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RESEARCH ARTICLE

Spline Longitudinal Multi-response Model for the Detection of Lifestyle-Based Changes in Blood Glucose of Diabetic Patients

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Abstract: ***Background*:** Blood sugar and lifestyle problems have long been problems in diabetes. There has also been a lot of research on that. However, we see that diabetic patients are still increasing even though many patients are not aware of the start of the disease occurrence. Therefore, we consider it very important to examine these two main problems of diabetes by using a more flexible statistical approach to obtain more specific results regarding the patient's condition.

***Objective*:** The form of data for type 2 diabetes patients is repeated measurements so that it is approached through longitudinal studies. We investigated various intervals of pattern change that can occur in blood glucose, namely fasting, random, and 2 hours after meals based on blood pressure and carbohydrate diets in diabetic patients in South Sulawesi Province, Indonesia.

***Methods*:** This research is a longitudinal study proposing a flexible and accurate statistical approach. It is a weighted spline multi-response nonparametric regression model. This model is able to detect any pattern of changes in irregular data in large dimensions. The data were obtained from Hasanuddin University Teaching Hospital in South Sulawesi Province, Indonesia. The number of samples analyzed was 418 from 50 patients with different measurements.

***Results*:** The optimal spline model was obtained at 2 knots for blood pressure and 3 knots for carbohydrate diets. There are three blood pressure intervals that give different patterns of increase in patient blood glucose levels, namely below 126.6 mmHg, 126.6-163.3 mmHg, and above 163.3 mmHg. It was found that blood sugar rose sharply at blood pressure above 163.3 mmHg. Furthermore, there are four carbohydrate diet intervals that are formed, which are below 118.6 g, 118.6-161.8 g, 161.8-205 g, and above 205 g. The result is that blood sugar decreased significantly at intervals of carbohydrate diet 161.8-205 g.

***Conclusion*:** Blood glucose increases with a very high increase in blood pressure, whereas for a carbohydrate diet, there is no guarantee that a high diet will be able to reduce blood glucose significantly. This may be affected by the patient's saturation of a very high carbohydrate diet.

Keywords: Blood glucose, blood pressure, carbohydrate diet, multi-response, nonparametric regression, spline longitudinal.

1. INTRODUCTION

Diabetes mellitus is a global disease and the number of patients suffering from this disease is increasing. It is estimated that half of the diabetic patients are unaware of their disease, making them more susceptible to diabetes complications [1]. Blood glucose and lifestyle problems are two very important aspects of diabetes [2]. The results of several studies show that factors related to blood glucose include body weight [3, 4], cholesterol [5, 6], triglycerides [7, 8], and lifestyle [9]. For lifestyle, it can be measured from several patient behaviors, including physical activity [10, 11], dietary factors [12, 13], and stress management [14, 15]. These studies use cross-sectional data, namely data obtained from one-time measurements only. However, for diabetic patients, especially inpatients, must undergo several examinations by the medical team. Therefore, it is necessary to conduct a study that considers repeated measurements based on time, namely a longitudinal study [16]. It was developed as a combination of cross-sectional with time series so that it has better accuracy [17, 18].

This study uses a longitudinal study to detect the lifestyle of diabetic patients resulting from several patterns of changes in blood sugar. There is a tendency for blood glucose to rise or fall very quickly, so a weighted multi-response non-parametric regression model approach is used.

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The model is able to analyze data whose patterns fluctuate and do not follow parametric patterns [19, 20]. The ability of the weighted spline regression method in longitudinal studies has been tested through simulation and a small error value is obtained [21, 22]. Furthermore, theory development has been carried out on one-response bi-predictors [23] and bi-response multi-predictors [24]. For cases of diabetes, it has been analyzed considering blood glucose 2 hours after meals based on the duration of treatment [25]. However, these studies have not considered three interrelated indicators of blood glucose, namely fasting, randomized, and 2 hours after eating. Therefore, in this study, the three types of blood glucose were simultaneously modeled based on dietary carbohydrate factors and the patient's blood pressure through a multi-response spline.

2. MATERIALS AND METHODS

2.1. Materials

Data obtained from Hasanuddin University Teaching Hospital in Indonesia were taken from the results of the patient's medical records. The data collection process at the hospital has gone through the administrative process from the university to the hospital. Recording was carried out based on data from patients who were hospitalized from 2015-2019. All patient data that we obtained were not analyzed in their entirety because there were some missing data, so they were not included as samples in this study. The number of data analyzed was 418 obtained from 50 patients and had been diagnosed with type 2 diabetes. Each patient's repeated measurements are different, which depends on the length of their stay in the hospital.

The data analyzed were fasting blood glucose factors, random and 2 hours after meals as response variables. As for lifestyle factors, it is measured from blood pressure as a measure of the patient's stress level in the hospital and dietary carbohydrate factors that are given by the medical to patients every day.

2.2. Method of Analysis

The approach we use is a weighted non-parametric multiresponse spline regression model which can be expressed as follows:

$$\mathbf{y}_{ij} = \mathbf{f}\left(x_{ij1}, x_{ij2}\right) + \boldsymbol{\varepsilon}_{ij},\ i = 1,2,\ldots,n,\ j = 1,2,\ldots,n_i\ , \quad (1)$$

where $\mathbf{y}_{ij} = \begin{bmatrix} y_{1.ij} \\ y_{2.ij} \\ y_{3.ij} \end{bmatrix}$, $\mathbf{f}\left(x_{ij1}, x_{ij2}\right) = \begin{bmatrix} f_1\left(x_{ij1}, x_{ij2}\right) \\ f_2\left(x_{ij1}, x_{ij2}\right) \\ f_3\left(x_{ij1}, x_{ij2}\right) \end{bmatrix}$, and $\boldsymbol{\varepsilon}_{ij} = \begin{bmatrix} \varepsilon_{1.ij} \\ \varepsilon_{2.ij} \\ \varepsilon_{3.ij} \end{bmatrix}$

Furthermore, y_1 is fasting blood glucose, y_2 is random blood glucose, and y_3 is blood glucose 2 hours after meals, x_1 is blood pressure and x_2 is dietary carbohydrate.

In Equation (**1**), the function of is $\mathbf{f}\left(x_{ij1}, x_{ij2}\right)$ estimated through the spline estimator with the following form:

$$\mathbf{f}\left(x_{ij1}, x_{ij2}\right) = \sum_{r=1}^{3}\left(\sum_{p=1}^{2}\left(\sum_{u=0}^{1}\beta_{r.u}\left(x_{ijp}\right) + \sum_{v_p=1}^{d_p}\beta_{r.(1+v_p)}\left(x_{ijp} - k_{v_p}\right)_+\right)\right), \quad (2)$$

where r is the number of responses, that is $r = 1,2,3$, p is the number of predictors, namely $p = 1, 2$, k is the point of knots, and v is the number of points of knots.

If Equation (**2**) is written in matrix form and included in Equation (1), then the model can be stated as follows:

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}. \quad (3)$$

Furthermore, the nonparametric multi-response spline regression parameter in (**3**) is estimated through the spline weighted the least square, which $\hat{\omega}$ as the weight of the covariance matrix with the following results:

$$\hat{\boldsymbol{\beta}} = \left(\mathbf{X}^T\hat{\omega}^{-1}\mathbf{X}\right)^{-1}\mathbf{X}^T\hat{\omega}^{-1}\mathbf{y}. \quad (4)$$

Based on Equation (**4**), the estimation of the multi-response nonparametric regression model with a weighted spline is as follows:

$$\hat{\mathbf{y}} = \mathbf{X}\hat{\boldsymbol{\beta}} = \mathbf{X}\left(\mathbf{X}^T\hat{\omega}^{-1}\mathbf{X}\right)^{-1}\mathbf{X}^T\hat{\omega}^{-1}\mathbf{y}.$$

3. RESULTS AND DISCUSSION

3.1. Results

Total data were 418 of 50 diabetic patients who were hospitalized. Factors measured in this study were fasting blood sugar, random and 2 hours after eating, blood pressure and dietary carbohydrates. Respondents' age ranged from 42-85 years with an average fasting blood glucose of 214.3 mg/dL, random blood glucose 236.6 mg/dL, and blood glucose 2 hours after eating 234.4 mg/dL. These values represent high diabetes indicator values in all patients. The same thing can be seen in Table **1**, where the average of the three blood glucose levels is high.

For the blood pressure category, there were 242 patients (57.9%) who had blood pressure below 130 mmHg, 112 patients (26.8%) who had blood pressure 131-150 mmHg, and 64 patients (15.3%) who had blood pressure above 150 mmHg. Furthermore, for the carbohydrate diet, most patients were on the 173-192 g diet, namely 186 patients (44.5%), 147 patients (35.2%) under 173 g, 81 patients (19.4%) of 193-235 g diet, and 81 patients (19.4%). High diet 236-275 g in only 4 patients (0.9%).

Diabetics patient data in longitudinal form looks irregular and does not follow the parametric form as shown in Fig. (**1**). This shows that in longitudinal studies for diabetic patient data, it is not possible to be analyzed by a parametric approach. In this study, we used a weighted multi-response spline non-parametric regression approach to show the pattern of changes in blood glucose based on blood pressure and carbohydrate diet. There were 3 responses from blood glucose, namely fasting, random, and 2 hours after eating which correlated above 0.5. For this reason, we used a weighted spline with a covariance variance matrix to overcome the correlation between responses and between repeated measurements in each patient.

Blood glucose data were modeled using a weighted spline approach that considered knot points on blood pressure factors and carbohydrate diets. The estimation results of the non-parametric multi-response spline weighted regression model at several points of knots, namely 1-8 knot points, are shown in Fig. (**2**). We can see that the regression curve estimation results that vary for each number of knot points. Furthermore, the optimal model selection is based on the knot point, which gives the minimum generalized cross validation value. The optimal knot points on blood pressure and carbohydrate diet were chosen 2 and 3 knot points, respectively, as in Fig. (**3**).

Table 1. Fasting blood glucose levels, random blood glucose, blood glucose 2 hours after meals from type 2 diabetes patients based on blood pressure and carbohydrate diet.

Average Blood Glucose	**Blood Pressure (mmHg)**			**Carbohydrate Diet (mg)**			
	≤ 130	**131 – 150**	**> 150**	**≤ 172**	**173 – 192**	**193 – 235**	**236 – 275**
Fasting	207.5	224.8	221.5	254.3	204.1	168.8	139.2
Random	228.7	251.3	240.8	254.5	236.1	208.1	182.5
2 Hours after meals	228.3	245.6	237.5	243.2	236.3	216.8	174.2
Total	242 (57.9%)	112 (26.8%)	64 (15.3%)	147 (35.2%)	186 (44.5%)	81 (19.4%)	4 (0.9%)

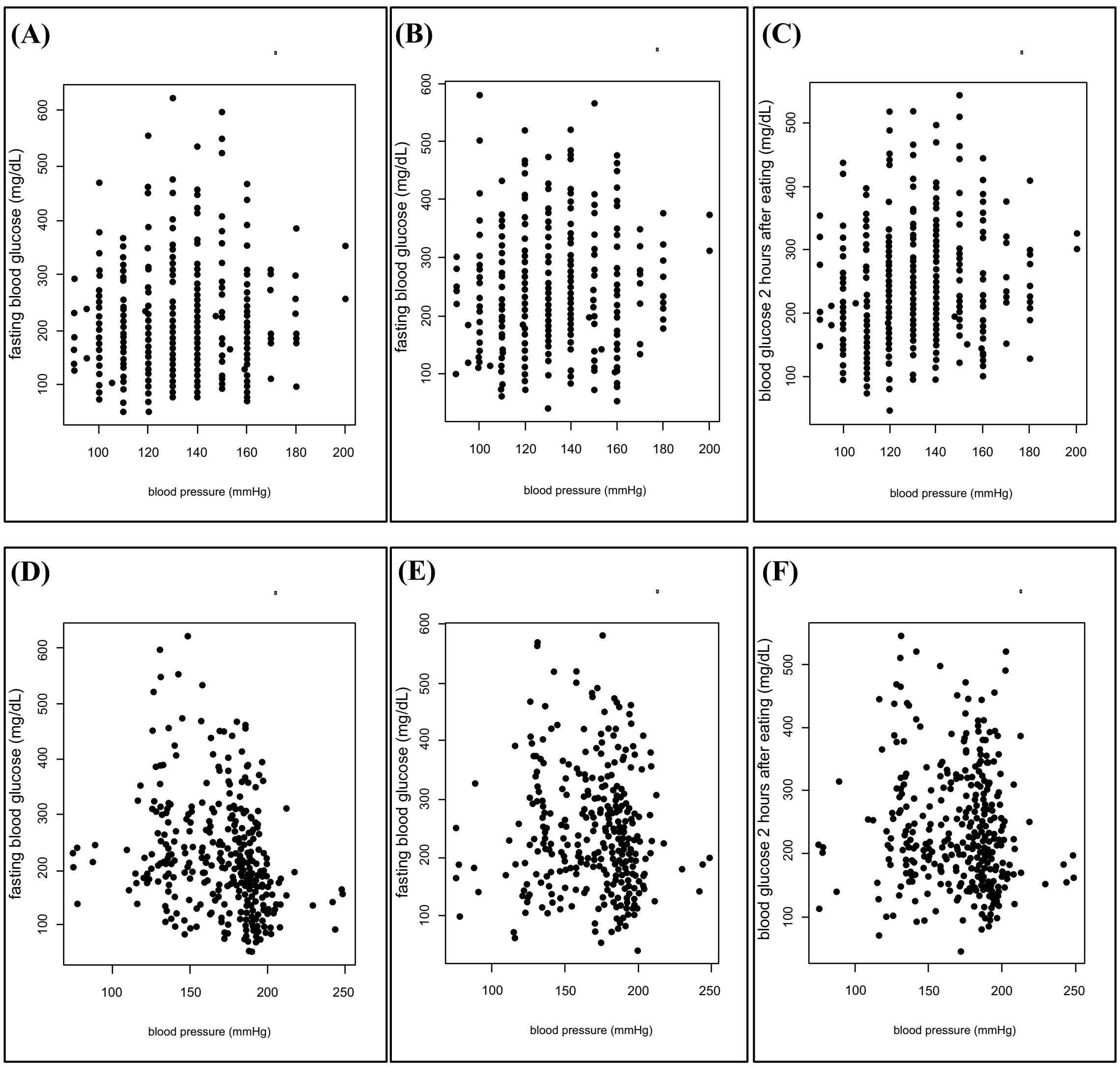

Fig. (1). Plot of data between blood glucose (**A**) fasting *vs.* blood pressure, (**B**) random *vs.* blood pressure, (**C**) 2 hours after meals *vs.* blood pressure, (**D**) fasting *vs.* carbohydrate diet, (**E**) random *vs.* carbohydrate diet, and (**F**) 2 hours after meals *vs.* carbohydrate diet.

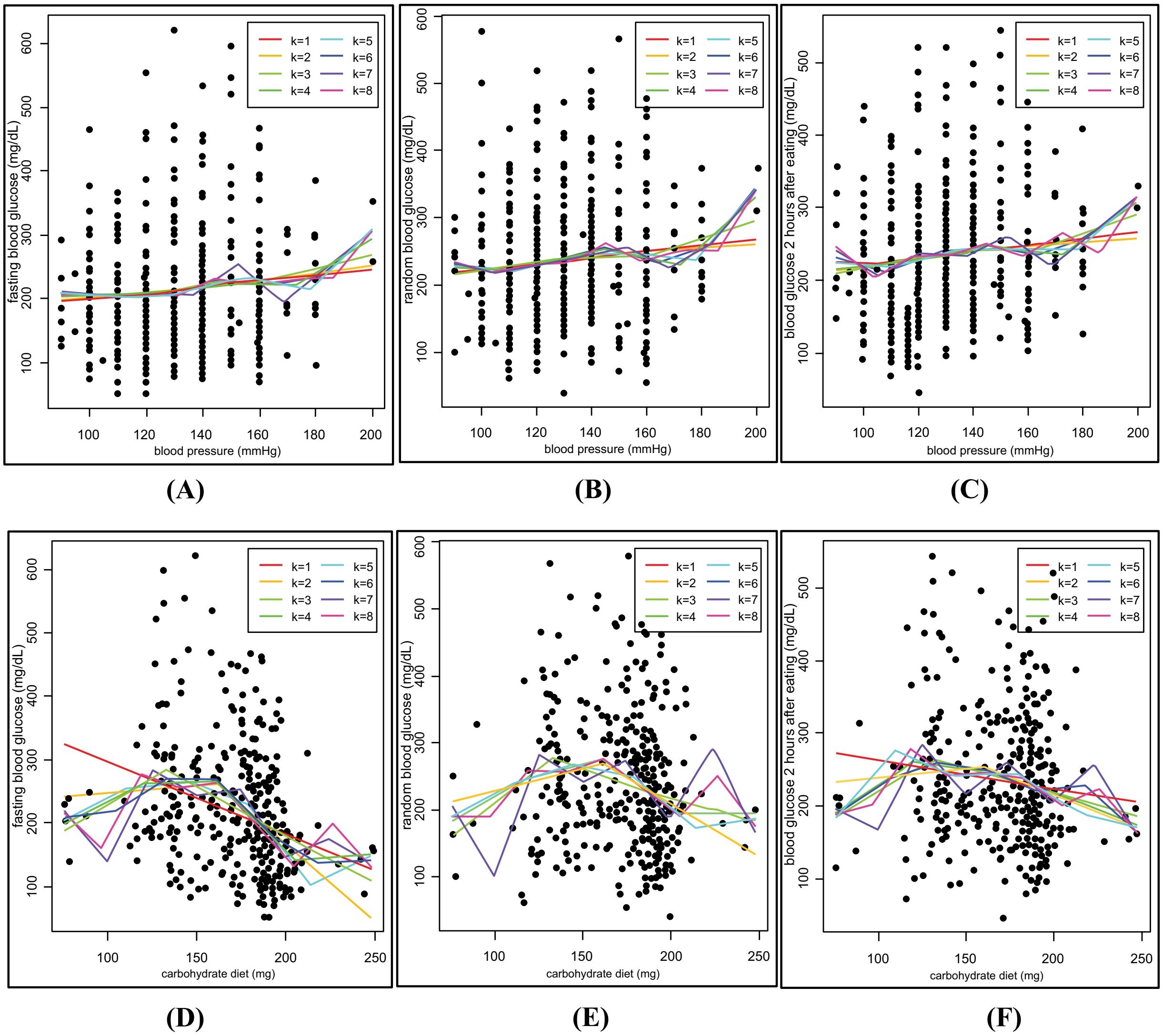

Fig. (2). Curve estimation results from non-parametric multi-response spline weighted regression at several knot points for blood glucose (**A**) fasting *vs.* blood pressure, (**B**) random *vs.* blood pressure, (**C**) 2 hours after meals *vs.* blood pressure, (**D**) fasting *vs.* carbohydrate diet, (**E**) random *vs.* carbohydrate diet, and (**F**) 2 hours after meals *vs.* carbohydrate diet.

The non-parametric multi-response spline weighted regression model according to Fig. (**3**) is as follows:

$\hat{y}_1 = 202.9 + 209.4x_1 + 228.6(x_1 - 126.6)_+ + 269.6(x_1 - 163.3)_+ + 198.2 + 258.9x_2 + 267.4(x_2 - 118.6)_+ + 143.1(x_2 - 161.8)_+ + 150(x_2 - 126.6)_+$

$\hat{y}_2 = 216.3 + 237.1x_1 + 245.4(x_1 - 126.6)_+ + 296.2(x_1 - 163.3)_+ + 182.9 + 247.8x_2 + 274.5(x_2 - 118.6)_+ + 194.6(x_2 - 161.8)_+ + 195.1(x_2 - 126.6)_+$

$\hat{y}_3 = 209.9 + 236.8x_1 + 241.9(x_1 - 126.6)_+ + 291.1(x_1 - 163.3)_+ + 185.3 + 259.6x_2 + 247.6(x_2 - 118.6)_+ + 214.7(x_2 - 161.8)_+ + 174(x_2 - 126.6)_+$

Based on the results of the model estimation, there are 3 patterns of changes in blood glucose that increase based on blood pressure, both on fasting blood glucose, random and 2 hours after eating. The three changes are the patterns for blood pressure below 126.6 mmHg, 126.6-163.3 mmHg, and above 163.3 mmHg. We can see that there is a sharp rise in all three types of blood glucose at blood pressure from 163.3 mmHg and a rather slow increase in blood pressure between 126.6-163.3 mmHg and below 126.6 mmHg. These results indicate that blood pressure has a significant effect on changes in patient blood glucose in general and needs special attention when blood pressure has reached 163 mmHg. We still have to pay attention to the blood pressure below it because it is still classified as abnormal but it takes a different handling treatment at each of these intervals.

Furthermore, for the carbohydrate diet, the optimal model is obtained at 3 knots, meaning that there are four patterns of changes in blood glucose based on the diet. It occurs at each dietary interval below 118.6 g, 118.6-161.8 g, 161.8-205 g, and above 205 g. The carbohydrate diet interval that was able to reduce fasting and random blood glucose was 161.8-205 g, while the other intervals still showed an upward pattern. There was a different result seen in the blood glucose pattern 2 hours after the meal, which had already fallen on the 118.6 g carbohydrate diet. These results indicate that the carbohydrate diet that is able to lower blood glucose properly is 161.8-205 g. The use of a diet below 161.8 g can be considered, but it needs commitment from the patient to maintain blood pressure and a better lifestyle so that even though the diet is low, it can still control the decrease in blood glucose.

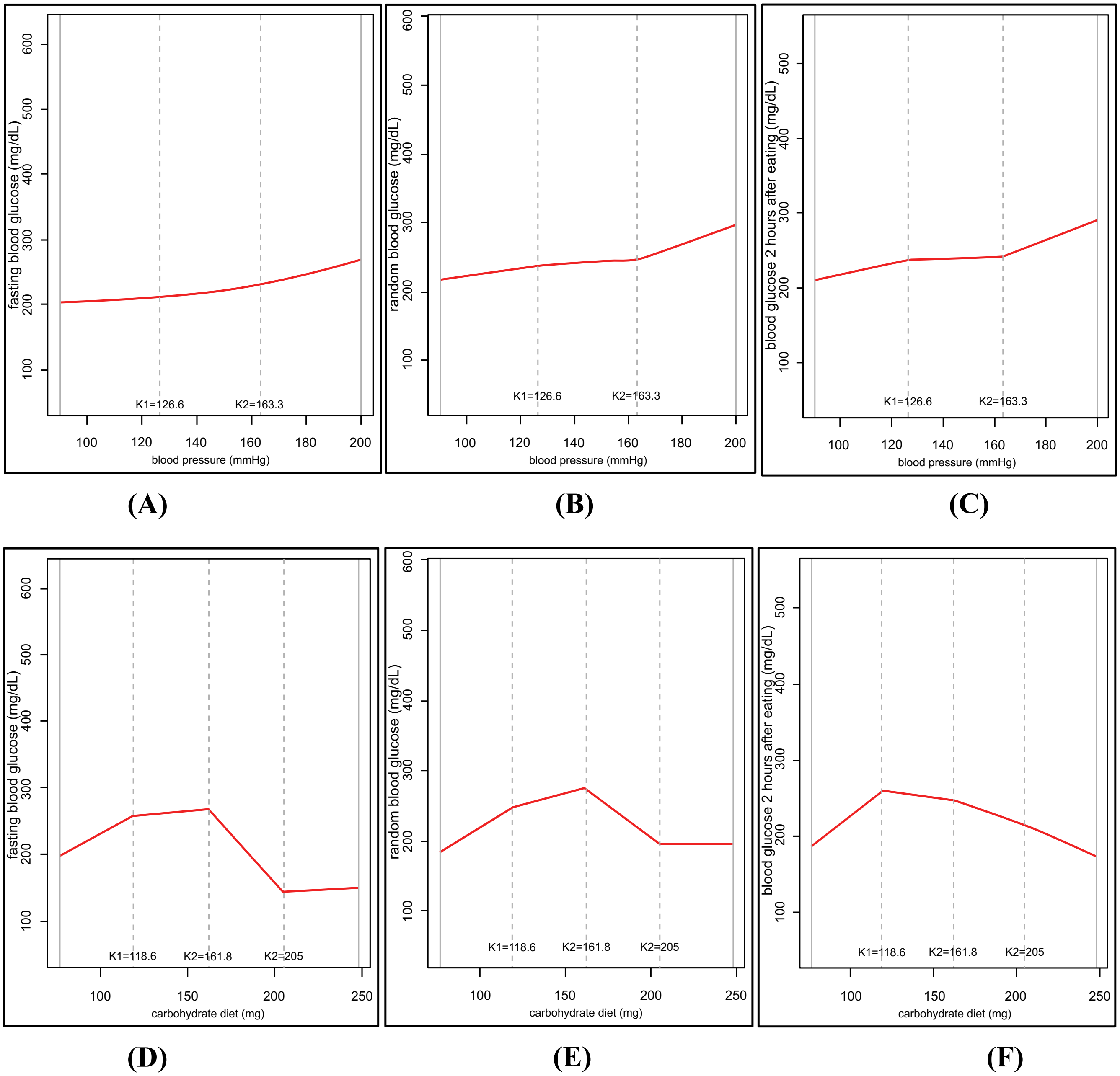

Fig. (3). Estimated optimal curve results from non-parametric regression multi-response weighted spline for blood glucose data (**A**) fasting *vs.* blood pressure, (**B**) random *vs.* blood pressure, (**C**) 2 hours after meals *vs.* blood pressure, (**D**) fasting *vs.* carbohydrate diet, (**E**) random *vs.* carbohydrate diet, and (**F**) 2 hours after meals *vs.* carbohydrate diet.

3.2. Discussion

This study resulted in several patterns of changes in blood sugar, both fasting, randomized, and 2 hours after eating based on blood pressure and dietary carbohydrates. The model used is a weighted spline multi-response nonparametric regression through a simultaneous process. Three patterns of changes were obtained based on blood pressure and four patterns based on carbohydrate diets. In the blood pressure factor, the effect is positive on all three types of blood sugar. This is indicated by the regression curve which tends to increase along with the increase in the patient's blood pressure. The trend of increasing blood sugar is different but on average, all three experience a sharp increase when blood pressure reaches 163.3 mmHg as shown in Figs. (**3A-C**). These results indicate that diabetics tend to have abnormal blood pressure and should be careful when reaching a blood pressure of up to 163.3 mmHg. It also means that someone who has high blood pressure can trigger an increase in blood sugar. These results are consistent with previous studies that blood pressure and blood sugar are correlated [26].

For dietary carbohydrate factors, the effect on changes in fasting blood sugar patterns, random and 2 hours after eating varies in the four patterns formed as shown in Figs. (**3D-F**). For fasting and random blood sugar, both have almost the same pattern of changes, namely blood sugar decreased at intervals of 161.8-205 g carbohydrate diet and increased at other intervals. As for blood sugar 2 hours after eating, it fell when the carbohydrate diet reached 118.6 g and further dropped when the diet reached 161.8-205 g. These results indicate that the appropriate carbohydrate diet interval to be considered for use is 161.8-205 g. Diabetic patients do not need to undergo a diet that is too high which can even lead to the appearance of complications. Carbohydrates are not considered from the amount but quality [27].

The use of the weighted longitudinal spline multi-response model in this study has been able to analyze fluctuating blood sugar data. In statistical studies, the accuracy of using data analysis models is very important because it is related to obtaining accurate results. For diabetes data, there are still many factors that play a role and are interrelated with each other. Therefore, we can suggest in future diabetes studies to consider the use of principal component spline nonparametric regression models [28]. Theoretically, the model has been tested in simulation studies for the case of two responses involving a large number of predictors and correlated with each other.

CONCLUSION

Diabetic patients have longitudinal measurement data because of the repeated measurements that occur to them. This study used 418 samples obtained from 50 type 2 diabetes patients by selecting 3 types of blood sugar from the measurement results. All three were used as responses, and lifestyle measured from blood pressure and carbohydrate diet were used as predictors.

Based on the results of data analysis from a non-parametric multi-response spline weighted regression model, the significant blood pressure that affects the patient's blood glucose increase occurs at very high blood pressure, which is above 163.3 mmHg. The difference in the increase in blood glucose in the three blood pressure intervals produced by the model shows that different treatment measures are needed at the three intervals. Furthermore, for the carbohydrate diet, the values that significantly lowered blood glucose were 161.8-205 g. At the fourth interval for a high diet, it actually gives an increase in blood glucose. This could be due to patient saturation in undergoing a diet so that it needs alternative actions from the medical team and the most important thing is motivation to the patient in following the right diet. The value of the intervals of the pattern of changes in blood glucose that we have obtained in this article can be a recommendation in the treatment of diabetes patients.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study does not involve direct human interaction. Data were collected from patient medical records on the approval of the hospital management with the Patient Data Code of Conduct Approval Letter.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

The author signs the Patient Data Code of Conduct Approval Letter.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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