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Glucose Exposure in Peritoneal Dialysis Is a Significant Factor Predicting Peritonitis

Herma Uiterwijk[a] Casper F.M. Franssen[b] Johanna Kuipers[a] Ralf Westerhuis[a] Ferdau L. Nauta[b]

[a]Dialysis Center Groningen, Groningen, The Netherlands; [b]Division of Nephrology, Department of Internal Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Keywords
Glucose exposure · Peritoneal dialysis · Peritonitis · Residual diuresis

Abstract
Introduction: Loss of residual renal function (RRF) as well as high peritoneal glucose exposure are associated with increased peritonitis frequency in peritoneal dialysis (PD) patients. Our objective was to investigate the contribution of RRF and peritoneal glucose exposure to peritonitis in PD patients. ***Methods:*** In this prospective longitudinal cohort study, 105 incident end-stage renal disease patients that started PD between January 2006 and 2015 were studied. Follow-up was 5 years with censoring at death or switch to another treatment modality. Cox regression models were used to calculate the association between glucose exposure, RRF, and peritonitis. Kaplan-Meier analysis was used to examine the difference in occurrence of peritonitis between patients with high and low glucose exposure and between those with and without residual diuresis. ***Results:*** One hundred and five patients were followed for a mean of 23 months. Fifty-one patients developed a peritonitis. Cox regression models at 6 months showed that glucose exposure and not residual diuresis significantly predicted PD peritonitis. Kaplan-Meier analysis after 6 months of follow-up showed that time to first PD peritonitis was significantly longer in the low glucose exposure group. Similarly, patients with RRF had a significantly longer interval to first peritonitis compared to patients without RRF. ***Conclusion:*** A higher exposure to glucose rather than loss of RRF is associated with an increased risk of peritonitis. This confirms the detrimental effects of glycemic harm to the peritoneal host defense on invading microorganisms and argues for the use of the lowest PD glucose concentrations possible.

Introduction

Worldwide, approximately 272,000 patients are treated with peritoneal dialysis (PD) because of end-stage renal disease [1]. The most common complication of PD is peritonitis which is associated with loss of ultrafiltration, hospitalization, catheter loss, technique failure, transfer to hemodialysis (HD), and considerable mortality [2, 3].

The most frequent etiological agents of PD-associated peritonitis worldwide are gram-positive cocci such as *Staphylococcus epidermidis* and other coagulase-negative *Staphylococci* and *Staphylococcus aureus* [4].

KARGER

E-Mail karger@karger.com
www.karger.com/ajn

Herma Uiterwijk
Dialysis Center Groningen
Hanzeplein 1
NL–9713 GZ Groningen (The Netherlands)
E-Mail h.uiterwijk@dcg.nl

Previous studies have identified various modifiable (malnutrition, the use of immunosuppressive drugs, patient training) and nonmodifiable risk factors (age, gender, diabetes, residual renal function [RRF]) for peritonitis [2, 5]. There is debate on whether high glucose exposure is a risk factor for peritonitis [6]. Long-term exposure to dialysis solutions may cause structural changes to the peritoneum and have a causative role in changes in peritoneal function. Changes in membrane function as a consequence of peritonitis are associated with recurrent peritoneal infections [6–8]. Studies that have specifically investigated the relation between high peritoneal glucose exposure and peritonitis frequency yield varying results. Some did not find a significant association between glucose exposure and peritonitis frequency [9, 10], whereas another study showed a significant increase in the incidence of relapsing and recurrent peritonitis in patients with a higher glucose exposure [11].

Several studies have shown the association between a decline in residual renal function and an increased risk of peritonitis [12–15]. Presently, it is unknown whether this is a direct association or whether it is mediated by other factors such as a higher glucose exposure. Patients with a decrease in RRF and loss of diuresis are almost inevitable treated with higher glucose concentrations to achieve sufficient peritoneal ultrafiltration, thus leading to a higher glucose exposure to the peritoneum [16]. Thus far, no studies investigated the relation between peritonitis frequency and RRF with taking the glucose exposure into account. Therefore, the aim of this study was to unravel the association between RRF, glucose exposure, and peritonitis rate.

Patients and Methods

Patients

In this longitudinal single-center cohort study with prospective data collection, all patients who visited our out-patient clinic between January 2006 and 2015 were eligible. All adult (≥18 years) patients that started PD therapy from the Dialysis Center Groningen were included (both continuous ambulatory PD and automatic PD). Follow-up was 5 years with censoring at death or until termination of PD treatment, whichever occurred first. Patients who had a peritonitis within 6 weeks of starting PD were excluded from the study since the possibility that the peritonitis was caused by the PD catheter insertion could not be ruled out. As measure for RRF, we primarily used the 24-h urine volume, since peritoneal glucose exposure is more closely related to volume homeostasis than to creatinine clearance (CrCl). As a sensitivity analysis, we used the mean of the urea and CrCl instead of residual diuresis as measure for RRF.

PD Treatment

The PD solutions prescribed were continuous ambulatory PD/DPCA 2 (glucose concentration 1.5%), 3 (4.25%), and 4 (2.3%) from Fresenius Medical Care (Bad Homburg, Germany). Peritonitis was defined in line with the International Society for PD guidelines definition as cloudy dialysate with a dialysate white cell count of >100 cells/μL and >50% polymorphonucleaire leucocytes. PD peritonitis was treated according to the most recent version of the International Society for PD committee guidelines [17].

Causes of discontinuation of PD were categorized as switching to HD, renal transplantation, or death.

Data Collection

All patients that started PD between January 2006 and 2015 were included. Follow-up was terminated at January 2016. Patient characteristics and clinical data including diuresis volumes were collected at the start of PD, at 6 weeks after the start of PD and at 6 months, 1 year and, next, annually for 5 years or until the end of PD. Patients with a urine production of >200 mL/24 h were considered to have residual diuresis. There was no loss to follow-up.

For each patient, the glucose exposure was calculated at 6 weeks after the start of PD, after 6 months, after 1 year, and next annually for 5 years or until the end of PD. The total glucose exposure in grams per 24 h was calculated as followed: As an example: a patient with a PD schedule of 2 dwells of 2 L 2.3% glucose and 2 dwells of 2 L 1.5% glucose: $(2 \times 2 \times 23\ g) + (2 \times 2 \times 15\ g) = 152$ g glucose exposure over 24 h [6]. We choose not to include icodextrin because this water-soluble polysaccharide has very different effects on the peritoneal membrane compared to glucose. CrCl was calculated using the following formula: CrCl = (urinary creatinine × serum creatinine/24-h urine volume)/1.44.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows software, version 20.0 (SPSS Inc., Chicago, IL, USA). Normally distributed data were expressed as mean ± SD and categorical data as number (%). Independent risk factors for peritonitis were assessed in univariate and multivariate Cox's proportional hazard models. In the multivariate model, we adjusted for sex, age, residual diuresis, daily peritoneal glucose exposure, serum albumin, and use of immunosuppressive drugs. p values <0.05 were considered significant. For the Kaplan-Meier analyses of glucose exposure, patients were stratified in 2 groups: group 1: glucose exposure 0–120 g/24 h and group 2: glucose exposure >120 g/24 h. Further Kaplan-Meier analysis was performed after residual diuresis. Therefore, patients were divided in 2 groups: group 1 had residual diuresis. Group 2 was anuric. Continuous data were used in de multivariate models. Comparisons of peritonitis frequency were performed using Kaplan-Meier method.

Results

Patient Characteristics and Clinical Data

As shown in Table 1, the mean age was 52.8 ± 17.4 years and 59% were male. About 87% of the patients had residual diuresis. Failure of a previous renal transplant and HD before PD are the main reasons of loss of residual di-

Table 1. Baseline patient characteristics and clinical data

Characteristic	$n = 105$
Age, years	52.8±17.4
Gender, male	62 (59)
Weight, kg	75.5±13.3
Length, cm	173±10.8
BMI, kg/m^2	25.2±3.6
Residual diuresis	91 (87)
CrCl, mL/min	7.5±9.9
Urea – CrCl, mL/min	10.0±6.1
Diabetes	10 (9.5)
Hypertension	99 (94)
Cardiovascular disease	37 (35)
Previous kidney transplantation	20 (19)
Previous heart transplantation	2 (2)
Albumin, g/L	38.6±4.8
Immunosuppressive drugs	25 (24)

Categorical variables are presented as number (percentage); continuous variables are presented as mean ± SD.

CrCl, creatinine clearance.

Table 2. Data during follow-up

Parameters	$n = 105$
Follow-up, months	22.9±20.3
Mortality during follow-up	34 (32)
Number of patients developing peritonitis	51 (49)
Peritonitis incidence, number/year	0.07±0.14
PD modality at 6 months	
CAPD	66 (63)
APD	39 (37)
Interval to 1st peritonitis all patients, months	16.9±18.6
Peritonitis on	
CAPD treatment	27 (41)
APD treatment	24 (62)
Number of patients without residual diuresis at the time of peritonitis	17 (31)
Number of patients with residual diuresis at 6 months	75 (75)
Peritoneal glucose exposure, g/24 h	
6 weeks	119.3±36.0
6 months	141.6±48.2
CrCl at 6 weeks, mL/min	7.5±9.9
Number of patients in follow-up	
At 1 year	55
At 2 years	28
At 3 years	11
At 4 years	4
At 5 years	7

Outcome parameters during follow-up. Categorical variables are presented as number (percentage); continuous variables are presented as mean ± SD.

CrCl, creatinine clearance; PD, peritoneal dialysis; CAPD, continuous ambulatory PD; APD, automatic PD.

uresis. Nineteen percent of the patients had previous kidney transplantation and 2% heart transplantation. Twenty-four percent of the patients used immunosuppressive drugs (Table 1). Mean follow-up time was 22.9 ± 20.3 months. A total of 49% of the patients experienced at least one peritonitis. Patients were on dialysis for 16.9 ± 18.6 months at the first episode of peritonitis. The average peritoneal glucose exposure at 6 weeks and after 6 months was 119.3 ± 36.0 and 141.6 ± 48.2 g/24 h, respectively (Table 2). The glucose exposure during follow-up remained fairly stable (at 1 year: 145 ± 49 g/24 h; at 2 years: 155 ± 61 g/24 h; at 3 years: 152 ± 40 g/24 h; at 4 years: 173 ± 57 g/24 h; at 5 years: 152 ± 46 g/24 h). After 6 months, 75% of the patients had residual diuresis. At time of peritonitis, 69% had residual diuresis.

Residual Diuresis, Glucose Exposure, and Peritonitis Incidence

Results of univariate Cox regression analyses are listed in Table 3. These data show that in univariate analysis, the use of immunosuppressive drugs and serum albumin (as parameter for nutritional status) significantly predicted time to first peritonitis ($p \leq 0.001$ and $p = 0.001$ respectively). Residual diuresis at baseline ($p = 0.50$) or glucose exposure at baseline ($p = 0.10$) did not significantly predict peritonitis. If the analyses was performed with the mean of the urea and CrCl instead of residual diuresis as measure for RRF similar results were obtained.

However, Cox regression with the same parameters at 6 months yielded different results. After 6 months of follow-up, both residual diuresis and glucose exposure were significant predictors for peritonitis ($p = 0.038$ and $p < 0.001$, respectively).

The multivariate model (Table 3) yielded identical results. In a multivariate model adjusting for age, sex, residual diuresis, daily glucose exposure, serum albumin, and use of immunosuppressive drugs, the use of immunosuppressive drugs and serum albumin significantly predicted peritonitis ($p \leq 0.001$ and $p = 0.004$, respectively). Furthermore, it showed that after 6 months of PD treatment, glucose exposure significantly predicted peritonitis ($p = 0.024$) whereas residual diuresis did not reach significance ($p = 0.75$).

Both univariate and multivariate analyses showed that peritoneal glucose exposure at 1 year after the start of PD also predicted peritonitis (hazard ratio [HR] 4.3, 95% CI [2.3–8.2], $p \leq 0.001$ and HR 4.0, 95% CI [1.72–9.46], $p = 0.001$, respectively), whereas residual diuresis was not significant. Analysis at 2 years after the start of PD showed

Table 3. Cox regression with univariate and multivariate analysis of baseline and 6 months characteristics and the outcome parameter peritonitis

Parameters	6 Weeks HR (95% CI)	*p* value	6 Months HR (95% CI)	*p* value
Univariate Cox regression analysis				
Residual diuresis	0.77 (0.35–1.66)	0.50	0.53 (0.29–0.97)	0.038
Glucose exposure (per 100 g/24 h)	1.99 (0.87–4.56)	0.10	2.93 (1.69–5.08)	<0.001
Use of immunosuppressive drugs	3.9 (2.14–7.21)	<0.001	–	–
Serum albumin, g/L	0.91 (0.85–0.96)	0.001	0.89 (0.82–0.96)	0.004
Multivariate Cox regression analysis				
Gender	0.92 (0.46–1.85)	0.82	0.54 (0.26–1.11)	0.09
Age, years	1.00 (0.98–1.01)	0.60	1.00 (0.98–1.02)	0.92
Residual diuresis	1.06 (0.37–3.05)	0.91	0.86 (0.34–2.18)	0.75
Glucose exposure (per 100 g/L)	1.48 (0.58–3.76)	0.41	2.19 (1.11–4.32)	0.02
Immunosuppressive drugs	4.04 (2.13–7.68)	<0.001	3.53 (1.66–7.53)	0.001
Albumin, g/L	0.92 (0.87–0.97)	0.004	0.91 (0.83–0.99)	0.02

Results of univariate and multivariate Cox regression analysis with peritonitis as outcome and listed the variables as covariate.
HR, hazard ratio.

that glucose exposure still predicted peritonitis univariately (HR 1.7, 95% CI [1.0–2.9], $p = 0.045$), but not multivariately; in this multivariate analysis at 2 years after the start of PD, only the use of immunosuppressive drugs remained significant.

Kaplan-Meier analysis of the peritonitis-free survival showed that patients with a high (>120 g/24 h) daily glucose exposure at 6 weeks and at 6 months had a shorter time to peritonitis compared to patients that had a low daily glucose exposure (≤120 g/24 h; Fig. 1a, b).

Kaplan-Meier analysis of the peritonitis-free survival of the patient groups categorized by the presence or absence of residual diuresis at 6 weeks and 6 months showed no significant difference ($p = 0.49$) between patients with or without residual diuresis (Fig. 1c) at 6 weeks. However, at 6 months there was a significant difference ($p = 0.033$; Fig. 1d).

Discussion

The goal of this study was to unravel the association between RRF, glucose exposure, and the time to peritonitis. The major finding in our study was that after 6 months follow-up the glucose exposure is the most important risk factor for the occurrence of peritonitis, independent of residual diuresis. This suggests that higher exposure to glucose rather than loss of RRF is associated with an increased risk of peritonitis.

In line with other studies, we confirm in this study that use of immunosuppressive drugs as wel as serum albimin are both strong significant predictors of PD peritonitis. Furthermore, the study showed that at 6 weeks both residual diuresis as well as daily peritoneal glucose exposure did not predict the occurrence of peritonitis. Sensitivity analyses with the mean of the urea and CrCl instead of residual diuresis as measure for RRF yielded similar results.

Several studies described the protective factor of RRF for peritonitis [2, 12, 18]. In our study, we only see after 6 months of PD that residual diuresis is a protective factor for peritonitis. When adjusting for other risk factors, it fails to demonstrate a significant role for residual diuresis. Obviously, residual diuresis and glucose exposure are closely related, because patients with limited residual diuresis usually need higher glucose exposure to ensure adequate ultrafiltration. As far as we know, this study is the first that included both residual diuresis as peritoneal glucose exposure. This study showed that it is not the residual diuresis itself, but peritoneal glucose exposure that relates to the peritonitis. Several studies have investigated the role of peritoneal glucose exposure on developing peritonitis. Some studies have found no effect [9, 10], whereas other found that glucose exposure was a significant factor [11]. These divergent results may be explained by differences in the categorization of glucose exposure. The studies that found no significant effect of glucose exposure on peritonitis have only investigated this by dividing patients in a high and low glucose group. This ap-

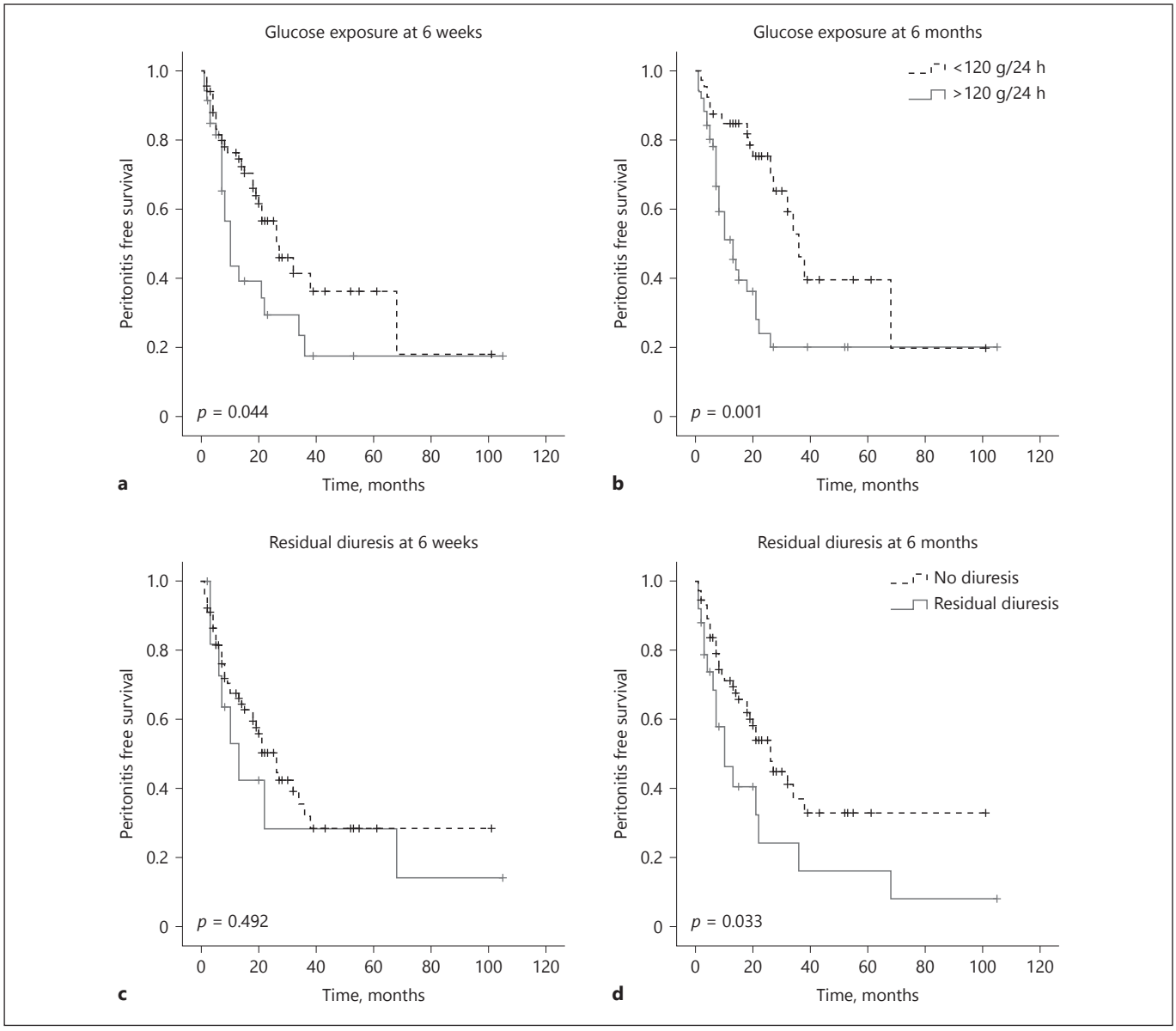

Fig. 1. a Kaplan-Meier curve showing time to first peritonitis according to glucose exposure at 6 weeks. Group 1, the dashed line, contains patients with a glucose exposure ≤120 g/24 h (n = 69); Group 2, the gray line, contains patients with a glucose exposure >120 g/24 h (n = 35). **b** Kaplan-Meier curve showing time to first peritonitis according to glucose exposure at 6 months. Group 1, the dashed line, contains patients with a glucose exposure ≤120 g/24 h (n = 40); Group 2, the gray line, contains patient with a glucose exposure >120 g/24 h (n = 51). **c** Kaplan-Meier analysis of peritonitis-free survival of the patient groups categorized by the presence or absence of residual diuresis at 6 weeks. The gray line represents the anuric patients, the dashed line patients with residual diuresis. **d** Kaplan-Meier analysis of peritonitis-free survival of the patient groups categorized by the presence or absence of residual diuresis at 6 months. The gray line represents the anuric patients, the dashed line patients with residual diuresis.

proach might not be sensitive enough to detect the effect of glucose exposure on peritonitis.

Other studies suggest that a high peritoneal glucose load increases the risk of peritonitis, perhaps as the effect of impaired host defenses, vascular disease, and damage to the peritoneal membrane [9–11]. The last years there is more knowledge about the influence of glucose exposure on the peritoneum [6, 11, 19, 20]. The human peritoneal mesothelial cells play a key role in early peritoneal membrane injury [21]. However, it is unclear whether

this explains the prevalence of peritonitis. Little is known about the glucose concentrations that are necessary to facilitate bactericidal activity in humans. In vitro studies however demonstrate that the bactericidal sugar concentrations were much higher than the maximum glucose concentrations in the dialysis solutions. In line with this, the osmolarity that was bactericidal in vitro was almost twice as high as the osmolality of a 3.86% dialysis solution [10, 22].

Clinical experience learns that the peritoneal membrane characteristics are fully known and developed after 6 months [23]. Therefore, we are convinced that the prescribed peritoneal glucose dose at 6 months does better reflect the true peritoneal characteristics. This is why we believe that only at 6 months the glucose exposure predicts peritonitis.

The present study has several strengths and weaknesses. For example, some potential risk factors such as socioeconomic status or personal hygiene were not included. Other relevant data representing nutritional status such as the subjective global assessment or incidence of culture negative peritonitis were also not included. Although adjustments for all major risk factors were made, residual confounding cannot be excluded due to the observational design of the study. Furthermore, this was a single center study.

Major strengths of this study were the inclusion of all incident PD patients visiting our center and the relative long-term follow-up time. The prospective design in that all patients were included directly from start PD and not during a random moment during their treatment we believe to be another strong plus. As already mentioned, this study is to our knowledge the first that included both residual diuresis as peritoneal glucose exposure.

In conclusion, this study showed that peritoneal glucose exposure and not residual diuresis predicts the occurrence of peritonitis. Further studies should shed more light to the mechanistical pathways that relate higher peritoneal glucose exposure to peritonitis. Future studies should further investigate which potential bactericidal properties of PD solutions might be clinically relevant. In our opinion, this demonstrates the importance of low glucose exposure in the prevention of peritonitis.

Disclosure Statement

J.K. received a general research grant not specifically related to this study. Further none declared. The results presented here have not been published previously in whole or part.

Author Contributions

H.U. included patients and collected data, designed the study, analyzed the data, and drafted the article. C.F.M.F. designed the study, interpreted the data, and revised the report. J.K. oversaw the analysis and made comments on the draft. R.W. oversaw the analysis and commented the original draft. F.L.N. compiled the data, analyzed the data, interpreted the data, and revised the draft.

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