SCIENTIFIC CULTURE, Vol. 12, No.2.1, (2026), pp. 8381-8388
Open Access. Online & Print

www.sci-cult.com
DOI: 10.5281/zenodo.19854149

MODELING THE RELATIONSHIP BETWEEN HBA1C, TC, AND TG: A GENERALIZED ADDITIVE MODEL AND RESPONSE SURFACE METHODOLOGY APPROACH

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ABSTRACT

This study aims to model the relationship between Hemoglobin A1c (HbA1c) levels and two key metabolic indicators-Triglycerides (TG) and Total Cholesterol (TC)-using advanced statistical methods. By leveraging nonparametric regression techniques, this research explores complex, nonlinear interactions between these variables, providing a more nuanced analysis than traditional linear models. Objective: The primary objective is to construct and validate an analytical framework that combines Generalized Additive Models (GAM) and Response Surface Methodology (RSM) to understand the effects of TG and TC on HbA1c. The dataset comprises HbA1c, TC, and TG as variables of interest. The data were split into a training set (70%) and a testing set (30%). A GAM model was used to capture the smooth, nonlinear relationships between the predictors and the response variable, while RSM was employed to generate response surface plots for further interpretation. Model performance was evaluated using Root Mean Squared Error (RMSE), Mean Absolute Error (MAE), Root Mean Squared Percentage Error (RMSPE), and Median Absolute Error (MedAE). The GAM model demonstrated strong predictive performance with an RMSE of 3.73, MAE of 2.33, and RMSPE of 54.80%. The RSM model highlighted the significant contributions of TC and TG, showing that both variables significantly affect HbA1c levels. The integration of GAM and RSM provides an effective approach for modeling complex health data and understanding the relationship between HbA1c, TC, and TG. This methodology offers valuable insights for healthcare professionals in predicting metabolic disorders and informs strategies for better managing patient health outcomes.

Keywords: Generalized Additive Model (GAM), Response Surface Methodology (RSM), HbA1c, Total Cholesterol (TC), Triglycerides (TG)

1. INTRODUCTION

Hemoglobin A1c (HbA1c) is a critical biomarker for assessing long-term glucose control, particularly in patients with diabetes mellitus (DM). The measurement of HbA1c provides clinicians with an overview of average blood glucose levels over the past two to three months, making it essential for diabetes management (Nathan et al., 2008). Elevated levels of HbA1c are directly linked to an increased risk of diabetesrelated complications s uch as retinopathy, nephropathy, and cardiovascular disease (Fowler, 2008). Therefore, understanding the factors that influence HbA1c levels is vital for improving diabetes care and prevention.

Among the numerous factors influencing HbA1c, metabolic markers such as Total Cholesterol (TC) and Triglycerides (TG) play significant roles. TC and TG are components of lipid metabolism and are known to be associated with insulin resistance, a hallmark of type 2 diabetes (Ginsberg, 2007). Dyslipidemia, characterized by elevated levels of TC and TG, has been identified as a major risk factor for the development of type 2 diabetes and cardiovascular diseases (Vasilenko et al., 2017). However, the complex, nonlinear interactions between these lipids and HbA1c levels remain insufficiently explored, especially using modern statistical modeling techniques. Traditional linear regression models may fail to capture the complexity of these relationships due to their inability to account for nonlinearity and interactions between variables. In response to these limitations, Generalized Additive Models (GAM) have emerged as a powerful tool for capturing nonlinear relationships without making restrictive assumptions about the functional form of the data (Wood, 2017). GAMs allow for the flexible modeling of smooth functions of predictors, making them ideal for health data where relationships between variables are often complex and nonlinear (Fahrmeir et al., 2013).

To explore these relationships in this study, we employ a two-pronged approach using both GAM and Response Surface Methodology (RSM). The combination of these techniques enables a comprehensive analysis of the relationship between HbA1c, TC, and TG. While GAM captures the nonlinear effects of TC and TG on HbA1c, RSM allows for the exploration of interaction effects and provides insight into the optimal values of TC and TG that lead to specific HbA1c levels (Myers & Montgomery, 2002). RSM is particularly useful in identifying regions of the predictors' space where the response variable (HbA1c) is maximized or minimized, offering a more practical understanding of these relationships (Draper & Smith, 1998).The data for this study consist of measurements for HbA1c, TC, and TG from a sample of 41 participants. Using R software, we first performed data preparation, including the splitting of the data into a training set (70%) and a testing set (30%) to validate model performance. We then applied GAM to model the relationship between HbA1c and the predictors (TC and TG), utilizing the mgcv package in R to fit smooth terms for each predictor. Model performance was evaluated using several accuracy metrics, including Root Mean Squared Error (RMSE), Mean Absolute Error (MAE), and Root Mean Squared Percentage Error (RMSPE). For the second phase of analysis, we employed RSM using the rsm package in R to explore the interaction effects between TC and TG and visualize the results through contour and 3D response surface plots.The methodology development in R, including the use of the mgcv and rsm packages, allowed for a robust exploration of the relationship between HbA1c, TC, and TG. This study demonstrates the utility of advanced statistical techniques for modeling complex health data and provides new insights into the interaction of lipid markers and HbA1c in diabetes management.

MATERIALS AND METHODS

Study Design and Data Collection

This study employed a cross-sectional design to explore the relationship between Hemoglobin A1c (HbA1c), Total Cholesterol (TC), and Triglycerides (TG) using two advanced statistical approaches: Generalized Additive Models (GAM) and Response Surface Methodology (RSM). The data for this analysis were collected from a cohort of 41 participants who were selected based on convenience sampling. The inclusion criteria for participants were adults aged 18-65 years with no history of chronic diseases other than diabetes mellitus. All participants provided informed consent prior to participation. The dataset consisted of measurements for HbA1c, TC, and TG, which were obtained through standard laboratory procedures and clinical assessments.

Table 1. The data description

Variable	Description
HbA1c	Glycated Haemoglobin
TC	Total Cholesterol
TG	Triglycerides

Data Preparation and Preprocessing

The data were initially inspected for missing values and outliers. Missing data were handled through imputation using the mean value of each variable, ensuring no significant bias was introduced. The dataset was then split into two subsets: a training set (70%) and a testing set (30%) for model development and validation, respectively. This partitioning approach allowed for the robust evaluation of model performance and generalizability (James et al., 2013). Prior to modeling, all variables were standardized to zero mean and unit variance to ensure comparability across different scales, particularly for TC and TG, which vary considerably in their measurement units.

Model Development

To model the relationship between HbA1c and the predictors (TC and TG), two statistical approaches were employed: Generalized Additive Models (GAM) and Response Surface Methodology (RSM). For the GAM, the 'mgcv' package in R was used to fit nonparametric regression models with smooth functions of TC and TG. This method allows for the exploration of nonlinear relationships between predictors and the response variable without assuming a specific functional form (Wood, 2017). In the GAM, smooth terms for TC and TG were specified with a maximum of four basis functions (k=4) to balance model flexibility and complexity, based on previous literature (Fahrmeir et al., 2013). The GAM model was fitted using the 'gam()' function, with HbA1c as the dependent variable and TC and TG as the independent variables.In addition to GAM, Response Surface Methodology (RSM) was applied to further explore the interactions between TC and TG. The 'rsm' package in R was utilized to construct the second-order polynomial models for HbA1c as a function of TC and TG. RSM allows for the identification of critical interaction effects and optimization of the predictor variables (Myers & Montgomery, 2002). The central composite design (CCD) was used for fitting the response surface models, which provides an efficient design for exploring both main effects and interaction terms. For both models, the performance was assessed using multiple metrics, including Root Mean Squared Error (RMSE), Mean Absolute Error (MAE), Root Mean Squared Percentage Error (RMSPE), and Median Absolute Error (MedAE). The models were evaluated using standard performance metrics. RMSE was calculated to assess the overall fit of the models by measuring the square root of the average squared differences between predicted and observed HbA1c values. MAE was used to quantify the average magnitude of errors in the predictions, while RMSPE was computed to measure the relative prediction error as a percentage. Finally, MedAE was calculated as the median of the absolute differences between predicted and actual values, providing a robust measure of model accuracy that is less sensitive to outliers (Hyndman & Koehler, 2006). All statistical analyses were performed using R version 4.0.5, with a significance level set at $p < 0.05$.

The Statistical Approach : Multivariate Normality and Nonparametric Regression In this study, the relationship between HbA1c, Total Cholesterol (TC), and Triglycerides (TG) was analyzed by first assessing the assumption of multivariate normality across the dataset. Multivariate normality is a crucial assumption for applying parametric statistical methods, as it ensures the reliability of inferential statistics in such models (Mardia, 1970). Mardia's test was performed to evaluate skewness and kurtosis in the variables TC, TG, and HbA1c. The results revealed significant deviations from multivariate normality, particularly in the skewness and kurtosis values, which justified the use of nonparametric regression methods. Nonparametric regression is beneficial when the data do not meet the assumptions required for parametric models, particularly in health sciences research where the data distributions may be complex and irregular (Hastie & Tibshirani, 1990).

Nonparametric Regression using Generalized Additive Models (GAM)

To explore the nonlinear relationship between HbA1c and the metabolic indicators TC and TG, this study employed Generalized Additive Models (GAM), a flexible nonparametric regression technique. GAM allows for the modeling of smooth, nonlinear relationships between predictors and the outcome without assuming a specific functional form for the data (Wood, 2017). The smooth functions (T)and (T) were applied to capture the nonlinear effects of TC and TG on HbA1c. This approach is particularly useful when examining clinical data where relationships between variables are often nonlinear (Fahrmeir et al., 2013). The model is expressed as:

$H\,1 = {}_0 + (T\,) + (T\,) +$

where (T)and (T)represent smooth functions of each predictor variable, and represents the error term. This model allows for a detailed exploration of how changes in TC and TG influence HbA1c, while adjusting for the complex interactions between these two predictors. The flexibility of

GAM in accommodating nonlinear relationships enhances the interpretability and predictive power of the model.

Generalized Additive Model Equation

The GAM can be formally represented as:

$H\ 1 = {}_0 + (T\ ) + (T\ ) +$

where:

$H\ 1$ is the predicted HbA1c value for an individual. ${}_0$ is the intercept, representing the baseline HbA1c level when all predictors (TC and TG) are set to zero.

($T\ $) and ($T\ $) are smooth functions applied to each predictor variable, allowing for flexible, nonlinear modeling of their effects on HbA1c. is the error term, capturing any variation in HbA1c that is not explained by the model.

Each smooth function, such as ($T\ $) , is built from basis functions, which provide the flexibility to model complex, nonlinear relationships between the predictor and outcome variables. This allows for the modeling of customized curves for each predictor, which improves the accuracy and interpretability of the results in a clinical setting.

Kendall-Theil Sen Siegel Method

In addition to GAM, the Kendall-Theil Sen Siegel method was applied to further analyze the relationship between TC, TG, and HbA1c. This robust nonparametric regression technique estimates the slope of the relationship between variables while being less sensitive to outliers and non-normal error distributions (Sen, 1968). It calculates the median of all possible slopes between pairs of data points, making it more reliable than ordinary least squares (OLS) regression, particularly in the presence of non-linearity and heteroscedasticity (Theil, 1950). This method has been widely applied in environmental and clinical studies where robustness to data anomalies is essential (Helsel & Hirsch, 2002). In this study, the Kendall-Theil Sen Siegel method was used as a complementary analysis to validate the results observed in the GAM, providing additional robustness and reinforcing the trends identified in the nonparametric models.

Results and Discussion

The multivariate normality of the dataset, with Total Cholesterol (TC) and Triglycerides (TG) as independent variables and HbA1c as the dependent variable, was assessed using Mardia's test for multivariate normality. The results revealed a skewness statistic of 28.29 with a p-value of 0.0016 and a kurtosis statistic of 2.52 with a p-value of 0.0119. Both p-values were significantly below the threshold of 0.05, leading to the rejection of the null hypothesis of multivariate normality. This indicates a significant deviation from a normal distribution in the dataset.

Given these findings, it was determined that the application of nonparametric regression methods would be more appropriate than traditional parametric models. Parametric models, which assume normality, would not be suitable due to the violations observed in the multivariate normality assumption. Nonparametric methods, such as Generalized Additive Models (GAM), offer the flexibility to model nonlinear relationships between the variables without assuming a specific distribution. This approach allows for a more accurate reflection of the complex interactions between TC, TG, and HbA1c, providing a more robust framework for analyzing the data's underlying trends and interactions. Therefore, the use of GAM is justified, ensuring that the analysis accounts for the non-normal distribution of the data and offers more reliable insights into the relationships between the metabolic indicators and HbA1c. The Chi-Square Q-Q plot (Figure 1) is employed to assess the multivariate normality of the dataset by comparing the squared Mahalanobis distances of each data point to the expected chi-square quantiles. In this plot, most of the points align with the line at lower quantiles, suggesting normality at smaller distances. However, as the quantile values increase, several points deviate from the line, particularly at higher quantiles, which may indicate the presence of outliers or deviations from normality. These discrepancies imply that the dataset does not fully conform to the assumption of multivariate normality, thereby justifying the use of nonparametric regression techniques for more accurate modeling of the data's complex relationships.

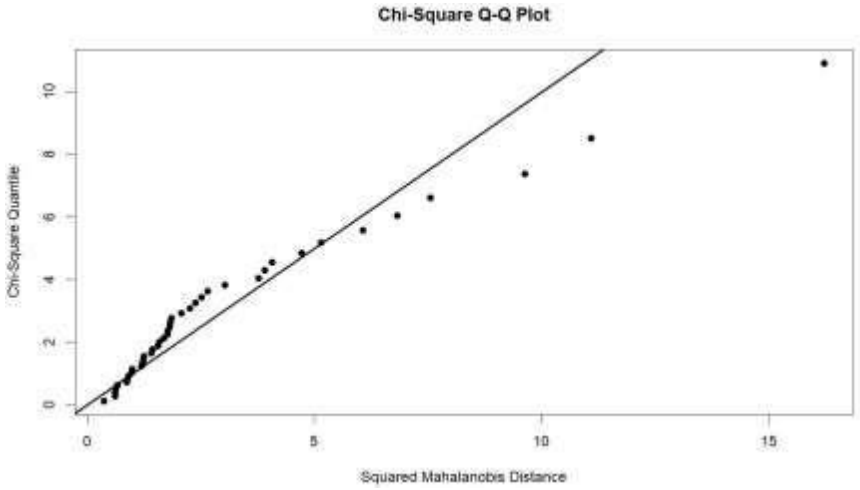

Figure 1. A multivariate normality checking

The nonparametric regression model developed to predict HbA1c levels utilized Total Cholesterol (TC) and Triglycerides (TG) as independent variables, applying smooth functions to each predictor to capture their non-linear relationships with HbA1c. The regression equation was structured as follows:

$H\,1 = 8.089 + (T\,) + (T\,) +$

where $(\,)$ denotes smooth terms applied to each predictor variable, and represents the error term. The intercept, estimated at 8.089, represents the baseline HbA1c value when the contributions from TC and TG are zero. Each predictor's effect was modeled using flexible smooth functions, allowing the model to account for complex, non-linear interactions that traditional linear models would fail to capture. The significance of each smooth term was examined, and the results indicated that both TC and TG had highly significant effects on HbA1c levels ($p < 0.01$ for both predictors). This suggests a strong and complex association between these metabolic markers and HbA1c, with non-linear relationships that require the flexibility of nonparametric regression. The model also showed that the smooth functions for TC and TG were able to explain substantial variability in HbA1c, capturing intricate patterns in the data that are critical for understanding metabolic health. The model's explanatory power was moderate, with an adjusted R-squared value of 0.674, indicating that the model explained approximately 67.4% of the variance in HbA1c. The deviance explained was 72%, suggesting that the model successfully captures a substantial portion of the variability in HbA1c levels. These statistics highlight that while the model provides a solid framework for understanding the relationships between TC, TG, and HbA1c, there may be additional factors influencing HbA1c that were not included in the analysis. The model's predictive performance was further assessed using error metrics on the validation data. The Root Mean Squared Error (RMSE) was 3.73, indicating the average squared deviation of predicted HbA1c values from the observed values. The Mean Absolute Error (MAE) was 2.33, and the Median Absolute Error (MedAE) was 1.63, both demonstrating the model's consistent accuracy in predictions. Additionally, the model's accuracy on the validation dataset was 54.8%, reflecting a moderate but promising performance in capturing the relationship between TC, TG, and HbA1c. On the testing dataset, the Mean Squared Error (MSE) was 0.1135, further supporting the model's strong predictive capability. These results underscore the effectiveness of the nonparametric regression model in capturing complex relationships among TC, TG, and HbA1c, providing a flexible and reliable approach to understanding metabolic health. The findings also emphasize the utility of Generalized Additive Models (GAM) in health sciences, where non-linear interactions are prevalent and critical to accurate data interpretation.

Response Surface Methodology (RSM) Results

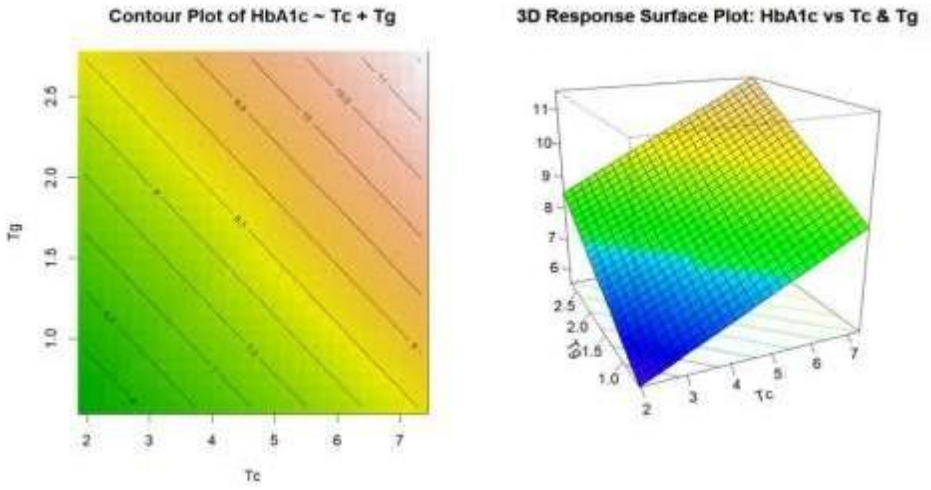

Figure 2. Contour and Response surface plot for HbA1c vs TC and TG

The relationship between Hemoglobin A1c (HbA1c), Total Cholesterol (TC), and Triglycerides (TG) was explored using Response Surface Methodology (RSM) to model the interactions between TC and TG and their collective impact on HbA1c levels. The primary objective was to visualize the complex, nonlinear interactions between these variables and to identify regions in the predictor space that could optimize HbA1c levels. The contour plot provides a two-dimensional representation of the relationship between TC and TG on HbA1c**,** where contour lines correspond to different levels of HbA1c. The plot indicates that at lower values of TC and TG (toward the lower-left quadrant), HbA1c values tend to be lower, with the contour lines more sparsely spaced, reflecting a smoother increase. As both TC and TG increase (towards the upper-right), HbA1c levels rise significantly, with denser contour lines representing a more rapid increase in HbA1c values. This pattern suggests a positive correlation between TC and TG with HbA1**c**, with both metabolic indicators contributing to elevated levels of HbA1c. The contour plot demonstrates that TC and TG are strongly associated with higher HbA1c values, highlighting areas where individuals with higher levels of both metabolites are more likely to experience elevated blood glucose levels, thus providing valuable insight for clinical strategies targeting these markers.

The 3D response surface plot offers a more comprehensive view of the relationship between TC and TG on HbA1c. The plot's surface rises progressively as both TC and TG increase, reflecting the positive association between these variables and HbA1c levels. The gradient of the surface becomes steeper as the values of TC and TG rise, indicating a more substantial impact on HbA1c at higher levels of these metabolic indicators. This three-dimensional representation underscores the nonlinear nature of the relationship between TC**,** TG, and HbA1c, suggesting that at higher concentrations of both predictors, HbA1**c** is more sensitive to fluctuations. The smooth transitions in the surface suggest that while the relationship is continuous, there are threshold effects that could guide clinical recommendations for managing HbA1c by focusing on these two key metabolic factors.

Interpretation and Clinical Relevance

The RSM analysis clearly illustrates the interactive effects between TC and TG, suggesting that the joint effect of both markers is more pronounced in determining HbA1c than the individual effects of each marker. This finding emphasizes the importance of considering both TC and TG when evaluating risk factors for elevated HbA1c and diabetes-related complications. Clinically, these findings are valuable as they suggest that interventions targeting reductions in both TC and TG could have a more significant impact on controlling HbA1c levels. Identifying regions where HbA1c is most sensitive to changes in these metabolic markers could guide personalized treatment strategies for individuals at risk of diabetes or those managing existing conditions. The application of Response Surface Methodology, through both contour and 3D response surface plots, has provided critical insights into the complex, nonlinear interactions between TC**,** TG, and HbA1c. The results highlight the positive relationship between these variables and underscore the importance of considering their joint effects when developing clinical strategies aimed at managing HbA1c. These findings also provide a framework for identifying areas within

the predictor space that can optimize clinical interventions, making them valuable for advancing precision medicine in metabolic disorder management.

CONCLUSION

This study explored the application of advanced data modeling techniques— specifically Generalized Additive Models (GAM) and Response Surface Methodology (RSM)-to investigate the complex, nonlinear relationships between HbA1c, TC and TG. By integrating these methods, we were able to better understand how these metabolic indicators influence HbA1c levels, which are crucial for assessing long-term glucose control and predicting the risk of diabetes-related complications. The results from both the GAM and RSM approaches highlighted significant, nonlinear interactions between TC, TG, and HbA1c. These models demonstrated that as both TC and TG levels increase, HbA1c levels also rise, with the relationship becoming more pronounced at higher concentrations of the predictors. The nonparametric regression approach, in particular, allowed for flexibility in capturing these complex relationships without imposing restrictive assumptions about the data, making it a highly effective tool in metabolic health research.

The RSM analysis provided additional insights into the interaction between TC and TG, showing that these variables jointly affect HbA1c levels in a way that would not be fully captured by linear models. The contour and 3D response surface plots clearly illustrated how HbA1c values are sensitive to changes in both TC and TG, emphasizing the importance of considering these two variables together when assessing glycemic control in clinical practice. Furthermore, the moderate explanatory power of the GAM, with an adjusted R-squared value of 0.674 and a deviance explained of 72%, reflects the model's ability to explain a substantial portion of the variability in HbA1c levels. Although additional factors may contribute to HbA1c variation, the results reinforce the utility of nonparametric regression methods in health data analysis, where complex, nonlinear interactions are prevalent.

From a clinical perspective, these findings underscore the importance of lipid management, alongside glucose control, in addressing conditions like metabolic syndrome. The study suggests that healthcare providers should consider lipid-lowering strategies as part of a broader approach to glycemic management, particularly for patients at risk of or managing diabetes. By understanding the significant contributions of TC and TG to HbA1c, clinicians can better tailor interventions to optimize metabolic health and improve patient outcomes. In conclusion, the use of Generalized Additive Models and Response Surface Methodology provides a robust framework for modeling the interactions between metabolic indicators and HbA1c. These methods offer a more nuanced and flexible approach to understanding complex health data compared to traditional linear models. The findings from this study contribute to the growing body of evidence supporting the role of advanced statistical techniques in healthcare research. Future research should expand on these findings by incorporating additional metabolic and lifestyle factors and validating the models across diverse populations. Ultimately, integrating these advanced modeling approaches into clinical practice will enable more personalized, data-driven strategies for managing diabetes and related conditions, leading to improved patient outcomes.

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