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People with diabetes and hypovitaminosis C fail to conserve urinary vitamin C

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ABSTRACT

Background: Hypovitaminosis C has negative health consequences. People with diabetes and hypovitaminosis C may fail to conserve vitamin C in the urine, thereby displaying evidence of inappropriate renal leak of vitamin C. This study describes the relationship between plasma and urinary vitamin C in diabetes, with a focus on the clinical characteristics of participants with renal leak.

Methods: Retrospective analysis of paired, non-fasting plasma and urine vitamin C, and also clinical characteristics, from participants with either type 1 or type 2 diabetes, recruited from a secondary care diabetes clinic. Plasma vitamin C thresholds for renal leak have been defined previously as 38.1 μmol/L for men and 43.2 μmol/L for women.

Results: Statistically significant differences in clinical characteristics were seen between those with; i) renal leak (N = 77) and; ii) hypovitaminosis C but no renal leak (N = 13) and; iii) normal plasma vitamin C levels (n = 34). Compared to participants with adequate plasma vitamin C levels, participants with renal leak tended to have type 2 (rather than type 1) diabetes, a lower eGFR and a higher HbA1c.

Conclusion: In the diabetes population studied, renal leak of vitamin C was common. In some participants, it may have contributed to hypovitaminosis C.

Introduction

Hypovitaminosis C has a myriad of health consequences [1], and is a risk factor for the development of cardio-renal disease [2–6]. Also, hypovitaminosis C is common in diabetes [7–10]. Dietary factors, oxidative stress and inflammation are some of the contributors to low vitamin C levels described in research participants [2,11–13]. Another potential contributor to hypovitaminosis C in diabetes is renal leak of vitamin C. Urinary loss of vitamin C has been described by several previous authors in studies with either small sample numbers or narrowly defined study populations [14–16]. A more recent study by Ebenuwa *et al* recruited a larger number of participants with either type 1 or type 2 diabetes and confirmed the presence of urinary loss of vitamin C, across a wide range of plasma vitamin C levels [17]. They showed that, in contrast to experimentally induced hypovitaminosis in healthy volunteers which results in conservation of urinary vitamin C, participants with diabetes and hypovitaminosis C may show an inappropriate renal leak of urinary vitamin C, on fasting sampling [17]. The mechanism(s) responsible for this renal leak are unknown.

The current retrospective study also aimed to describe the relationship between plasma and urinary vitamin C in non-fasting participants with either type 1 or type 2 diabetes. Stored samples were available from a previous unrelated study, which recruited participants with a wide range of renal function, spanning the spectrum of normal and reduced eGFR and normal and elevated urinary albumin [18].

Abbreviations: BMI, Body mass index, eGFR, estimated glomerular filtration rate; MET, Minimal elimination threshold, SGLT2, sodium glucose cotransporter 2; T1 diabetes, Type 1 diabetes, T2 diabetes, Type 2 diabetes; HbA1c, glycated haemoglobin, HPLC, high-performance liquid chromatography.

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Methods

Study population and data source

Adult participants were recruited from a secondary care outpatient clinic that preferentially reviews complex patients with both type 1 and type 2 diabetes. In the original study from which the current participants are recruited, potential confounding associated with the presence of renal hyperfiltration was minimised using the following inclusion and exclusion criteria: Patients with type 1 diabetes of five years duration or more and those with type 2 diabetes aged 30 years or older, were asked to participate. Study exclusions were aged > 80 years and any life-threatening co-morbidities [18]. The current study was approved by the New Zealand Health and Disability Ethics committee. Participants provided updated written consent, which gave permission for their demographic and clinical data and also stored laboratory samples to be made available for the current study. Clinical data, including blood and urine samples were collected for the initial study at a non-fasting research clinic visit. Samples were stored at minus 80 °C. Vitamin C was measured using reverse-phase high-performance liquid chromatography (HPLC), as described previously [7]. Plasma vitamin C results but not urinary vitamin C results from these stored samples have been reported previously [7]. The lower limit of assay detection, which is of relevance when considering whether urinary vitamin C was detectable or not, was 0.4 μmol/L.

Clinical variables

The clinical variables selected for inclusion in the current study were those considered to have potential clinical or mechanistically explainable associations with plasma and urinary vitamin C concentrations. They include type of diabetes, body weight, BMI, HbA1c, smoking status, presence of complications such as kidney, eye and heart disease, and also blood pressure and antihypertensives.

Clinical categorisation of plasma vitamin C concentrations

Plasma vitamin C levels are discussed throughout this study. Plasma vitamin C ranges were defined using the following criteria: Saturating ≥ 70 μmol/L; adequate ≥ 50–69 μmol/L; inadequate 23 < 50 μmol/L; hypovitaminosis (or deficient) < 23 μmol/L [1].

Minimal elimination threshold (MET) for vitamin C and renal leak

Vitamin C is water soluble and excess vitamin C is excreted in the urine [17,19]. However, if a person with diabetes has a plasma vitamin C level that is in the 'adequate' to 'inadequate' range and also has detectable urinary vitamin C, it can be unclear if this represents physiologic excretion of excess vitamin C, or alternatively represents inappropriate renal leak. (See supplementary Fig. 1 for a more detailed explanation of this concept). The recent paper by Ebenuwa *et al* approached the problem of defining a conservative renal threshold value for plasma vitamin C, below which the presence of urinary vitamin C is likely to be abnormal, by calculating a 'minimal elimination threshold' in healthy volunteers [17]. Plasma vitamin C levels below 38.1 μmol/L for men and 43.2 μmol/L for women, represent 'minimal elimination threshold' (MET) values. These values are used in the current study.

Statistical analysis

Participants were grouped according to the presence or absence of renal leak as follows: Participants in Group A had plasma vitamin C concentrations above the MET threshold, either with or without detectable urinary vitamin C; Group B had plasma vitamin C concentrations below MET but no detectable urinary vitamin C, thus had no evidence of renal leak; Group C had plasma vitamin C concentrations below MET, with detectable urinary vitamin C, thus Group C had inappropriate renal leak. Clinical variables in these three participant subgroups were statistically compared using one-way ANOVA or chi-square tests as appropriate. Where these indicated significant differences ($p < 0.05$) amongst the three groups, pair-wise comparisons of the groups were undertaken, using Fisher's least significant difference tests, chi-square tests or Fisher's exact tests. The urinary vitamin C: creatinine ratio and the urinary albumin: creatinine ratio were both $\log_e$ transformed prior to analysis to normalise distributions.

Results

Participant characteristics

Of the original 201 study participants [17], 124 provided updated written consent and also had paired urine and plasma samples available for further analysis. Five of the 124 participants were receiving vitamin C supplementation, with three of these participants also having hypovitaminosis C. Excluding these five participants from analysis did not affect overall results and these participants are therefore included in the analysis. Only one participant was on an SGLT2 (sodium glucose co-transporter 2) inhibitor. Table 1 outlines the clinical characteristics of these 124 participants, sub-grouped according to their urinary and plasma vitamin C, as discussed in the Methodology section. The highest eGFR value for all participants was 107 mL/min, thus this study is unable to provide any insights about a possible relationship between

Table 1
Clinical characteristics of participants, grouped according to minimal elimination thresholds and renal leak of vitamin C.

	A Plasma vitamin C above MET[a] (N = 34)	**B** Plasma vitamin C below MET[a] but no renal leak (N = 13)	**C** Renal leak (N = 77)
Age (mean, years)	53.2 (15.7)	60.0 (12.7)	52.7 (17.3)
Male: Female (N)	15:19	8:5	37:40
Ethnicity[b] (M:P:E:other, N)	1:0:28:5	3:1:8:1	8:3:63:3
Urinary Vit C: Creatinine ratio (μmol/mmol)[c]	12.7 (2.8–30.3)	0.0	4.6 (1.5–15.1)
T1 diabetes: T2 diabetes (N)	27:7	3:10	40:37
Body weight (kg)	80.6 (19.8)	103.1 (18.5)	88.9 (24.2)
BMI (kg m^{-2})	28.4 (6.4)	34.8 (5.3)	30.9 (7.3)
HbA1c (mmol/mol)	59.0 (13.1)	71.3 (13.2)	67.8 (16.9)
Current smoker (Yes: No)	5:29	4:9	7:70
eGFR (mL/min)	77.3 (17.3)	67.9 (15.7)	66.07 (21.2)
Urinary albumin: creatinine ratio (g/mol)[c]	1.4 (0.6–4.2)	2.0 (1.1–12.7)	1.7 (0.9–19.9)
Retinopathy (Yes: No)	8:26	4:9	29:48
Systolic (mmHg)	136.8 (23.0)	129.7 (20.9)	137.9 (22.3)
Diastolic (mmHg)	75.7 (10.5)	77.1 (9.5)	79.6 (10.6)
On antihypertensive medications (Yes: No)	17:17	10:3	43:34
Heart disease (Yes: No)	5:29	3:10	12:65

Values in parenthesis represent either standard deviations or interquartile ranges. A more detailed explanation of the definition of Groups A, B and C is provided in the Methodology Section; Statistical analysis.

[a] Minimal elimination thresholds (MET) represent conservative values for plasma vitamin C below which healthy volunteers show no evidence of urinary vitamin C. They are 38.1 μmol/L for men and 43.2 μmol/L for women. Participants with plasma vitamin C levels below threshold and detectable urinary vitamin C are described as having renal leak.

[b] Ethnicity abbreviations: M = Māori, P = Pasifika, E = European New Zealander.

[c] Ratios were $\log_e$ transformed prior to analysis.

glomerular hyperfiltration and renal leak of vitamin C.

Comparison of plasma and urine vitamin C concentrations

Fig. 1a compares individual plasma and urinary vitamin C concentrations for all study participants. Visual inspection of this Figure shows that the four participants with saturated plasma vitamin C levels (>70 μmol/L) had the expected finding of a high urinary vitamin C concentration. Fig. 1b focuses on individual plasma and urinary vitamin C concentrations from the subgroup of participants with lower plasma vitamin C levels. Fig. 1b shows that urinary vitamin C was detectable in the majority of these participants, including those who had plasma vitamin C concentrations in the deficiency range. For example, only 17% of study participants with plasma vitamin C below 23 μmol/L conserved their urinary vitamin C, that is had values below the lower limit of assay detection of 0.4 μmol/L.

Comparison of participant groups by renal leak.

Details of participant groupings are provided in the Methodology section. In brief, participants were grouped by vitamin C status as follows: Group A plasma vitamin C concentrations above MET; Group B plasma vitamin C concentrations below MET but no renal leak; Group C plasma vitamin C concentrations below MET, with 'inappropriate' renal leak. The median urinary vitamin C concentration for those in Group C ('renal leak') was 32 μmol/L. Table 2 includes only those variables that showed statistical differences between these groups. When compared to participants with adequate plasma vitamin C levels (Group A), participants with renal leak (Group C) tended to have type 2 (rather than type 1) diabetes, a lower eGFR and a higher HbA1c. The thirteen participants with plasma vitamin C below MET but with no renal leak (Group B), had a higher body weight than those with renal leak (Group C). The statistical relationship between the clinical characteristics of participants with and without renal leak was not however strong and there was much overlap in clinical characteristics between the three groups.

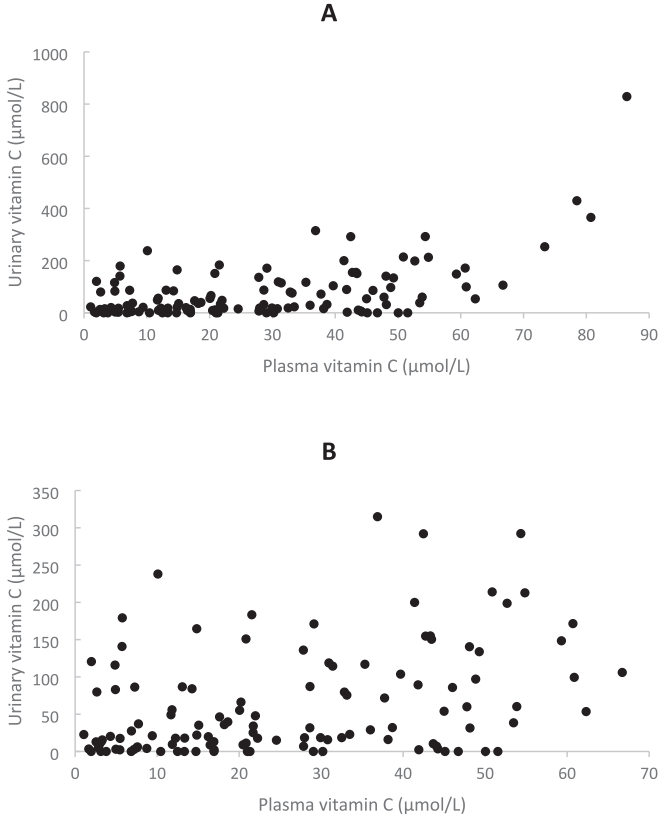

Fig. 1. Comparison of plasma and urinary vitamin C. Figure 1A shows data for all participants. Figure 1B excludes participants with higher ('saturating') concentrations of plasma vitamin C.

Table 2
Statistical comparison of participant groups.

	A v. B[a]	B v. C[a]	C v. A[a]
Urinary Vit C: Creatinine ratio (μmol/mmol)[b]	–	–	**0.015**
T1 diabetes: T2 diabetes (N)	**<0.001**	0.054	**0.006**
Body weight (kg)	**0.003**	**0.038**	0.079
BMI (kg m^{-2})	**0.005**	0.060	0.085
HbA1c (mmol/mol)	**0.017**	0.453	**0.007**
eGFR (mL/min)	0.148	0.755	**0.007**

[a] P values for pairwise comparisons between Groups A, B or C (ie A v. B, B v.C and C v. A) are provided only for those variables that showed significance on initial group-wise analysis. (A more detailed explanation of the definition of Groups A, B and C is provided in the Methodology Section; Statistical analysis).
[b] The Group B urinary vitamin C: creatinine ratio is predefined as being zero, thus the only comparison available is a pairwise comparison between Groups C versus A.

Discussion

The current study extends the findings of earlier studies of urinary vitamin C loss in diabetes, by including a greater number of participants displaying evidence of hypovitaminosis C and renal leak. The relationship between renal leak of vitamin C and the presence of other diabetes complications, was not however strong enough to allow identification of patients within a clinic setting who are likely to have renal leak. It is also acknowledged that the definition of renal leak used in the current study was derived from a previous study using healthy fasting volunteers and that the current study used non-fasting participants with diabetes. Some participants in the current study who were at the margin of plasma vitamin C values for renal leak may in effect have been misclassified.

The median urinary vitamin C concentration for those participants with renal leak was 32 μmol/L. Assuming an average urine volume of around 1 to 2 L a day, then this corresponds to a urinary loss of around 5–10 mg of vitamin C each day. The daily recommend intake of dietary vitamin C varies across health systems [20]. As an example, USA recommendations are 75 mg for women and 90 mg a day for men [21]. Although the urinary loss of vitamin C in the participants studied appears modest when compared to these dietary recommendations, if considered in the clinical context of hypovitaminosis C, even a small increase in urinary vitamin C leak may push some patients with inadequate plasma vitamin C into the deficiency range [22].

There are multiple potential reasons for both the hypovitaminosis C andthe renal leak seen in people with diabetes. Although the current study did not address these potential mechanisms directly, it helped with the generation of hypotheses that might be explored in future studies. Three examples are discussed. Firstly, renal leak was observed to be more common in participants with type 2 compared to type 1 diabetes. Type 2 participants are likely to have a higher burden of inflammation and oxidative stress compared to those with type 1 diabetes [23]. Also, inflammation and oxidative stress have been associated with hypovitaminosis C [24]. Secondly, this current study showed that participants with the phenotype of hypovitaminosis C but no renal leak had a higher body weight (but not a higher BMI) compared to those with renal leak and hypovitaminosis C. Dietary vitamin C requirements are known to be higher in those with a high body weight, in relation to their higher volume of distribution [25]. This second phenotype may therefore represent participants in whom dietary insufficiency is the predominant cause of hypovitaminosis C. In contrast, those participants with both hypovitaminosis C and also renal leak may have oxidative stress or inflammation as a major contributor to their low vitamin C levels. Exploration of these hypotheses will require studies that include

measures of inflammation and oxidative stress, and also detailed dietary assessments. A third hypothesis is that medications such as SGLT2 inhibitors reduce renal leak of vitamin C [26]. The current study's observational design and relatively small sample size precluded any detailed exploration of the relationship between renal leak and medications. Also, only one study participant used SGLT2 inhibitors. A possible relationship between renal leak and medications is best explored with interventional studies.

This study has several limitations. The study did not include a control group. It is exploratory, partly because samples were analysed retrospectively, also participants were recruited from a secondary care clinic which preferentially reviews complex patients. Thus, in contrast to some other studies, many participants in the current study had a high complication burden with evidence of renal disease, suboptimal glycaemic control, and a high BMI. No inference can therefore be made about the frequency (percentage) of participants with 'renal leak' of urinary vitamin C from the current study that is directly applicable to other clinical populations. Samples were non-fasting, thus results obtained from participants with a high dietary vitamin C intake are likely to differ from results that might have been obtained on fasting sampling, also there was no data available on dietary intake. Samples were stored, which may have impacted on vitamin C integrity [27]. Additionally, the sample size for two of our three groups was relatively small, which limited the statistical power for between-group comparisons and may therefore have increased the probability of a type II error. The current study does however include a greater number of participants with 'renal leak' than previous studies. When taking into consideration the level of metabolic burden seen in participants in the current study and also methodological differences between studies, the current results are nevertheless broadly concordant with those described by Ebenuwa *et al.* [17].

Conclusions

Some individuals with diabetes and low plasma C levels fail to conserve their urinary vitamin C. This inappropriate urinary vitamin C loss (renal leak) has the potential to contribute to the hypovitaminosis C that is commonly seen in diabetes, which in turn may contribute to the diabetes cardiorenal disease burden. In addition to considerations about the role of increasing vitamin C intake in this setting, either through increased dietary intake or using supplements, future studies that explore possible mechanisms for reducing urinary vitamin C loss would also be of interest.

Ethics approval and consent to participate

The study was approved by the New Zealand Northern B Health and Disability Ethics committee (19/NTB/207). All participants provided written, informed consent.

CRediT authorship contribution statement

Helen Lunt: Conceptualization, Methodology, Writing – original draft, Visualization. **Anitra C Carr:** Conceptualization, Supervision, Writing – review & editing. **Helen F Heenan:** Investigation, Data curation, Writing – review & editing, Visualization, Project administration. **Emma Vlasiuk:** Investigation. **Masuma Zawari:** Investigation. **Tim Prickett:** Resources. **Chris Frampton:** Formal analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Helen Lunt and Helen F Heenan participate in multicentre diabetes clinical trials through their institution, but have not been involved in any trials utilising vitamin C.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcte.2023.100316.

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