insulin resistance, there would be a risk of hypoglycemia. This would be of clinical significance in predisposed individuals. In this individual, the beta cell dysfunction may have been associated with the recent SARS-CoV-2 infection.

There are multiple dietary supplements used for their antioxidant-like effects. These are available over the counter. The exact impact of these nutritional supplements on glycemic parameters has not been studied well. Grape seed extract may improve glucose and cholesterol metabolism.[9] The active component of grape seed extract is proanthocyanidin.[10] Proanthocyanadins have multiple effects on glucose metabolism, which include an improvement of insulin sensitivity, lipid and glucose homeostasis, enzyme inhibition, enhanced hepatic glucose uptake, and hepatic glucose homeostasis.[11,12]

This individual had a lean body habitus and was a long-distance marathon runner. Thus, she had a very high insulin sensitivity, as demonstrated by the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) following complete recovery. We postulate that the proanthocyanidin in the grape seed extract associated with beta cell dysfunction and increased insulin sensitivity had predisposed her to episodes of hyperinsulinaemic hypoglycemia. This was a transient phenomenon; there was no recurrence of hypoglycemia during a 6-month follow and repeat CGMS evaluations.

4 | CONCLUSION

Hypoglycemia episodes may be associated with multiple contributing etiologies. Hypoglycemia may be a complication associated with recovery from SARS-CoV-2 infection. Dietary supplements may alter homeostatic mechanisms in predisposed individuals leading to metabolic complications.

AUTHOR CONTRIBUTIONS

JG, VV, AM, and TD were involved in conception, review of literature, and critical review of this manuscript. VV drafted the initial manuscript. JG, VV, AM, and TD have read and approved the final draft of the manuscript.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

All relevant data sources are cited in this article.

ETHICAL APPROVAL

Informed written consent was taken from the subject. Institutional ethics review is not required for case reports.

CONSENT

Informed written consent was taken from the patient.

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REFERENCES

1. Nirantharakumar K, Marshall T, Hodson J, et al. Hypoglycemia in non-diabetic in-patients: clinical or criminal? *PLoS One*. 2012;7(7):e40384. doi:10.1371/journal.pone.0040384
2. Gupta M, Dey S, Marbaniang D, Pal P, Ray S, Mazumder B. Grape seed extract: having a potential health benefits. *J Food Sci Technol*. 2020;57(4):1205-1215. doi:10.1007/s13197-019-04113-w
3. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2009;94(3):709-728. doi:10.1210/jc.2008-1410
4. Shah P, Rahman SA, Demirbilek H, Güemes M, Hussain K. Hyperinsulinaemic hypoglycaemia in children and adults. *Lancet Diabetes Endocrinol*. 2017;5(9):729-742. doi:10.1016/S2213-8587(16)30323-0
5. Güemes M, Rahman SA, Kapoor RR, et al. Hyperinsulinemic hypoglycemia in children and adolescents: recent advances in understanding of pathophysiology and management. *Rev Endocr Metab Disord*. 2020;21(4):577-597. doi:10.1007/s11154-020-09548-7
6. Geravandi S, Mahmoudi-Aznaveh A, Azizi Z, Maedler K, Ardestani A. SARS-CoV-2 and pancreas: a potential pathological interaction? *Trends Endocrinol Metab*. 2021;32(11):842-845. doi:10.1016/j.tem.2021.07.004
7. Montefusco L, Ben Nasr M, D'Addio F, et al. Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. *Nat Metab*. 2021;3(6):774-785. doi:10.1038/s42255-021-00407-6
8. Wu L, Girgis CM, Cheung NW. COVID-19 and diabetes: insulin requirements parallel illness severity in critically unwell patients. *Clin Endocrinol (Oxf)*. 2020;93(4):390-393. doi:10.1111/cen.14288
9. Grohmann T, Litts C, Horgan G, et al. Efficacy of bilberry and grape seed extract supplement interventions to improve glucose and cholesterol metabolism and blood pressure in different populations-a systematic review of the literature. *Nutrients*. 2021;13(5):1692. doi:10.3390/nu13051692
10. Hernández-Jiménez A, Gómez-Plaza E, Martínez-Cutillas A, Kennedy JA. Grape skin and seed proanthocyanidins from Monastrell x Syrah grapes. *J Agric Food Chem*. 2009;57(22):10798-10803. doi:10.1021/jf903465p
11. Koudoufio M, Feldman F, Ahmarani L, et al. Intestinal protection by proanthocyanidins involves anti-oxidative and anti-inflammatory actions in association with an improvement of insulin sensitivity, lipid and glucose homeostasis. *Sci Rep*. 2021;11(1):3878. doi:10.1038/s41598-020-80587-5
12. Krishnan V, Rani R, Awana M, et al. Role of nutraceutical starch and proanthocyanidins of pigmented rice in regulating hyperglycemia: enzyme inhibition, enhanced glucose uptake and hepatic glucose homeostasis using in vitro model. *Food Chem*. 2021;335:127505. doi:10.1016/j.foodchem.2020.127505

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[Correction added on 21 Nov 2022, after first online publication: The ethics statement was amended.]