Intra-individual association between C-reactive protein and insulin administration in postoperative lumbar spinal canal stenosis patients: A retrospective cohort study

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ABSTRACT

The association of intra-individual variability in insulin requirements with C-reactive protein levels among acute phase patients remains unclear. This retrospective cohort study aimed to evaluate this association. Patients with type 2 diabetes undergoing surgery for lumbar spinal canal stenosis were included in the study. We analyzed 286 records of 49 patients using the linear mixed effects model. The model showed C-reactive protein levels to be significantly associated with insulin requirements, with an effect size of 0.60 U/day for an elevation of 1 mg/dL. The effect size was increased in patients with higher hemoglobin A1c levels. Our findings imply that C-reactive protein levels could be a useful clinical biomarker when blood glucose levels are controlled in acute phase patients.

INTRODUCTION

Evidence from numerous studies suggests that insulin resistance increases during the acute phase in patients with type 2 diabetes mellitus; controlling blood glucose levels is therefore particularly important[1–3]. However, determining optimal insulin requirements for adequately controlling blood glucose levels without inducing hypoglycemia remains a particular challenge, even for experts[4].

C-reactive protein (CRP) is a frequently measured inflammatory marker. The association between CRP or high-sensitivity CRP levels and insulin resistance in the chronic phase has been well-studied[5–8]. However, this association has not been adequately investigated in acute phase patients. In particular, intra-individual variability in insulin requirements and its association with CRP levels remains unclear. Although the postoperative correlation between CRP levels and insulin resistance was evaluated in a cohort study, intra-individual variability was not considered[9].

Therefore, we aimed to determine the association between CRP levels and insulin requirements in acute phase patients.

Understanding the intra-individual correlation between CRP levels and insulin requirements in the acute phase might aid accurately estimating insulin requirements.

METHODS

Ethics statement

The present study was approved by the institutional review board of Yokohama Rosai Hospital (No. 31-25); the requirement for informed consent was waived, as the data were anonymous and the interventions were non-invasive.

Participants

This retrospective cohort study carried out at a tertiary hospital included patients with type 2 diabetes mellitus admitted between April 2016 and March 2019 for lumbar spinal canal stenosis surgery; their blood glucose levels were controlled by endocrinologists. Patients with lumbar spinal canal stenosis were selected owing to the low postoperative infection risk[10], high post-surgery CRP levels[11] and restricted physical activity, which impairs glucose tolerance[12]. Patients undergoing hemodialysis, receiving steroids and with postoperative infections were excluded[13–15].

Statistical analysis

Owing to intra-individual variability in serum CRP levels, we used the linear mixed effects model to analyze hierarchical data; that is, a nested dataset in which multiple recordings belonged to each participant[16–18].

We analyzed records on days when CRP levels were measured after surgery. The difference between the daily amount of insulin administration and that of preoperative phases was used as the outcome (ΔInsulin). CRP levels, glucose intake, and oral hypoglycemic agent use were used as explanatory variables. These were time-changing and had a temporal association with ΔInsulin. They were therefore incorporated in the level 1 equation. We also included hemoglobin A1c (HbA1c) levels, estimated glomerular filtration rate and body mass index for their importance in type 2 diabetes mellitus [19]. We assumed that the values of these variables remained unchanged during the observational period, and accordingly incorporated them into the level 2 equation. To increase interpretability, we used them as the differential value from the mean of the study participants.

We used two-thirds and one-third of patients' data as the training and test datasets, respectively. Using the training dataset, we developed the linear mixed effects model by full information maximum likelihood. By calculating the Pearson's correlation coefficient between the predicted and actual amounts of ΔInsulin using fivefold cross-validation[20–22], we determined to add each variable or random effect. During cross-validation, the model was evaluated using the data of patients not included in model development, similar to leave-subject-out cross-validation[23,24]. We also validated the model on the independent test dataset and finally calculated the effect size using the entire dataset.

To confirm sample size sufficiency, we calculated the performance in cross-validation by changing the sample size from small to entire datasets[25], and also carried out power analysis for the significance of the CRP coefficient.

All analyses were carried out using open source software R (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria) with a library "lmerTest" (version 0.3.1, https://cran.r-project.org/web/packages/lmerTest/citation.html) and "simr" (version 1.0.5, https://cran.r-project.org/web/packages/simr/citation.html). $P < 0.05$ was considered significant.

Measurements

Serum CRP levels were measured using latex coagulation (Nittobo Medical Co., Ltd., Tokyo, Japan). The estimated glomerular filtration rate was calculated using serum creatinine levels measured by the enzyme method (Serotec Co., Ltd., Sapporo, Japan). Serum HbA1c levels were measured using high-performance liquid chromatography (Tosoh Co., Ltd., Tokyo, Japan).

RESULTS

Overall, 286 records were obtained from 49 patients; their descriptive data are shown in Table 1. We used 190 records from 32 patients as the training dataset and 96 records from 17 patients as the test dataset. The final model achieved an average Pearson's correlation coefficient of 0.429 on cross-validation and achieved a significantly positive Pearson's correlation coefficient of 0.444 (95% confidence interval [CI] 0.267–0.592) in the test dataset.

The coefficients of the model are shown in Table 2 (see Appendix S1 for the equation). The intercept, CRP, and interaction terms of CRP and HbA1c were statistically significant. The intercept showed that patients required an average of 3.11 U/day (95% CI 1.14–5.07 U/day) of additional insulin than the preoperative state. The model also showed that an increase in CRP levels to 1 mg/dL increased the amount of insulin to 0.60 U/day (95% CI 0.33–0.86 U/day), and 1% differences in HbA1c levels increased the effect size to 0.91 (95% CI 0.52–1.30). Other variables were not significant, but improved model performance. The model and data are shown in Figure 1.

The relationship between the accuracy and sample size is shown in Figure 2. The accuracy was almost saturated on achieving sample sizes of 30. The power for significance of the CRP coefficient was 0.989. Both results implied that the sample size was almost sufficient for analysis.

DISCUSSION

Using longitudinal data of diabetes patients who had undergone lumbar spinal canal stenosis surgery, we found that CRP levels were significantly associated with insulin requirements during the postoperative acute phase.

Intra-individual correlation observed in the postoperative state might improve the current understanding regarding the

Table 1 | Characteristics of study participants

Patients (n = 49)		
Continuous variables	Mean (SD)	Median (IQR)
Age (years)	74.04 (7.37)	74 (11)
HbA1c (%)	7.19 (1.01)	6.9 (1.0)
eGFR (mL/min/1.73 m²)	71.42 (15.91)	72.70 (21.21)
BMI (kg/m²)	24.58 (4.41)	23.95 (3.97)
Glucose intake (g/day)	190.67 (48.33)	198.00 (65.90)
Peak CRP (mg/dL)	7.14 (5.04)	6.65 (7.74)
Peak ΔInsulin (U/day)	7.61 (10.76)	4 (8)
Categorical variables		n (%)
Male sex		26 (53)
OHA use		39 (80)

No patient used glucagon-like peptide-1 receptor agonists. Δ, Differential value from the mean; BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; IQR, interquartile range; OHA, oral hypoglycemic agent; SD, standard deviation.

Table 2 | Coefficients of the linear mixed-effect model

Total n = 286	Mean (95% CI) effect	*P*-value
Independent effects		
Intercept	3.11 (1.14 to 5.07)	**0.0026**
ΔHbA1c (%)	1.91 (−2.48 to 6.30)	0.39
CRP (mg/dL)	0.60 (0.33 to 0.86)	**<0.001**
OHA	−1.32 (−3.11 to 0.47)	0.15
Interactive effects		
CRP × ΔHbA1c	0.91 (0.52 to 1.30)	**<0.001**
Glu (g/day) × ΔHbA1c	0.0042 (−0.015 to 0.024)	0.67
OHA × ΔeGFR (mL/min/1.73 m²)	−0.089 (−0.18 to 0.0004)	0.053

Bold values indicates *P* < 0.05. Δ, Differential value from the mean; CI, confidence interval; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Glu, glucose intake; HbA1c, hemoglobin A1c; OHA, oral hypoglycemic agent use.

association between CRP levels and insulin resistance[5–9]. There are two potential explanations for our findings. First, CRP is a proxy of other inflammatory cytokines, such as interleukin-6 or tumor necrosis factor-α, which have been reported to induce insulin resistance[26,27]. Second, CRP directly impairs glucose tolerance, as shown in an *in vivo* study[28]. Further studies are required to identify such potential underlying mechanisms.

As shown by the significant interaction between CRP and HbA1c, the degree of association between CRP levels and insulin resistance was higher in patients with higher HbA1c levels. Although previous studies have identified preoperative HbA1c levels to be associated with postoperative glycemic control[29], they only examined the independent effect. The present findings probably indicate the synergistic effects of postoperative inflammation and preoperative glycemic control on insulin resistance.
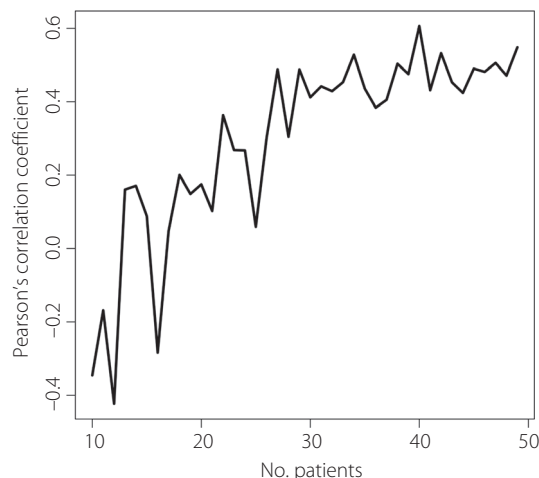

Figure 2 | The relationship between the performance of the model and sample size. The model performance was evaluated based on the Pearson's correlation coefficient between the predicted and actual amounts of ΔInsulin on fivefold cross-validation, by increasing the study sample from small (n = 10) to the current entire cohort size (n = 49). The graph shows that after attaining a sample size of 30, the accuracy was almost saturated.

As evident from the significantly positive intercept of the model, patients in this cohort required more insulin postoperatively. This might reflect the activity of pathways associated with hormones other than inflammatory cytokines, such as glucagon or catecholamine[30].

The present study had several limitations. First, as we used insulin requirements as the outcome, the maintenance of blood glucose levels within the optimal range was not validated;
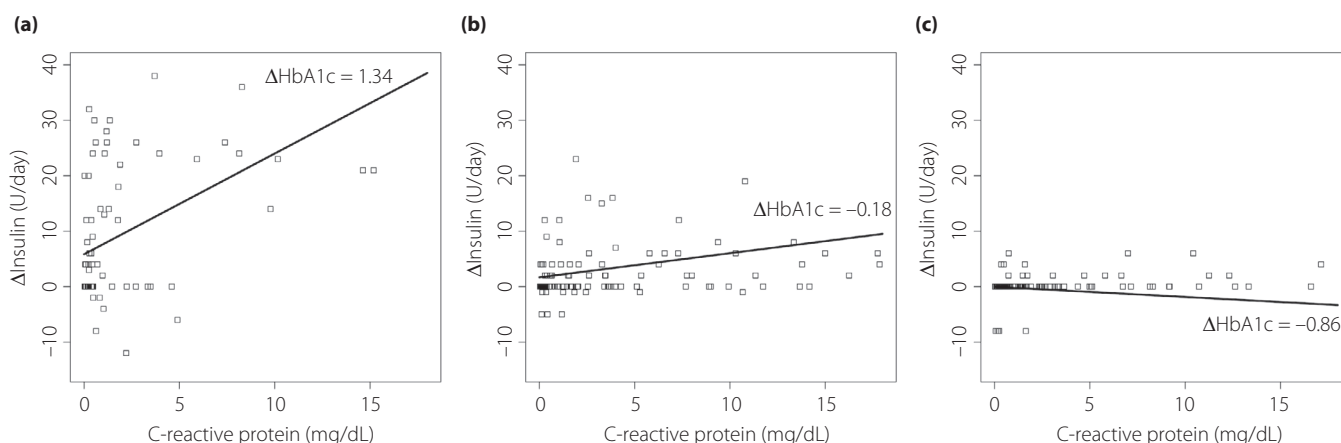

Figure 1 | Representation of the model and data. ΔInsulin represents the differential value of the doses of insulin administered compared to preoperative requirements. ΔHbA1c represents the remainder after subtracting the mean HbA1c of all patients (7.19%) from the HbA1c of each patient. The coefficients of the model are shown in Table 2. The data have been categorized into three groups based on hemoglobin A1c (HbA1c) levels, namely, high, moderate and low, with approximately one-third of patients in each. The graphs have been drawn using the mean value in each group. (a) The mean ΔHbA1c of the high HbA1c group is 1.34; the graph has a steep slope. (b) The mean ΔHbA1c of the moderate HbA1c group is −0.18; the graph has a shallow slope. (c) The mean ΔHbA1c of the low HbA1c group is −0.86; the slope of the graph is almost flat.

however, the lack of insulin was partially compensated for by the sliding scale. Second, there was no specified protocol for controlling blood glucose levels; therefore, the insulin doses might have varied among physicians. Third, we could not incorporate C-peptide or immunoreactive insulin owing to missing data. Fourth, the types and amounts of oral hypoglycemic agents were not considered to streamline the analysis. Fifth, although CRP elevation is delayed by 24–72 h after inflammation[11], the time lag was not considered. Finally, elevation of CRP levels strongly depends on bacterial species[15]; therefore, the effect size would not be generalizable to other diseases.

In conclusion, we found an association between postoperative CRP levels and the doses of insulin administered. The findings led us to speculate that CRP levels could be a metric for determining insulin requirements. Further prospective multicenter studies are required to validate the present findings.

DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 | The equation of the linear mixed effects model.