



CLINICAL PRACTICE ARTICLE

Impact of evening carbohydrate intake on the resolution of persistent night sweats in patients with long COVID: a case series [version 1; peer review: 2 not approved]

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Abstract




Up to 25% of patients with long COVID experience persistent night sweats. However, in most cases they remain untreated until they disappear on their own. Since SARS-CoV-2 is known to disrupt glucose homeostasis, we hypothesized that impaired mitochondria would result in faster glycogen depletion at night due to reduced ATP production yield, inducing adrenaline production ultimately leading to the onset of persistent night sweats. To test our hypothesis we investigated whether incorporating carbohydrates into the diet of three non-diabetic patients with long COVID before bedtime would have any effect decreasing their night sweats. Remarkably, after one week with the dietary intervention, the patients reported that their night sweats had completely disappeared. Therefore, we propose carbohydrate supplementation as an affordable solution for night sweats in long COVID patients.

Keywords

night sweats, long COVID, SARS-CoV-2, diet, carbohydrate, glucose, glycogen, pseudohypoglycemia

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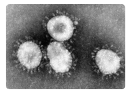
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Introduction

Carbohydrates are the most abundant macromolecules on our planet and play a central role in cell metabolism, providing a rapid source of energy. Following carbohydrate intake, our body stores excess glucose in the form of glycogen, either in skeletal muscles (~500 g) for local consumption during exercise, in the liver (~100 g) to maintain blood glucose homeostasis during periods of daily fasting and stress,¹ or to a minor extent in the brain (~1 g) to provide lactate during the memory process.²

Imbalanced blood glucose levels lead to metabolic disorders such as diabetes, cardiovascular diseases, inflammatory diseases, or cancer. In addition, infectious diseases like COVID may deregulate energy homeostasis of patients by altering their mitochondria and, consequently, the amount of energy their cells can retrieve.³⁻⁵

In such cases, when mitochondria are damaged, cells rely on glycolysis instead of aerobic oxidation. However, due to the lower yield of glycolysis (2 ATP instead of 30-38 ATP) higher amounts of glucose are required to maintain normoglycemia, resulting in a much faster depletion of glycogen stores.

Among COVID patients, about 20% of them experience symptoms several months after acute infection that can last for an indefinite period. This form of disease is colloquially referred to as “long COVID” and usually affects women, regardless of their need to be hospitalized or not.⁶ The most common symptoms reported by these patients are fatigue, headache, dyspnea, and brain fog, which relapse with physical or mental activity and stress.⁷⁻⁹ Among systemic manifestations, an international cohort study revealed that 25% of 3,762 participants with long COVID experienced night sweats without a history of the condition.⁷ Similarly, another cohort of 5,163 patients with persistent COVID symptoms reported a night sweat prevalence of 28%, with a mean duration of 69 days and almost half of them still ongoing.⁸ Although night sweats can disappear over time, they cause significant discomfort and have not been attended in COVID patients.

Since night sweats are common in glycogen storage diseases and in diabetic patients with poor glucose control, we reasoned that glycogen depletion due to mitochondrial damage could be the underlying cause of persistent night sweats in patients with long COVID, and that replenishment of glycogen stores would revert them.

Here we describe three case reports of non-diabetic patients with long COVID whose persistent night sweats disappeared after increasing the carbohydrate content in their diets before bedtime. To our knowledge, this is the first time in the literature that persistent night sweats are addressed and resolved in COVID patients.

Methods

Persistent night sweats associated with long COVID were defined as having night sweats that required changing bedding (waking up with soaked sheets) even when it was not hot in the bedroom and that did not occur before SARS-CoV-2 infection.

Long COVID patients over 18 years of age, who were experiencing persistent night sweats for more than one month, and had no diabetes or previous history of night sweats were invited to participate in the study.

Volunteers were asked to report their night sweats on a Likert scale, ranging from 1 (sheets “completely dry” upon awakening) to 5 (sheets “soaking wet” upon awakening), the week before the intervention and daily during the 7-day diet intervention, along with their symptoms and exact diet. Agreed dietary interventions consisted of including carbohydrate-rich foods of the choice of the patients to their dinners. Sociodemographic characteristics, clinical conditions, and medications were described by the patients or consulted through access to their clinical histories, when possible.

Results

Only three patients participated in the study. All three shared a low evening carbohydrate intake (no dinner, early dinner, low-carb diet) before the nutritional intervention. Their characteristics are described in [Table 1](#) and below in the text. Five volunteers backed out and decided not to join the study due to fear of weight gain once they learned about the nature of the intervention. One patient had a worsening of her symptoms before starting the intervention and declined to participate.

Case 1: High-protein, low-carb, gluten-free diet

Patient 1 was a 42-year-old Caucasian female with dysgeusia and anosmia as her first symptoms of SARS-CoV-2 infection. Two and a half months after testing positive by PCR she started showing night sweats in the absence of fever that soaked the sheets. No alcohol or illegal drug use was declared. When asked about previous medical conditions, she reported anxiety, depression, recurrent miscarriages, mild polycystic ovarian syndrome (PCOS), and irritable bowel syndrome (IBS). Consequently, regular use of antidepressants and anxiolytics in the past without concomitant sweating,

Table 1. Characteristics of the participants.

Variable	Patient 1	Patient 2	Patient 3
Age	42 years	44 years	54 years
Height	178 cm	161 cm	173 cm
Body-mass index	25.2	32.8	24.7
Place of residence	Indianapolis, USA	Cadiz, Spain	Oslo, Norway
Pre-existing conditions	Anxiety, depression, recurrent miscarriages, PCOS, IBS	None diagnosed	None diagnosed
Toxic substances	No	10 cigarettes/day	No
Medication on admission	Metoprolol (25 mg/day) Alprazolam (0.5 mg/day)	Omeprazole (40 mg/day) Amlodipine (5 mg/day) Simvastatin (40 mg/day) Enalapril (20 mg/day) Montelukast (20 mg/day) Diazepam (5 mg/day)	Fexofenadine (120 mg/day) Famotidine (10 mg/day)
Other COVID symptoms	Anosmia, dysgeusia, chest pain, sore throat, cough, fatigue, neuropathy, muscle pain, insomnia, chills, skin rash, anxiety, headache, confusion, tinnitus, diarrhea, pre-atrial contractions, high blood pressure	Dysgeusia, sore throat, cough, fatigue, neuropathy, articular pain, insomnia, chills, difficulty breathing, anxiety, headache, confusion, memory loss, eczema, hair loss, diarrhea, tachycardia, high blood pressure	Fatigue, difficulty focusing, confusion, memory loss, stammering, photophobia, hyperacusis
COVID-19 vaccination	No	Yes	Yes
Duration of night sweats	2.5 months	12 months	19 months
Mean sleeping time	13 hours/day	3 hours/day	7 hours/day
Fasting glucose	93 mg/dL	85 mg/dL	95 mg/dL
Diet before intervention	High-protein, low-carb, gluten-free	No dinner	Early dinner
Moderate physical activity during the intervention	No	No	9.5 hours/week

and occasional use of antipyretics, were disclosed. She had taken low-dose metformin (250 mg/day) intermittently between 2011 and 2014 trying to become pregnant, given the diagnosis of mild PCOS, but she had no history of diabetes and her fasting blood glucose level was 93 mg/dL as tested after COVID-19 diagnosis. A wide variety of persistent long COVID symptoms were mentioned (anosmia, dysgeusia, chest pain, sore throat, cough, fatigue, neuropathy, muscle pain, insomnia, chills, skin rash, anxiety, headache, confusion, tinnitus, diarrhea, pre-atrial contractions, and high blood pressure).

She started the dietary intervention after two and a half months of persistent night sweats. At admission to the study, the patient only took Metoprolol (25 mg/day) to treat her pre-atrial contractions and Alprazolam (0.5 mg/day) for the anxiety. She had a mean of 5 out of 5 (soaking wet sheets) on the night sweat scale the week before modifying her diet. After the introduction of gluten-free macaroni on her dinners (Table 2), patient 1 experienced a progressive decline in her symptomatology, reaching completely dry sheets (1 out of 5) on the sixth and seventh days (Figure 1).

Case 2: No dinner

Patient 2 was a 44-year-old Caucasian female diagnosed with COVID-19 who developed night sweats that soaked the sheets in the absence of fever for the following 12 months before starting the intervention. She had no history of diabetes

Table 2. Diet during the intervention (dinner). In italics, food that was introduced.

Variable	Patient 1	Patient 2	Patient 3
Day 1	Salmon, salad of mixed greens with cucumber, carrot and avocado + <i>a large serving of gluten-free macaroni and cheese</i>	<i>Sandwich with cooked ham, and cereals with skimmed milk</i>	A piece of salmon an vegetables + <i>three slices of brown bread with a boiled egg (later)</i>
Day 2	Tilapia and green beans + <i>a large serving of gluten-free macaroni and cheese</i>	<i>Sandwich with cooked ham, and cereals with skimmed milk</i>	Two large slices of pizza + <i>three slices of bread with a boiled egg (later)</i>
Day 3	Lentil soup + <i>a large serving of gluten-free macaroni and cheese</i>	<i>Sandwich with cooked ham, and cereals with skimmed milk</i>	A pork fillet with carrots, one potato and a turnip + <i>three slices of bread with a boiled egg (later)</i>
Day 4	Salad of mixed greens with grilled steak and avocado + <i>a large serving of gluten-free macaroni and cheese</i>	<i>Sandwich with cooked ham</i>	Home-made vegetable soup + <i>one portion of fried potatoes and onions (later)</i>
Day 5	Salad of mixed greens with chicken and avocado + <i>a large serving of gluten-free macaroni and cheese</i>	<i>Sandwich with quail eggs and bacon</i>	Large serving of cod, with potatoes, carrots and broccoli + <i>one portion of fried potatoes and onions (later)</i>
Day 6	Salad of mixed greens with chicken and avocado + <i>a large serving of gluten-free macaroni and cheese</i>	<i>Sandwich with semicured cheese</i>	Chicken and pumpkin + <i>one portion of fried potatoes and onions (later)</i>
Day 7	Salad of mixed greens with chicken and avocado + <i>a large serving of gluten-free macaroni and cheese</i>	<i>A bun with beef hamburger and fries</i>	Two slices of pizza + <i>one portion of fried potatoes and onions (later)</i>

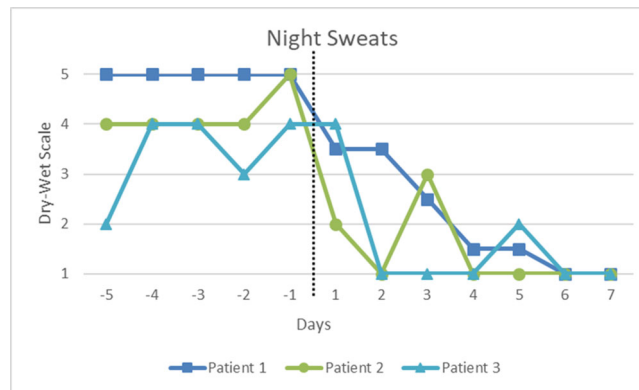


Figure 1. Night sweats reported by the participants before and after the nutritional intervention. Likert scale ranging from 5 (soaking wet) to 1 (completely dry). The vertical dashed line shows the beginning of the intervention. The days before the diet modification are shown in negative.

and her fasting blood glucose level was 85 mg/dL. Perimenopause or menopause was discarded through hormone tests. She reported no previous medical conditions other than obesity (body mass index 32.8), but suffered a wide range of persistent symptoms associated with long COVID (dysgeusia, sore throat, cough, fatigue, neuropathy, articular pain, insomnia, chills, difficulty breathing, anxiety, headache, confusion, memory loss, eczema, hair loss, diarrhea, tachycardia, and high blood pressure). Upon joining the study, she was taking Amlodipine (5 mg/day) and Enalapril (20 mg/day) to treat her high blood pressure, Simvastatin (40 mg/day) to lower cholesterol levels, Montelukast (20 mg/day) to improve her breathing, and Diazepam (5 mg/day) for her anxiety. She smoked about 10 cigarettes a day, but did not drink alcohol or use illegal substances. She completed her second dose of the BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNTech) ten and a half months after her COVID-19 diagnosis.

During the week prior to the intervention, she presented an average night sweats of 4.2 out of 5 on the Likert scale. The patient did not dine previously due to difficulty swallowing and breathing during COVID. The dietary intervention

consisted in small snacks for dinner (Table 2). A significant decrease in her sweating was achieved after the first day without skipping dinner (2 out of 5), and no sweating at all (1 out of 5) for the remaining five days, except for a rebound on day 3 (3 out of 5) (Figure 1).

Case 3: Early dinner

Patient 3 was a 54-year-old Caucasian female who had been experiencing night sweats 3-4 times per week for 19 months following her PCR diagnosis of COVID-19. She had no history of diabetes and her fasting blood glucose level was 95 mg/dL after COVID-19 diagnosis. She reported no other previous medical conditions, nor symptoms or diagnosis of menopause or perimenopause. She did not smoke or use illegal substances, and had been alcohol-free since being diagnosed with COVID-19. Persistent long COVID symptoms were mainly neurological (fatigue after cognitive activity, difficulty focusing, confusion, memory loss, stammering, photophobia, and hyperacusis). At admission to the study, the patient only was taking the antihistamine medicines Fenofenadine (120 mg/day) and Famotidine (10 mg/day) to improve her breathing. She completed her second dose of the Spikevax mRNA-1273 COVID-19 vaccine (Moderna) 16 months after her COVID-19 diagnosis. She averaged 9.5 hours of exercise per week (weights and walking).

The week before the intervention, she showed a mean of 3.4 out of 5 on the night sweat scale. The participant used to dine early, with a large gap of hours before bedtime, so she incorporated a snack four hours after dinner (1.5 hours before bedtime). The first three nights the snack consisted in slices of bread with a boiled egg, but the patient felt fatigued in the morning, having great difficulty getting going. Therefore, the next four nights she ate fried potatoes instead, having the same effect on night sweats, but no fatigue in the morning (Table 2). No impact was observed on the day after the intervention. However, she did not report any sweating on the remaining days, except for a small rebound on day 5 (2 out of 5) (Figure 1).

All patients confirmed that no similar decrease in symptomatology was shown during the previous months of persistent sweating. In all three cases, night sweats resolved completely after the dietary intervention (Figure 1). Participants continued the dietary modification on their own accord beyond the initial week, until they eventually stopped without a return of night sweats.

Discussion

Night sweats can be caused by multiple factors such as infections, stress, cancer, medications, substance addiction, menopause or diabetes.¹⁰ However, none of the participants had a history of persistent night sweats prior to developing COVID.

Although the patients were women between 42-54 years of age, and that COVID-19 can elicit premature ovarian insufficiency,^{11,12} no significant clinical or analytical signs suggestive of menopause were detected in any of the participants. Even if night sweats had been due to perimenopausal symptoms, they vanished after increasing their carbohydrate intake at night. On the other hand, medicines taken by Patient 1 (i.e. Alprazolam) and Patient 2 (i.e. Amlodipine, Simvastatin, Enalapril, Montelukast, and Diazepam) at the time of the intervention could potentially trigger night sweats in a very low percentage of patients (mainly women) after long periods of time; but the fact that they disappeared completely after the dietary intervention rules out this possibility. Patient 3 quit alcohol since being diagnosed with COVID-19, which could have played a role in her night sweats at the beginning, but not after 19 months, when the study took place.

Additionally, hypoglycemia is a common trigger in diabetic patients with poorly controlled glucose levels. However, none of the participants were diabetic, and their fasting glucose levels, accessed through medical records, were normal. Nevertheless, we hypothesized that faster depletion of the glycogen reservoirs in COVID patients could be the underlying cause of their persistent night sweats.

SARS-CoV-2 has been reported to alter mitochondrial metabolism³⁻⁵ by reducing oxidative phosphorylation (yield: 30-38 ATP/glucose). This is compensated by a higher rate of glycolysis (yield: 2 ATP/glucose) and a greater dependence on glucose over glutamine and long-chain fatty acids (which require mitochondria for energy production). In consequence, cells need more molecules of glucose to achieve the same number of ATP molecules, which may precipitate premature exhaustion of the glycogen pools. Accordingly, postmortem biopsied hepatocytes from COVID-19 patients show damaged mitochondria and decreased glycogen granules,¹³ whereas mRNAs coding for proteins involved in glycogen biosynthesis are significantly downregulated in blood samples.¹⁴ Supporting this notion, continuous glucose monitoring of non-diabetic patients with mild COVID-19 revealed greater glycemic fluctuations and higher postprandial peaks accompanied by lower glycemic values throughout the night compared to healthy controls,¹⁵ which evidences an alteration of the liver glycogen metabolism.

Under normal conditions, during the overnight fast, metabolism gradually progresses to a catabolic state, promoting the breakdown of liver glycogen to support normoglycemia. At night, about half of the glucose supply is due to glycogenolysis, whereas the other half comes from gluconeogenesis in the liver and kidneys.^{16,17}

However, in COVID patients, the liver glycogen pool is smaller and the energy recovered by the cells relying on glycolysis is much less. This can lead to two possible scenarios. First, that faster depletion of the hepatic glycogen reservoir requires higher gluconeogenic rates to compensate, but these are not enough on their own to maintain constant normoglycemia, and hypoglycemic episodes develop at night. Second, that despite normoglycemic blood values are supported, cells do not get the needed energy output and patients display symptoms suggestive of hypoglycemia, despite normal test results. This condition is known as type I pseudohypoglycemia,¹⁸ and is due to lower energy obtained by cells with compromised mitochondrial function.⁴

In either case, epinephrine is released as part of the fight-or-flight response. Epinephrine is a potent stimulator of hepatic glucose output leading to a 2.5-fold increase in glucose production.¹⁹ It also triggers narrowing of the blood vessels and increased heart rates, raising the blood pressure and the apparent concentration of blood sugar to promote its delivery. In addition, it also facilitates breathing by relaxing the airways. On top of that, epinephrine can also activate adrenal receptors in the eccrine and apocrine glands, resulting in sweating.²⁰

Therefore, by increasing the carbohydrate intake of the participants right before going to bed, we were able to augment their hepatic glycogen pool and avoid the release of epinephrine and consequent night sweats. Curiously, all three shared a low evening carbohydrate intake (no dinner, early dinner, or low-carb diet) before the nutritional intervention.

It has been described that, under resting conditions, only 19% of the ingested glucose load is stored as glycogen in the liver, at a rate of approximately 6 g/h.²¹ This would explain the need to maintain carbohydrate supplementation for several days before the night sweats disappeared completely. In this study, we allowed participants to choose the carbohydrates of their choice pointing them the preference for starch sources over simple sugars, to avoid hyperglycemic peaks.

Epinephrine is secreted not only in case of hypoglycemia, but also under anxiety, stress, or shortness of breath. It is noteworthy that other symptoms reported by the patients may be due to either high or low epinephrine values (i.e. palpitations, high blood pressure, headaches, anxiety, insomnia) or hypoglycemic episodes (i.e. fatigue, difficulty focusing, confusion, memory loss).

Also compatible with our hypothesis is the fact that night sweats are more prevalent in women (all our cases were females). This may reflect a reduced hepatic glycogen content in females compared to males, as well as a reduced hepatic glucose output.^{22,23}

Although greater attention has been paid to high glycemic peaks, the greater risk of nocturnal hypoglycemia in COVID-19 patients has gone largely unnoticed by professionals. Current management guidelines for long-COVID symptoms are still sparse and imprecise, offering mainly holistic support or symptomatic treatments, but ignoring the underlying pathologies. Contrary to the general trend of thought, the endorsement of gradual physical activity and limited carbohydrate intake to improve overall patient condition may not be appropriate for everyone at all stages and may worsen some symptoms or contribute to their perpetuation.

Despite the limited number of patients included, our findings could be extrapolated to night sweats triggered by other diseases where mitochondrial impairment and faster hepatic glycogen depletion occur. We hope that future trials with more patients and resources confirm our results and the mechanisms proposed here. Unfortunately, fear of weight gain was the main reason to decline participation in the study.

Conclusions

Our study shows that persistent night sweats in long COVID patients can be resolved with dietary carbohydrate supplementation before bedtime. This is compatible with the hypothesis of rapid depletion of the hepatic glycogen store and insufficient cellular energy production due to mitochondrial damage in these patients.

This work also highlights the necessity to pay more attention to symptoms of hypoglycemia despite normal laboratory results in non-diabetic patients.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Provincial Ethics Committee of Granada (code NS_23052021 approved on 02/02/2022).

Consent

Written informed consent for publication of their clinical details and/or clinical images was obtained from all the patients involved in the study.

Data availability

Data shared by the participants is confidential and not publicly available. However, researchers and reviewers may be granted access, once any personal information that could identify them is removed, and upon written request to the corresponding author, after explaining the reasons and stating that they will be treated confidentially and will be used only for research purposes.

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This paper reports 3 cases of subjects with post-COVID complications expressed as excessive night sweating. Authors report that providing high carbohydrate dinner abolish night sweating. It is an interesting observation which highlights the nutrient-intake modulation of the autonomic nervous system activity which can be of therapeutic value for excessive night-sweating.

Authors suggest that an insufficient carbohydrate metabolism of cells due to mitochondria damage by COVID, triggers sympathetic activation leading to increased hepatic glucose production but also excessive sweating. Thus, in order to compensate for the glucose deficit, authors suggest to supply carbohydrate-rich food before the night time. Although apparently effective against sweating, both the mechanism of action and the clinical utility are nevertheless questionable.

In order to support their mechanistic hypothesis, i.e. altered mitochondrial function, authors did not measure ATP before and after intervention. The capacity of the hepatic glucose production was not studied either. Moreover, the contribution of carbohydrates to the obtained effect was not controlled; each patient received a complex meal rich in all macronutrients. Thus, the mechanistic hypothesis remained a speculation.

Excessive night sweating occurs when the autonomic nervous system activity is dysregulated with an elevation of the sympathetic tone. Various acute and chronic infections are typically associated with such dysregulation which can be accompanied or not by altered glucose metabolism.

In my view, the present results may rather reflect a carbohydrate non-specific general effect of food ingestion which is accompanied by increased parasympathetic tone, which in turn, counteracted the sympathetic activity resulting in decreased sweating. Whatever the underlying mechanism of action of decreased night-sweating, the idea of increased carbohydrates intake before the night time is nutritionally unacceptable because of multiple risk factors for development of metabolic disorders. In particular, this approach should be avoided in obese patients. Instead, a pharmacological approach aimed at reduction of sympathetic tone should be

explored in a carefully designed study to help patients with increased night sweating post-COVID or other infections.

Is the background of the cases' history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Partly

Is the conclusion balanced and justified on the basis of the findings?

No

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Physiology of appetite, neuroendocrinology, gut-brain axis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Reviewer Report 06 December 2022

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Comments to authors:

In this paper authors speculate that impaired mitochondria function after COVID-19 would result in faster glycogen depletion at night, ultimately leading to the onset of persistent night sweats. To investigate that possible mechanism they incorporated carbohydrates into the diet of three non-

diabetic patients with long COVID before bedtime and registered disappearing of night sweats.

- The background in the article is adequately described and literature sufficiently cited to explain the author's hypothesis.
- The study design is not clear. Is this a case report study or an intervention study? The authors present the paper as a case report study, but they subsequently describe a 7-days diet intervention. Authors should redefine the study design. In case of intervention study, as the study presented, authors should also redefine the sample size basing on a power analysis and include a control population. Moreover the follow up period should be probably prolonged.
- Finally authors describe glucose metabolism in these patients only based on fasting glucose. It should be specified when fasting glucose was evaluated. Can authors provide data on fasting glucose, insulin and C-Peptide, liver function tests and nutritional status before and after the diet-intervention? Basing on author's hypothesis of a sort of augmented adrenaline secretion leading to night sweats, it maybe interesting to see if any change in 24hr urinary catecholamines and metanephrines can be before and after diet intervention.
- At present conclusions are not fully supported by the study design.

Is the background of the cases' history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Yes

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the conclusion balanced and justified on the basis of the findings?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Diabetes and immune system

We confirm that we have read this submission and believe that we have an appropriate level of expertise to state that we do not consider it to be of an acceptable scientific standard, for reasons outlined above.

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