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The Impact of Hormone-Related Factors on Wedge Deformity in Middle-Aged Populations

Junming Chen[1,4,*], Yiyang Jiang[2,5], Enze Li[3,6]

[1]Department of Biostatistics, Columbia University in the City of New York, New York, 10032, United States
[2]Department of Mathematics and Economics, New York University, New York, 10003, United States
[3]Suzhou Science and Technology City Foreign Language School, Suzhou, 215000, China

[4]jc6342@cumc.columbia.edu
[5]yj2857@nyu.edu
[6]1218354421@qq.com
*corresponding author

Abstract. Vertebral deformity, particularly among adult over 50, poses significant public health challenges. This study explores the role of hormones and their metabolites in vertebral wedge deformities, using data from 1,317 individuals aged 40 and older from the NHANES 2013-2014 dataset. Key features included testosterone, estradiol, insulin, and related metabolites. Advanced machine learning models, notably XGBoost, were employed to predict deformity risk. A comprehensive cross-analysis of multiple machine learning interpreters identified testosterone, RBC folate, and insulin as significant predictors, with elevated levels indicating a higher deformity risk. These findings reinforce the link between hormone levels and vertebral deformities, suggesting that regular biomarker monitoring could aid early detection and intervention. The study offers new insights for improving clinical outcomes and guiding future research in vertebral health.

Keywords: Vertebral deformity. Hormones, Machine learning models, Age study, Biomarker monitoring

1. Introduction

Vertebral deformity is increasingly prevalent, raising serious public health concerns. A previous U.S. study found that over 25% of women over 50 in the sample have spinal deformities, indicating that this pathological disorder impacts more than 7 million white women nationwide [1]. Additionally, vertebral deformity is linked to other spinal diseases, with fracture risk at common deformity sites being 5 times higher [2]. However, clinical intervention for critical vertebral issues faces unique challenges due to complex pathological factors in vertebral deformation [3] and intricate morphological assessment methods [4]. As a result, researchers are continuing exploring clinical approaches for risk intervention and pathology before vertebral deformation leads to more severe conditions.

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This research primarily focuses on the Wedge Deformity, which is the most significant and common type deformity indicated by researchers [5]. The criteria for this experiment were based on a previous study, where the standard and computer algorithms showed promising results [6]. This research aims to improve model training reliability and feature interpretation with formal standards.

After establishing the evaluation criteria, the subsequent step involves selecting the appropriate spinal assessment method. Current studies indicate that semi-quantitative assessment using standardized radiological testing is the most feasible approach for detecting pathological deformities, proving highly effective but often resulting in a high false positive rate, indicating room for model optimization [4]. Additionally, it requires both X-ray quantification and clinical observer evaluation [7]. Thus, despite vertebral deformities being the most prevalent type of osteoporotic fracture, they are underreported by clinicians, resulting in a surprisingly low number of timely documented patient cases in clinical practice [2]. Therefore, the process remains complex, which exacerbates the difficulty of assessing vertebral deformities and reduces the feasibility of regular testing among the public.

Given these challenges in vertebral deformity assessment, researchers have increasingly focused on alternative biomarkers. Among these, hormone levels, closely tied to bone cell metabolism, have gained significant attention as a cause of vertebral deformity alongside osteoporosis and inflammation [5]. Hormone and their metabolites testing, especially through blood tests, is both convenient and widely used in clinical practice [3, 8], offering more comprehensive physiological insights than standard bone quality assessments [9]. Studies have shown strong correlations between sex hormones, SHBG, and bone quality [10, 11], as well as elevated metabolic markers like folate and vitamin B12 with fracture risk [12, 13]. This supports the development of more efficient models for predicting vertebral deformities based on hormone data. Therefore, the focus of this research is to explore the relationship between hormones, their metabolites, and vertebral deformities.

This research aims to analyze the role of easily collectible hormones and hormone metabolites in the pathogenesis of vertebral wedge deformities. The subsequent research within the text will involve using algorithms and models to compare and explore their significance, with the aim of laying a foundation for future studies and providing constructive recommendations for the development of theoretical research and predictive models for vertebral deformity risk assessment.

2. Method

2.1. Dataset Description

The data used in this research were obtained from the National Health and Nutrition Examination Survey (NHANES) during the 2013-2014 examination period. The wedge deformity percentage data used in this research were acquired through Dual-Energy X-ray Absorptiometry (DXA) [14]. The DXA system automatically analyzed the images during the scanning process, generating morphological data for each vertebra, including the degree of wedge deformity. Subjects with blood test data were included for better adjusting the covariates. Variables representing hormones (testosterone, estradiol, insulin[10,11]) and hormone-related metabolites (folate, vitamins B and D, cholesterol [12,13]) were selected for this analysis. A total of 1,320 individuals were left after removing multicollinearity (correlation greater than 0.8 with other features) and invalid values. The experiment subsequently identified outliers using the Mahalanobis distance method. Given that our independent variable set includes 9 features, the degrees of freedom is set to 8. Typically, values above 0.4 are indicative of severe wedge deformity [15], and extremely skewed values could compromise the model's robustness and stability. Therefore, the research aimed to remove a sufficient number of outliers by setting the Mahalanobis distance threshold to 8, which resulted in the exclusion of 3 outliers. These 1,317 individuals were sourced from across the United States, with an age range of 40 years and older. The NHANES dataset used in this study is age-matched, with all individuals aged 80 years or older categorized as 80. The dataset happens to include 663 males and 663 females, resulting in an equal sex distribution.

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2.2. Wedge Deformity Percentage of Vertebrae

Spinal segments were chosen as outcome variable because wedge deformity is particularly common in T5 to L4, and they are critical areas for the study of spinal deformities [5]. The wedge deformity percentage is calculated by measuring the anterior and posterior heights of the vertebra, then dividing their difference by the posterior height. Based on criteria depending on the specific vertebrae in previous research [6], with the wedge deformity index generally considered indicative of mild or greater abnormal deformation when the threshold exceeds 0.1 to 0.2 [6].

2.3. Model Development and Training

Feature standardization was applied to avoid scale differences. Building on this foundation, the research employed Elastic Net regularization to facilitate subsequent feature interpretation and enhance model performance, with an L1 regularization ratio set at 0.5. Subsequently, the research partitioned the dataset into training and test sets, allocating 20% of the data to the test set. ADASYN (Adaptive Synthetic Sampling) algorithm was implemented for oversampling the minority class in the training sets. In this research, after confirming that the linear regression model was suboptimal, the research applied machine learning models to capture higher-dimensional and deeper correlations between Wedge Deformity Percentage of Vertebrae and several hormone level variables. We selected MLP (Multilayer Perceptron), Naive Bayes Model, LightGBM (Light Gradient Boosting Machine), XGBoost, Random Forest, and Support Vector Machine (SVM) for comparison. The research aimed to identify the most reliable and efficient model or combine them into a more robust ensemble model. To evaluate the robustness of the models, the research employed 8-fold cross-validation (KFold). After each fold's training and testing, the research calculated AUC, accuracy, precision, recall, and F1 score to evaluate the feasibility of the model and comprehensively assess the classification performance of the models. Upon completion of the evaluation and verification of the models' reliability, SHAP interpreters, AnchorTabular interpreters, and bivariate partial dependency plots were extracted to visualize the most important features and respective importance value. These important features help researchers better understand the decision-making process of the models and the real-world impact of the corresponding features on the risk of vertebral wedge deformity in middle-aged and elderly individuals.

3. Result

A summary of population statistics is provided in Table 1. Triglyceride and vitamin B12 levels attracted more attention. In the sample, 15% (200 individuals) exhibited vitamin B12 levels exceeding 900 pg/mL, while 24% (323 individuals) had triglyceride levels above 150 mg/dL. This suggests that the dataset may include a significant number of individuals with potential over-supplementation and metabolic issues. Given that the sample consists of individuals over 40 years old from the U.S. healthcare system, whose lifestyle habits closely align with those of the North American population, these anomalies can be understood and should be incorporated into the model for training. In Table 1, we also noticed that 68 individuals (5%) had a mean T5-L4 vertebrae wedge deformity percentage greater than 0.1, while 1256 individuals (95%) had a mean value less than or equal to 0.1. This distribution is reasonable and expected, as most individuals over 40 years old exhibit vertebral deformities within an acceptable range (0.10 to 0.16). However, an anomaly arises in that 1256 individuals (95%) had a maximum wedge deformity percentage greater than 0.1 in at least 1 of the twelve vertebrae, while only 68 individuals (5%) had a maximum value less than or equal to 0.1. This indicates that, while the overall risk of pathological vertebral deformity is low, a significant portion of the population has at least 1 vertebra with deformity exceeding the 0.1 threshold. This suggests a potential public health concern among the population over 40 years old, wherein the overall risk to the spine is low, but the risk of localized vertebral deformity is high.

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Table 1. Key Population Features Statistics:

	Condition / Level	Count
HDL	Male > 40 mg/dL or Female >50 mg/dL	941
	Male <=40 mg/dL Female <=50 mg/dL	385
Total Cholesterol	>200 mg/dL	551
	<200 mg/dL	775
Insulin	>25 mIU/L	121
	<=25 mIU/L	1205
Triglyceride	>150 mg/dL	323
	<=150 mg/dL	1003
Testosterone	Female 15-70 ng/dL	419
	Female Out of 15-70 ng/dL	244
	Male 250-800 ng/dL	573
	Male Out of 250-800 ng/dL	90
Estradiol	Female in Normal Range{30-400pg/mL(40-55) & <30pg/mL(55+)}	513
	Female Out of Normal Range	150
	Male 10-40 pg/mL	605
	Male Out of 10-40 pg/mL	58
Vitamin D2 + D3	30-150 ng/mL	1227
	Out of 30-150 ng/mL	99
Vitamin B12	200-900 pg/mL	1099
	Out of 200-900 pg/mL	227
RBC Folate	140-628 ng/mL	892
	Out of 140-628 ng/mL	203
Deformity Mean	<0.1	1256
	>0.1	68
Deformity Max	<0.1	68
	>0.1	1256

Table 1 summarizes key statistics, highlighting elevated vitamin B12 and triglyceride levels, and noting a significant prevalence of localized vertebral deformity in individuals over 40 years old from the U.S. healthcare system.

A linear regression was conducted to assess the linear relationship between hormone levels and the deformity. The results showed that, except for age and gender, all variables had p-values significantly greater than 0.05, indicating no significant linear relationship with vertebral wedge deformity. VIF analysis revealed low multicollinearity for both age (1.24) and gender (4.28). Given these results, Age and Gender were excluded from further analysis without impacting the model's integrity, as no significant linear relationships were found with vertebral deformities.

Table 2. Linear Regression Analysis of Hormone Levels and Vertebral Deformity:

	Coef	P>| t |	std err
const	0.117	0.000	0.013
Insulin	2.63e-05	0.57	4.65e-05
HDL	-5.30e-05	0.56	9.08e-05
Total Cholesterol	-2.93e-05	0.38	3.35e-05
Triglyceride	-8.90e-06	0.61	1.72e-05

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Table 2. (continued).

Testosterone	1.13e-05	0.22	9.26e-05
Estradiol	-1.14e-05	0.63	2.37e-05
Vitamin D2+D3	4.44e-05	0.35	4.69e-05
Vitamin B12	-1.67e-06	0.16	1.19e-06
RBC Folate	7.74e-06	0.12	4.93e-06
Gender	-9.24e-03	0.05	4.78e-03
Age	8.37e-04	0.00	1.10e-04
R-squared: 0.12			
Adj. R-squared: 0.11			

Table 2 shows the linear regression results, revealing no significant relationships between hormone levels and vertebral deformity, except for age. Age and Gender were excluded from further analysis due to their lack of impact on the model.

The research utilized various machine learning models capable of feature interpretation, including MLP, Naive Bayes (Gaussian), SVM(Linear), Random Forest, LightGBM, and XGBoost. Following hyperparameter tuning, only 3 models—XGBoost, Random Forest, and LightGBM—achieved an AUC greater than 0.7 and an F1 score exceeding 0.8. Among these, XGBoost demonstrated superior performance, with an AUC of 0.71 and an F1 score of 0.87 on the test set, significantly surpassing the other models. This suggests that XGBoost excels in precision and recall, reflecting its robust classification capabilities. Moreover, the selection of features and their importance was validated through this analysis.

Table 3. Performance Comparison of Machine Learning Models in Predicting Vertebral Deformity:

	XGBoost	Random Forest	LightGBM	MLP	SVM	Bayes
Test AUC	0.71	0.70	0.70	0.71	0.73	0.75
Test F1 Score	0.87	0.82	0.80	0.78	0.70	0.39
Test Accuracy	0.78	0.70	0.68	0.66	0.56	0.29
Test Precision	0.97	0.97	0.97	0.97	0.99	1
Test Recall	0.80	0.70	0.69	0.66	0.70	0.25

Table 3 summarizes the performance of different machine learning models in predicting vertebral deformity, highlighting the top-performing models.

For feature importance analysis, the Elastic Net feature selection algorithm was used, and the model identified the 3 most important and significant features: insulin, testosterone levels, and RBC folate levels. By studying these 3 features, the experiment intuitively demonstrated relationships beyond 1-dimensional linearity. The model first analyzed the impact of these features on vertebral wedge-shaped pathological deformity using the SHAP explainer shown in Figure 1. In the plot, each dot represents a specific observation, where the color indicates the value of the feature for that observation: red indicates a higher value of the feature, and blue indicates a lower value. The position of the dots on the horizontal axis shows the impact on the model's output: dots further to the left represent a greater decrease in the predicted probability of the positive class (i.e., indicating a negative impact), while dots further to the right represent a greater increase in the predicted probability of the positive class (i.e., indicating a positive impact). In Figure 2, the result is observed that many red dots accumulate on the right side of

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the plot for the testosterone and RBC folate features. This indicates that higher values of these 2 features (e.g., the cases that standardized testosterone levels or RBC folate levels larger than 0.5) significantly contribute to the model's prediction of the positive class, as evidenced by SHAP values greater than 0.5. Therefore, the SHAP explainer notably highlights that high levels of RBC folate or testosterone have a significant impact on vertebral wedge-shaped pathological deformity. However, the impact of insulin levels on the model's output, as illustrated by the SHAP explainer, is not as straightforward and intuitive as that of RBC folate or testosterone. This necessitates further investigation of the 3 features using additional methods.

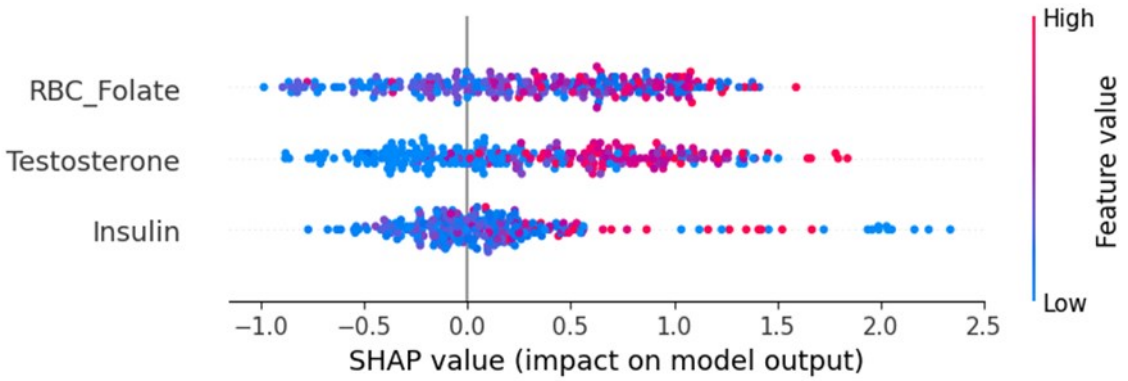

Figure 1. SHAP Analysis of Feature Impact on Vertebral Deformity

Figure 1 illustrates the SHAP values, where red dots indicate higher feature values and blue dots indicate lower values. Dots on the left suggest a negative impact on the model's prediction, while dots on the right indicate a positive impact.

Based on the findings from Figure 2 and Figure 3, the research constructed 2-dimensional partial dependence plots and applied the Anchor Tabular explainer for further analysis, and the results were further validated. In Figure 2, the color gradient from blue to yellow represents changes in the model output (i.e., predicted probability). Blue areas indicate lower predicted probabilities, while yellow areas indicate higher predicted probabilities. While the Anchor Tabular explainer in Figure 3 further supports this conclusion. The Anchor Tabular explainer can aggregate and analyze the most relied upon combinations of conditions used by the model during predictions, converting them into anchor rules along with their frequencies. This, in turn, explains how the model effectively generates well-performing outputs based on these rules. The results show that when testosterone levels are above average and RBC folate levels are either excessively high or low (with testosterone greater than 0.5 and RBC folate exceeding ±0.5 in the standard distribution), the model's predicted risk probability significantly increases, turning the color to yellow. Notably, in Anchor Tabular explainer, the same rule "Testosterone > 0.55 AND RBC_Folate > -0.30" appeared most frequently, occurring 29 times. This indicates a significant association between elevated testosterone levels and RBC folate above a certain threshold with the outcomes observed in the study. Conversely, when testosterone levels are low (around -0.5), the predicted risk probability is low, represented by the blue areas. A similar significant pattern is observed between RBC folate and insulin levels. The results indicate that when insulin levels are high (greater than 0.4) and RBC folate levels are also high (greater than 1.0), the model's predicted risk probability significantly increases. This suggests that high levels of RBC folate and insulin are associated with a higher risk of vertebral deformity, while low levels of insulin (around -0.4) and low levels of folate (around -1.0) are associated with a lower risk probability. Additionally, among the top 7 anchor rules in Figure 3, those involving testosterone levels exceeding 1 standard deviation above the mean appeared 6 times, highlighting its importance and significance as a determining feature. Additionally, the influence of either high or low RBC folate levels on the determination of vertebral deformity is also notable. 5 out of the top 7 anchors rules involved RBC folate levels, including 1 rule

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solely associated with RBC folate, "RBC_Folate > 0.41." Thus, the dependence plots and explainer in Figure 2 and Figure 3 not only confirm the conclusions of the SHAP explainer but also reveal the significant relationship between insulin and the model's output, helping researchers understand how the model combines these features to make a reasonable prediction of the risk of vertebral wedge deformity.

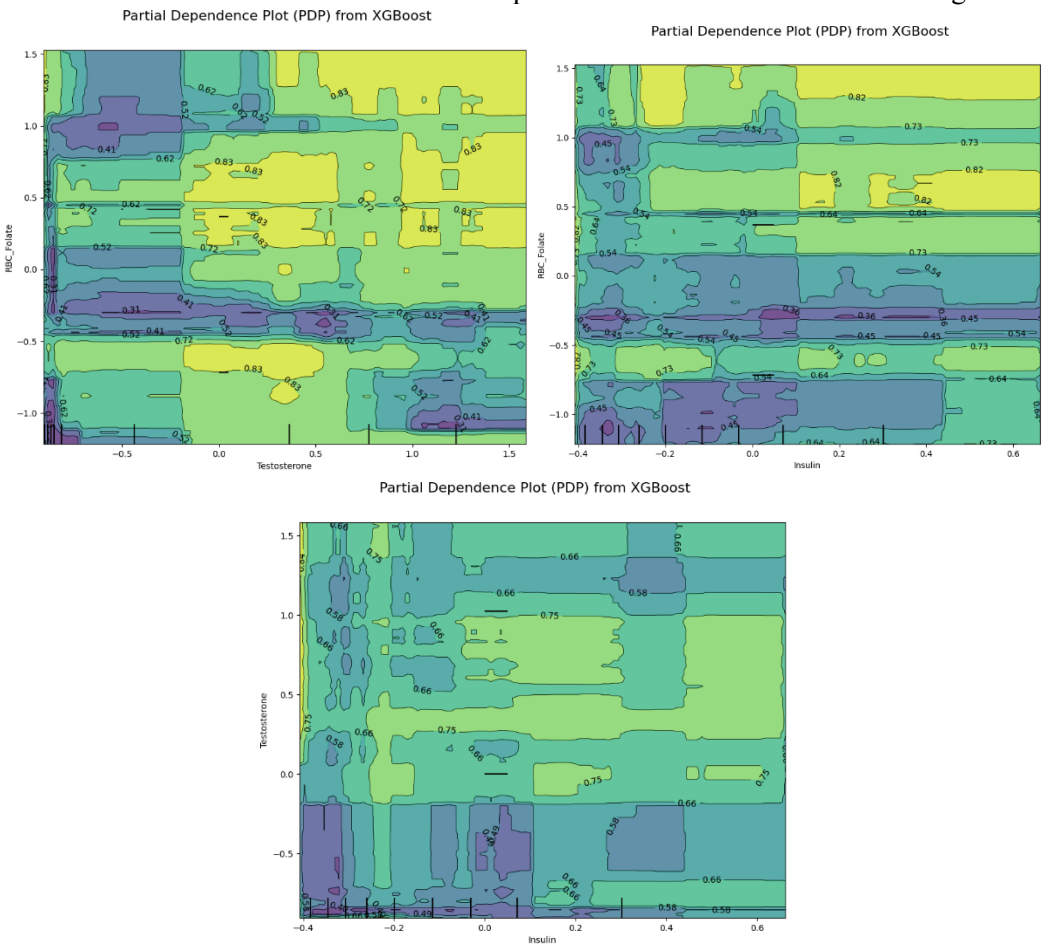

Figure 2. 2-Dimensional Partial Dependence Plots

Figure 2 shows 2-dimensional partial dependence plots, where the color gradient from blue to yellow represents changes in predicted probabilities. Blue areas indicate lower risk, while yellow areas indicate higher risk.

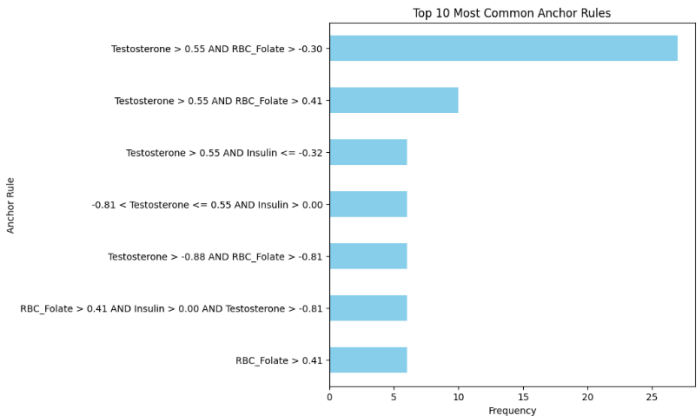

Figure 3. Anchor Tabular Explainer Visualization

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Figure 3 presents the Anchor Tabular explainer, highlighting the most frequently used combinations of feature conditions in the model's predictions, converting them into anchor rules.

Overall, these findings suggest that testosterone and RBC folate are critical features in predicting outcomes. Testosterone consistently features prominently among the most common anchor rules. The interaction between these features, particularly when insulin is also considered, underscores their importance in the model's decision-making process. The significance of these specific combinations may indicate potential relationships between these biological factors and the condition under research.

4. Discussion

The primary findings of the above study indicate that testosterone, RBC folate, and insulin are significant features in predicting vertebral wedge deformity. Compared to previous studies, this research further confirms the close relationship between hormone levels and vertebral deformities. Although previous studies have shown correlations between hormones and hormone-related factors with bone quality [10-13], this research strengthens the scientific interpretation of this association by incorporating multiple hormone-related variables and advanced algorithms. Additionally, by introducing RBC folate and insulin as key variables in a multivariate cross-study, this research provides new insights into areas that have been relatively underexplored in existing literature. These findings have important implications for clinical practice. Given the strong correlation between testosterone, RBC folate, and vertebral deformities, the application of routine blood tests in high-risk populations could serve as an effective method for early detection and intervention. By regularly monitoring these key biomarkers, healthcare professionals can identify individuals at risk of vertebral deformities earlier and take appropriate preventive measures to mitigate the progression of these deformities. In previous studies, researchers often focused on the effects of testosterone treatment on vertebral diseases. However, based on this research data analysis, high testosterone levels under certain conditions also have a significant positive correlation on vertebral deformities, an area that has been less explored in past research. Moreover, this also indicates that testosterone, insulin, and RBC folate levels have a greater impact on vertebral wedge deformity than factors closely related to overweight, such as cholesterol and triglycerides. This finding may offer new perspectives and insights for studies that have traditionally focused on the relationship between weight and vertebral deformity.

This research, by identifying testosterone, RBC folate, and insulin as key predictive factors, provides new directions for early detection and intervention in vertebral wedge deformities. The strengths of this study include the use of a nationally representative dataset, and the comprehensive analysis conducted with various machine learning models. The high AUC and F1 scores of these models demonstrate their superiority in terms of prediction accuracy and robustness. These findings are not only academically significant but also offer practical clinical application potential for improving patient outcomes and reducing the incidence of vertebral deformities. However, the research also has some limitations. For example, inherent biases and exclusion of certain confounding variables might affect the comprehensiveness of the results. Additionally, the generalizability of the findings may be limited by the geographical and demographic characteristics of the sample. Future research should further explore other hormone-related metabolites to enrich the predictive capabilities of existing models. Furthermore, incorporating data on dynamic hormone level changes to develop more complex longitudinal predictive models would contribute to a more accurate assessment of vertebral deformity risk. Long-term cohort research are recommended to validate the causal relationships between these biomarkers and the progression of vertebral deformities, thereby optimizing existing predictive models. To further enhance the accuracy and applicability of the models, broader validation and optimization in future research are still needed.

5. Conclusion

This research demonstrates that hormone levels, particularly testosterone, RBC folate, and insulin, play a crucial role in assessing the risk of vertebral wedge deformity. By utilizing advanced machine learning models, the study has uncovered associations that could guide early interventions and more personalized

monitoring strategies. Despite some limitations, including sample specificity and the need for broader validation, the study lays a foundation for refining predictive models in vertebral health. Future work should focus on incorporating dynamic hormone level changes and exploring additional biomarkers to further improve prediction accuracy and support targeted clinical interventions.

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Junming Chen, Yiyang Zhang, and Enze Li contributed equally to this work and should be considered co-first authors.

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