A Novel Approach: The Akl-Ahmed Insulin Sensitivity Prediction Equation (AA-ISPE) as an Alternative to HOMA-IR for Predicting Insulin Resistance

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Abstract

Insulin resistance (IR) is a key factor in the pathogenesis of type 2 diabetes mellitus (T2DM) and other metabolic disorders. This paper presents the development of a novel predictive model, the Akl-Ahmed Insulin Sensitivity Prediction Equation (AA-ISPE), aimed at assessing insulin resistance sensitivity. The equation integrates three biomarkers: Body Mass Index (BMI), C-reactive protein (CRP), and Interleukin-6 (IL-6). Through rigorous statistical analyses and validation procedures using independent datasets, the AA-ISPE equation demonstrates robust performance in predicting insulin resistance sensitivity. By incorporating multiple indicators associated with insulin resistance into a unified model, the AA-ISPE equation offers a comprehensive tool for early detection and risk assessment of metabolic disorders. The equation's applicability across diverse patient populations underscores its potential for personalized risk assessment and targeted therapeutic interventions in the management of insulin resistance.

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1. *Introduction*

Insulin resistance is a pathological condition where cells in the body exhibit a diminished response to insulin, a hormone essential for glucose metabolism. This resistance impairs glucose uptake and utilization in tissues such as muscle, fat, and liver, leading to elevated blood glucose levels. It is a precursor to various metabolic disorders, notably type 2 diabetes mellitus (T2DM), and is associated with an increased risk of cardiovascular diseases, non-alcoholic fatty liver disease (NAFLD), and polycystic ovary syndrome (PCOS).[1] One of the primary challenges in addressing insulin resistance is its often asymptomatic nature in the early stages, complicating timely diagnosis. Standard diagnostic methods, including fasting glucose and HbA1c levels, may not detect the condition until significant metabolic disturbances have occurred. Advanced techniques such as the hyperinsulinemic-euglycemic clamp and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) are more precise but not routinely used in clinical practice due to their complexity and cost.[1][2] Despite its utility, HOMA-IR has several limitations that undermine its accuracy in diagnosing insulin resistance. Derived from fasting insulin and glucose levels, HOMA-IR is susceptible to significant variability influenced by stress, illness, and laboratory measurement variations. It primarily reflects hepatic insulin resistance and may not accurately represent peripheral insulin sensitivity. Furthermore, HOMA-IR's reliance on fasting measurements means it does not capture postprandial insulin dynamics, leading to an incomplete assessment.[3][4]

Body Mass Index (BMI) is crucial in understanding and predicting insulin resistance, serving as an important indicator of potential metabolic dysfunction. Elevated BMI, especially levels indicating overweight or obesity, is strongly correlated with an increased risk of insulin resistance.[5]

Excess adipose tissue, particularly visceral fat, releases higher levels of free fatty acids (FFAs) and pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which interfere with insulin signaling pathways, reducing the tissues' ability to respond effectively to insulin.[6]

C-reactive protein (CRP) is another important biomarker in understanding and predicting insulin resistance, serving as an indicator of underlying inflammatory processes. Elevated CRP levels often reflect chronic inflammation and associated metabolic disturbances. Studies show that individuals with high CRP levels are at a significantly increased risk of developing insulin resistance and type 2 diabetes.[7] Interleukin-6 (IL-6) plays a significant role in predicting insulin resistance, acting as a key mediator in the inflammatory processes that contribute to metabolic dysfunction. Increased IL-

6 levels, particularly from visceral fat, interfere with insulin signaling pathways, reducing the capacity of muscle and liver cells to respond to insulin. Elevated IL-6 levels are associated with an increased risk of developing insulin resistance and type 2 diabetes.[8] Given the limitations of current diagnostic methods like HOMA-IR and the significance of biomarkers such as BMI, CRP, and IL-6, we propose a new equation to predict insulin resistance sensitivity. This novel approach, named the AKL-Ahmed Insulin Resistance Index, incorporates BMI, CRP, and IL-6, offering a more comprehensive and accurate assessment tool for clinical and research settings.

2. *Insulin Resistance: Its Role, Significance, and Challenges in Measuring Sensitivity and Resistance*

Insulin resistance is a pathological condition characterized by a diminished response of cells to the action of insulin, a hormone crucial for the regulation of glucose metabolism. In a state of insulin resistance, cells in key metabolic tissues such as muscle, adipose tissue, and liver exhibit impaired glucose uptake and utilization. This leads to elevated blood glucose levels, which can progress to hyperglycemia and contribute to the development of type 2 diabetes mellitus (T2DM). The significance of insulin resistance extends beyond glucose metabolism, as it is a major risk factor for several metabolic disorders, including cardiovascular diseases, Metabolic dysfunction-associated steatotic liver disease (MASLD), and polycystic ovary syndrome (PCOS).[9]

The pathophysiology of insulin resistance involves several intricate mechanisms. One key aspect is the disruption of insulin signaling pathways. In a healthy state, insulin binds to its receptor on the cell surface, triggering a cascade of events that promote glucose uptake. However, in insulin resistance, this signaling pathway is impaired, often due to chronic inflammation and the accumulation of free fatty acids (FFAs). Adipose tissue, especially visceral fat, secretes various pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). These cytokines activate inflammatory signaling cascades, such as the c-Jun N-terminal kinase (JNK) and nuclear factor kappa B (NF-κB) pathways, which interfere with insulin receptor signaling and glucose transporter translocation, thereby impairing glucose uptake by cells.[10][11]

Measuring insulin sensitivity and resistance accurately remains a significant challenge in clinical practice. Traditional diagnostic methods, including fasting glucose levels and glycated hemoglobin (HbA1c), often fail to detect insulin resistance until considerable metabolic dysfunction has occurred. More sophisticated techniques, such as the hyperinsulinemic-euglycemic clamp, provide a precise assessment of insulin sensitivity but are labor-intensive, costly, and impractical for routine clinical use.[12][13] The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) is another widely used method, calculated from fasting insulin and glucose levels. However, HOMA-IR has limitations, including variability due to external factors such as stress, illness, and laboratory inconsistencies. Furthermore, it primarily reflects hepatic insulin resistance and may not accurately represent peripheral insulin sensitivity, thereby providing an incomplete picture of overall metabolic health.[14]

3. *The Impact of Body Mass Index on Insulin Resistance: Insights and Clinical Implications*

Body Mass Index (BMI) serves as a pivotal factor influencing insulin resistance, whereby deviations from the normal BMI range of 18.5 to 24.9 kg/m² can significantly impact insulin sensitivity. Individuals within this range typically maintain normal physiological insulin sensitivity, facilitating efficient glucose uptake and utilization by cells. Conversely, overweight or obese individuals (BMI ≥ 25 kg/m²) face an elevated risk of insulin resistance due to increased adipose tissue mass, leading to systemic inflammation and interference with insulin signaling pathways.[15] Conversely, individuals with lower BMI values indicative of underweight status may initially exhibit improved insulin sensitivity due to reduced adipose tissue mass. However, prolonged malnutrition or severe underweight status can lead to metabolic dysfunction and insulin resistance.[16]

The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index is commonly utilized to assess insulin resistance. In healthy individuals, HOMA-IR values below 2.5 are considered indicative of normal insulin sensitivity, while values above 2.5 suggest impaired insulin sensitivity and increased resistance, particularly in the presence of metabolic disorders such as obesity or type 2 diabetes mellitus (T2DM).[17]

Comparing BMI levels to HOMA-IR thresholds offers valuable insights into the relationship between body composition and insulin sensitivity. Maintaining a BMI within the normal range is essential for preserving optimal insulin sensitivity and reducing the risk of insulin resistance and associated metabolic complications. Regular BMI monitoring alongside other clinical parameters can aid in the early detection and management of insulin resistance and related metabolic disorders.[18]

In a study analyzing insulin resistance among Korean non-obese patients with type 2 diabetes mellitus, BMI emerged as a significant determinant. The study, encompassing 267 patients with a BMI < 25 kg/m², identified Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) values ≥ 2.5 as indicative of insulin resistance. Higher log-transformed triglyceride (TG) levels and lower high-density lipoprotein-cholesterol (HDL-C) levels were observed in insulin-resistant individuals compared to insulin-sensitive counterparts, even after adjusting for BMI. Furthermore, logistic regression analysis highlighted BMI as the primary factor associated with HOMA-IR, suggesting its paramount importance in determining insulin resistance in non-obese patients with type 2 diabetes mellitus in Korea.[19]

4. *Association between Serum C-Reactive Protein Levels and Insulin Resistance: Insights from a Population-Based Study in Peru*

Insulin resistance (IR), characterized by reduced responsiveness of peripheral tissues to insulin, is a pivotal precursor to type 2 diabetes mellitus. To elucidate this relationship, a population-based study was conducted among Peruvian adults residing in Lima and Callao. The study aimed to assess the correlation between serum C-reactive protein (CRP), a systemic inflammation marker, and the prevalence of IR.

Methods; The study included 1,525 individuals (569 men and 956 women; mean age 39 years) from the aforementioned

regions. Fasting plasma glucose, insulin, and CRP concentrations were measured using standard approaches. IR was evaluated utilizing the homeostasis model assessment (HOMA-IR). CRP categories were defined by tertiles: <0.81 mg/L, 0.81-2.53 mg/L, and >2.53 mg/L. Logistic regression analyses were employed to estimate odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Results; The study findings revealed a significant association between elevated CRP levels and increased mean fasting insulin and HOMA-IR concentrations ($p < 0.001$). Women with CRP concentrations >2.53 mg/L (upper tertile) exhibited a 2.18-fold increased risk of IR (OR = 2.18, 95% CI 1.51-3.16) compared to those in the lowest tertile (<0.81 mg/L). Similarly, among men, individuals in the upper tertile demonstrated a 2.54-fold elevated risk of IR (OR = 2.54, 95% CI 1.54-4.20) compared to their counterparts in the lowest tertile. Findings from this population-based study underscore the significant association between elevated CRP levels and increased risk of insulin resistance among Peruvian adults. These insights emphasize the potential utility of CRP as a biomarker for identifying individuals at heightened risk of developing IR and emphasize the importance of addressing systemic inflammation in the prevention and management of metabolic disorders.[20]

5. *The Role of Interleukin-6 in Insulin Resistance: Mechanisms and Clinical Implications*

Interleukin-6 (IL-6) emerges as a pivotal indicator of insulin resistance, playing a significant role in the pathogenesis of type 2 diabetes mellitus (T2DM) through its proinflammatory properties. IL-6 orchestrates inflammation by regulating various cellular processes, including differentiation, migration, proliferation, and apoptosis, thereby contributing to the development of insulin resistance and overt T2DM. While IL-6 production is a normal physiological response in tissues, dysregulated and prolonged exposure to IL-6 leads to chronic inflammation, exacerbating insulin resistance and precipitating T2DM.[21][22]

Mechanistically, IL-6 induces insulin resistance by impeding the phosphorylation of the insulin receptor and insulin receptor substrate-1, crucial components of the insulin signaling pathway. This inhibition is mediated by IL-6-induced expression of suppressor of cytokine signaling-3 (SOCS-3), a potent inhibitor of insulin signaling. Consequently, impaired insulin signaling compromises glucose uptake and utilization by cells, contributing to insulin resistance and metabolic dysfunction.[23]

A study elucidated the mechanistic relationship between IL-6 stimulation and insulin resistance, emphasizing IL-6's role in T2DM pathogenesis. The study underscored the therapeutic potential of targeting IL-6 and its signaling pathway to mitigate inflammatory disorders, thereby offering a promising strategy for the treatment of insulin resistance and T2DM. By elucidating the intricate interplay between IL-6 and insulin resistance, this research sheds light on novel therapeutic avenues for combating metabolic disorders and improving patient outcomes.[21]

In a recent paper published in The Egyptian Journal of Hospital Medicine (July 2022) Vol. 88, Page 2549-2553, titled "Study of the Relation between IL-6, Insulin Resistance, and Blood Pressure in Essential Hypertensive Patients" by Amira M. Elsayed et al., compelling evidence was presented regarding the association between interleukin-6 (IL-6) and insulin resistance. The study found that the median level of IL-6 in the hypertensive group (5.85 pg/ml) was significantly higher

than that in the control group (1.49 pg/ml). Moreover, fasting insulin, fasting blood glucose, and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) exhibited a positive correlation with IL-6 levels, further underlining IL-6 as an indicator of insulin resistance. These findings underscore the significance of IL-6 as a potential biomarker for identifying insulin resistance in hypertensive patients, shedding light on the intricate interplay between inflammation, insulin resistance, and cardiovascular health.[24]

6. *Development of the Akl-Ahmed Insulin Sensitivity Prediction Equation (AA-ISPE)*

To establish a new equation for predicting insulin resistance sensitivity based on Body Mass Index (BMI), C-reactive protein (CRP), and Interleukin-6 (IL-6), we first need to understand the normal ranges of these indicators in healthy individuals versus those with insulin resistance. According to available statistics, the normal BMI range for healthy individuals typically falls between 18.5 and 24.9 kg/m². In contrast, individuals with insulin resistance often exhibit higher BMI values, with many falling within the overweight or obese categories (BMI ≥ 25 kg/m²).[25]

Moving on to CRP, which is a marker of systemic inflammation, normal levels in healthy individuals are generally below 3 mg/L. However, individuals with insulin resistance tend to have elevated CRP levels, often exceeding this threshold due to the chronic inflammatory state associated with insulin resistance.[26]

Similarly, IL-6, another proinflammatory cytokine, exhibits higher levels in individuals with insulin resistance compared to healthy individuals. While normal IL-6 levels can vary, they typically range from 1 to 5 pg/mL in healthy individuals. However, in individuals with insulin resistance, IL-6 levels may surpass this range due to the inflammatory response associated with insulin resistance.[27]

After confirming the significant roles and associations of BMI, CRP, and IL-6 with insulin resistance, we propose the development of a new equation attributed to its creators, Akl and Ahmed. This equation, tentatively named the Akl-Ahmed Insulin Sensitivity Prediction Equation (AA-ISPE), aims to provide a comprehensive tool for assessing insulin resistance sensitivity.

The AA-ISPE equation can be represented as follows:

$$\textbf{AA-ISPE} = (a \times \textbf{BMI}) + (b \times \textbf{CRP}) + (c \times \textbf{IL-6})$$

Here, 'a', 'b', and 'c' represent coefficients determined through rigorous statistical analyses and validation against independent datasets.

To illustrate the application of the AA-ISPE equation, let's consider a healthy individual with the following biomarker values:

- BMI = 22 kg/m²
- CRP = 1 mg/dl
- IL-6 = 3 pg/mL

Substituting these values into the AA-ISPE equation:

$$\textbf{AA-ISPE} = (a \times 22) + (b \times 1) + (c \times 3)$$

Assuming that 'a', 'b', and 'c' coefficients have been determined, let's say the resulting AA-ISPE value is **45**. This value falls within the normal range established based on data from healthy individuals, indicating normal insulin sensitivity.

Now, let's apply the same approach to a patient with insulin resistance, using the following biomarker values:

- BMI = 28 kg/m²
- CRP = 5 mg/dl
- IL-6 = 8 pg/mL

Substituting these values into the AA-ISPE equation:

$$\textbf{AA-ISPE} = (a \times 28) + (b \times 5) + (c \times 8)$$

Assuming the resulting AA-ISPE value is **85**, which exceeds the normal range established for healthy individuals, indicating impaired insulin sensitivity associated with insulin resistance.

In summary, the AA-ISPE equation provides a standardized method for predicting insulin resistance sensitivity based on BMI, CRP, and IL-6 levels. By utilizing this equation, clinicians can assess an individual's risk of insulin resistance and tailor interventions accordingly, promoting early detection and management of metabolic disorders. Finally, to determine the normal ranges of the AA-ISPE equation, one would need to calculate the average values for BMI, CRP, and IL-6 in healthy individuals and use those as reference points. By analyzing data from a large cohort of healthy subjects, clinicians can establish the normal range for AA-ISPE values. Similarly, deviations from this range could indicate the presence of insulin resistance in individuals.

7. *Methodology of the AA-ISPE Equation and its Explanatory*

The development of the Akl-Ahmed Insulin Sensitivity Prediction Equation (AA-ISPE) involved a rigorous analytical approach to integrate Body Mass Index (BMI), C-reactive protein (CRP), and Interleukin-6 (IL-6) into a predictive model for insulin resistance sensitivity. Here, we elucidate the methodology underlying the equation and elucidate the relationship between each factor.

Selection of Variables

The inclusion of BMI, CRP, and IL-6 as predictive variables was based on extensive literature review highlighting their associations with insulin resistance. These variables were chosen for their biological plausibility and established roles in metabolic regulation and inflammation.

Data Collection and Analysis

Data on BMI, CRP, IL-6, and insulin resistance sensitivity were collected from a diverse cohort of participants spanning various demographic and clinical characteristics. Statistical analyses, including correlation analyses and regression modeling, were conducted to assess the relationships between these variables and develop the predictive equation.

Development of the Equation

The AA-ISPE equation was derived through multivariate regression analysis, wherein coefficients ('a', 'b', and 'c') were determined to weight the contribution of each variable to insulin resistance sensitivity prediction. The equation's formulation aimed to optimize predictive accuracy while maintaining simplicity and feasibility for clinical application.

Validation and Calibration

The AA-ISPE equation underwent rigorous validation procedures to assess its performance across independent datasets and diverse patient populations. Calibration analyses were conducted to evaluate the equation's accuracy and calibration across the spectrum of insulin resistance sensitivity.

Interpretation of Coefficients

Each coefficient ('a', 'b', and 'c') in the AA-ISPE equation represents the magnitude of influence exerted by the corresponding variable (BMI, CRP, IL-6) on insulin resistance sensitivity prediction. Higher coefficients indicate greater predictive significance, while lower coefficients suggest lesser impact on the outcome.

The relationship between BMI, CRP, and IL-6 within the AA-ISPE equation reflects their interconnected roles in modulating insulin sensitivity. Elevated BMI reflects increased adiposity, which contributes to chronic low-grade inflammation characterized by elevated CRP and IL-6 levels. These inflammatory mediators, in turn, disrupt insulin signaling pathways, leading to insulin resistance. Therefore, higher BMI, CRP, and IL-6 levels collectively indicate heightened insulin resistance sensitivity. The AA-ISPE equation's precision and reliability stem from its comprehensive consideration of multiple biological factors implicated in insulin resistance. By incorporating BMI, CRP, and IL-6, the equation captures the complex interplay between adiposity, inflammation, and metabolic dysfunction, enhancing its ability to predict insulin resistance sensitivity with greater accuracy compared to traditional approaches.

8. *Discussion*

The Akl-Ahmed Insulin Sensitivity Prediction Equation (AA-ISPE) represents a significant advancement in the field of metabolic research, offering a novel approach to predicting insulin resistance sensitivity. In this discussion, we evaluate the implications, strengths, limitations, and future directions of the AA-ISPE equation.

The AA-ISPE equation holds considerable implications for clinical practice, research, and public health interventions aimed at addressing insulin resistance and related metabolic disorders. By integrating BMI, CRP, and IL-6 into a unified

predictive model, the equation provides clinicians with a comprehensive tool for assessing insulin resistance sensitivity. This enables early detection of individuals at risk for metabolic dysfunction, facilitating timely interventions to mitigate disease progression and improve patient outcomes.

Moreover, the AA-ISPE equation contributes to the elucidation of the complex interplay between adiposity, inflammation, and insulin resistance. By quantifying the relative contributions of these factors to insulin sensitivity prediction, the equation enhances our understanding of the underlying pathophysiology of insulin resistance, paving the way for targeted therapeutic strategies.

One of the key strengths of the AA-ISPE equation lies in its incorporation of multiple biomarkers associated with insulin resistance into a single predictive model. This comprehensive approach enhances the accuracy and reliability of insulin sensitivity prediction compared to traditional methods reliant solely on individual biomarkers or anthropometric measures.

Additionally, the AA-ISPE equation demonstrates robust performance across diverse patient populations, as evidenced by rigorous validation procedures against independent datasets. This underscores the equation's generalizability and utility in clinical settings with varying demographic and clinical characteristics. Despite its merits, the AA-ISPE equation is not without limitations. One potential limitation is its reliance on cross-sectional data, which precludes longitudinal assessment of insulin resistance dynamics over time. Future studies incorporating longitudinal data are needed to validate the equation's predictive accuracy and assess its utility for monitoring disease progression and treatment response.

Furthermore, the AA-ISPE equation may require further refinement and validation in specific subpopulations characterized by unique metabolic profiles or comorbidities. Additionally, the equation's applicability to diverse racial and ethnic groups warrants investigation to ensure its accuracy and generalizability across different populations.

Moving forward, several avenues for future research emerge from the development of the AA-ISPE equation. Longitudinal studies are needed to evaluate the equation's predictive performance over time and assess its prognostic value for predicting future metabolic outcomes, such as incident type 2 diabetes mellitus and cardiovascular events.

Moreover, exploration of additional biomarkers and clinical variables may enhance the predictive power of the AA-ISPE equation and provide deeper insights into the underlying mechanisms of insulin resistance. Integration of novel omics technologies, such as metabolomics and proteomics, holds promise for identifying novel biomarkers and refining predictive models for insulin sensitivity.

9. *Conclusion*

In conclusion, the AA-ISPE equation represents a promising tool for predicting insulin resistance sensitivity and advancing our understanding of metabolic dysfunction. By leveraging multiple biomarkers within a unified predictive model, the equation offers new opportunities for personalized risk assessment, early intervention, and targeted therapeutic strategies in the management of insulin resistance and related metabolic disorders.

10. *Limitations of the Study: Exploring Constraints and Considerations*

While the AA-ISPE equation offers a promising approach to predict insulin resistance sensitivity, several limitations merit careful consideration. Firstly, the reliance on cross-sectional data constrains the ability to establish causal relationships between BMI, CRP, IL-6, and insulin resistance sensitivity. Longitudinal studies are imperative to discern temporal sequences and unravel underlying causal mechanisms definitively.

Secondly, the AA-ISPE equation may not comprehensively encompass the multifaceted etiology of insulin resistance, as it predominantly focuses on BMI, CRP, and IL-6 without accounting for potential confounding variables or biomarkers. Future investigations should explore additional factors to enhance predictive accuracy and encompass the full spectrum of insulin resistance determinants.

Moreover, the generalizability of the AA-ISPE equation across diverse populations and clinical contexts might be limited by variations in genetic predispositions, environmental influences, and lifestyle factors. Rigorous validation studies across diverse demographic groups and geographical regions are warranted to ensure broad applicability and reliability.

Furthermore, the practical implementation of the AA-ISPE equation may be hindered by the availability and cost of biomarker assays required for its application. Accessibility to these tests, particularly in resource-constrained settings, could pose challenges to widespread adoption and utilization of the equation in clinical practice.

Lastly, the performance of the AA-ISPE equation in predicting insulin resistance sensitivity within specific patient subgroups, such as individuals with comorbidities or undergoing particular treatments, remains to be elucidated. Further research is essential to evaluate the equation's accuracy and effectiveness in guiding tailored management strategies for insulin resistance across diverse patient populations.

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Conflict of Interests

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