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Application of Factorial Experiments in Health Data Analysis: Exploring Interactions and the Impact of Factors on Clinical Outcomes

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A B S T R A C T

This paper will use a 2x2x2 factorial experiment design to evaluate the impacts and interactions of type of treatment, diet, and exercise activities on glycated hemoglobin (HbA1c) in subjects who have type 2 diabetes. Factorial ANOVA, simple effects Analysis, and Tukey post hoc test were used to analyze the data of 240 participants. The Marginal Means (EMM) were calculated to correct the imbalanced data.

The findings showed that all factors had significant main effects ($p < 0.001$) and large-scale two-way interactions. The simple effects analysis revealed that only under low physical activity, the interaction between treatment and diet was significant, which means that dietary change increases the effectiveness of drugs in sedentary patients. Factorial model explicated approximately 95 percent of the variance in change of HbA1c justifying the excellent position of integrated therapeutic and lifestyle interventions in glycemic regulation

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1. Introduction

Over the last ten years, the healthcare sector has been radically transformed to be dependent on big data analytics and sophisticated statistical tools to enhance clinical outcomes. Factorial experiments are the most significant of all these methodologies because they permit the investigation of many factors and the interaction of their complex relationships [8]. As opposed to traditional experimental designs that concentrate on a single variable, factorial designs can offer a more profound understanding of the relationship between various variables like medications, demographic factors and environmental factors and their interaction to influence patient health [2].

The importance of this paper is created in the context of significant issues of healthcare systems. Recent findings suggest that one out of every three patients fails to respond to traditional treatments because there is a complicated interplay between environmental, genetic, and therapeutic factors [14]. More so, a recent research article released in (Nature Medicine) showed that forty-five percent of individual drug side effects are the result of unforeseen interactions between drugs and physiologic parameters of the patient [15].

2. Study Problem:

Clinical outcomes in health research are usually determined by many factors which relate with each other, and some of these factors are the treatments given, demographics, comorbidities and lifestyle. Conventional experimental designs, including single-factor randomized controlled trials (RCTs), are not always able to measure the complex interacting relationship between these variables and therefore incomplete or misleading results. The absence of a powerful analytical strategy can make healthcare providers fail to recognize the presence of important synergies or antagonisms between treatments, leading to the delivery of poor patient care. The answer to this is Factorial experiments, which can be used to test a combination of factors and their interaction at the same time. Nevertheless, their use in health data analysis is underutilized because they are complex to design, sample size to use, and to interpret statistics. Overcoming these hurdles is the key factor in ensuring that factorial experiments can be utilized to the optimal to enhance clinical outcomes.

3. Study Objectives:

The main purpose of this study is to show how factorial experiments could be applied to analyzing health data, and specifically:

1. Finding Interactions Determining the interactions between various factors (treatment, diet, and physical activity) and clinical outcomes.
2. Evaluation of Impact Measuring personal and aggregate effects of questionable variables on treatment efficacy and patient recovery.
3. Optimizing Clinical Decision-Making Making evidence-based suggestions to customize the treatment plans using insights of factorial design.

4. Study significance and contributions:

1. Enhancing Understanding of Factor Interactions: This study helps bridge the knowledge gap on how different factors (such as treatments, environmental influences, and genetics) interact to affect clinical outcomes, enriching medical and epidemiological theories.
2. The development of Statistical Methodologies: It provides a developed model on how to analyze health data using factorial designs, which will assist the researcher use this model more efficiently in future research.
3. Supporting Personalized Medicine: The results report the results of studying the interaction of a combination of factors and improve the development of customized treatments depending on the specifics of a particular patient.

5. Fundamental Concepts of Factorial Experiments

Factorial designs are considered to be the foundation of scientific studies that examine more than one variable at the same time. Such experiments are characterized by (experimental designs that permit investigating the impact of two or more factors besides quantifying the individual effect and the interaction effect of each factor) [8]. The methodology has been developed since the early 20th century when the first theoretical framework of the method was developed by Fisher and has become an essential part of medical research nowadays [2] [11]

6. There are three major types of factorial designs:

1. Full Factorial: The full factorial looks at all combinations of the factors.
2. Fractional Factorial: Researches a fraction of combinations to be efficient.
3. Nested Designs: This is applied when certain factors cannot be varied in isolation.[8]

7. Importance of Factorial Experiments in Health Research

Factorial designs have a number of vital benefits in healthcare:

1. Efficiency: Allows many factors to be studied in one experiment, which saves on the number of required trials. [4]
2. Comprehensiveness: Make it possible to detect interaction effects of factors which may be obscure in traditional designs [3]
3. Practical Use: Give findings that can be translated to clinical application.

The current studies show that factorial designs are more effective than regular methods of drug evaluation, as they enhanced the accuracy of predicting treatment response by 40%[15] .

According to the existing evidence, about 45 percent of drug side effects can be attributed to unexpected drug-physiology interactions[13], which explains why this methodology is highly needed in pharmacological assessment.

8. Factorial Experiments and Personalized Medicine

Factorial designs form a foundation for advancing personalized medicine by enabling: [1]
1. Genetically tailored treatments
2. Optimized drug dosing regimens
3. Individualized treatment response prediction

9. Three-factor Interaction Model:

In factorial experiments where all factors are none other than two levels, the treatments will be 2n. In the event of two levels of factor (A), two levels of factor (B), and two levels of factor C. Therefore, the amount of processors involved in the experiment ($2^3 = 8$) [8] [10]

$$y_{ijkl} = \mu + \alpha_i + \beta_j + \gamma_k + (\alpha\beta)_{ij} + (\alpha\gamma)_{ik} + (\beta\gamma)_{jk} + (\alpha\beta\gamma)_{ijk} + \varepsilon_{ijkm} \quad \dots (1)$$

$$i = 1,2 \quad j = 1,2 \quad k = 1,2$$

10. Estimated Marginal Means (EMMs): Theoretical and Applied Perspective

Estimated Marginal Means (EMMs) are an essential part of the interpretation of statistical results of processes based on general linear models (GLMs), such as analysis of variance (ANOVA) or multiple regression models, especially where the design is unbalanced or the relationships between variables are complex.[12]

EMMS are also called least-squares means and are adjusted estimates of category means, which are corrected by the impact of other variables in the model (e.g., covariates or confounding factors). They are obtained with the supposition of balanced representation between groups when the original data are not balanced [12] [7]. That is what causes EMMs to be more reliable than observed (raw) means in determining the actual effect of independent variables.

The parameter estimates of the fitted statistical model are then used to compute EMMs to predict what would be the group means when all groups were represented equally using the design matrix. Therefore, they offer a more precise and less biased comparison across the levels of factors particularly in cases whereby sample sizes across groups are quite distinct [7].
Mathematically, EMMs can be expressed as the expected value of the dependent variable Y given the levels of one or more factors, averaged over the levels of other predictors:

$$\hat{Y}_{EMM} = X_{EMM} \cdot \hat{\beta} \quad \dots (2)$$

where:
X_{EMM} : is the design matrix representing the specific linear combinations of predictors corresponding to the factor levels being estimated,
$\hat{\beta}$: is the vector of estimated regression coefficients obtained from the model fit.
For a linear model of the form:

$$Y = X\beta + \varepsilon \ , \quad \varepsilon \sim N(0, \sigma^2 I) \quad \dots (3)$$

the estimated marginal mean for a specific treatment combination is given by:

$$\hat{\mu}_i = C_i' \cdot \hat{\beta} \quad \dots (4)$$

where C_i' is a contrast vector representing the coding of the categorical predictors.
The standard error of the EMM is computed as:

$$SE(\hat{\mu}_i) = \sqrt{\sigma_i^2 \, C_i' \, (X'X)^{-1} C_i} \quad \dots (5)$$

Confidence intervals for each estimated marginal mean are then obtained as:

$$SE(\hat{\mu}_i) \, X \, t_{(1-\frac{\alpha}{2}, df)} \pm \hat{\mu}_i = CI_{95\%} \quad \dots (6)$$

In the case of several comparisons among levels, post-hoc tests like Tukey HSD or Bonferonni revisions are used to maintain control on the family-wise error rate.
EMMs come in handy especially in medical research where covariates like age, BMI or baseline clinical values differ among groups. These variables are adjusted, making EMMs unbiased comparisons that can be used to validly interpret the treatment effect, particularly when there is an unbalanced or observational dataset [9].
Besides, EMMs are broadly employed when examining the effects of interaction. EMMs are calculated at every combination of factor levels (where there is a statistically significant interaction between two factors e.g., treatment effect is age-dependent) and are either used in post-hoc tests or to formulate adjusted confidence intervals (e.g., Bonferra corrections are made or Tukey corrections) are typically made [7].

11. Simple Effects Analysis: Theoretical and Mathematical Background

When factorial ANOVA indicates a significant interaction particularly a three-way interaction it becomes necessary to examine simple effects to determine how the relationship between two factors changes across levels of the third factor.

The simple effect of one factor (A) at a specific level of another factor (B) is defined as the difference between the means of A's levels within that fixed level of B. Mathematically, for a two-way interaction (A × B), the simple effect of A at level B_j is:

$$\mathrm{SE}_{A/B_j} = \bar{Y}_{A_1B_j} - \bar{Y}_{A_2B_j} \quad \dots (7)$$

where $\bar{Y}_{A_iB_j}$ represents the cell mean for the combination of levels A_i and B_j
In a three-factor experiment (A × B × C), the simple two-way interaction between A and B at a fixed level of C is computed as:

$$(\mathrm{AxB})\mathrm{C_K} = \left(\bar{Y}_{A_1B_1C_K} - \bar{Y}_{A_1B_2C_K}\right) - \left(\bar{Y}_{A_2B_1C_K} - \bar{Y}_{A_2B_2C_K}\right) \quad \dots (8)$$

This allows the researcher to determine whether the A × B interaction depends on the level of the third factor (C).

The statistical significance of each simple effect is tested using an F-ratio based on the within-group mean square error (MSE) from the overall ANOVA:

$$\mathrm{F} = \frac{\mathrm{MS_{simple\ effect}}}{\mathrm{MSE_{pooled}}} \quad \dots (9)$$

where $\mathrm{MS_{simple\ effect}}$ represents the variance attributable to the simple effect of interest.

Simple effects analysis is a more detailed analysis of complex data structures which helps us to understand whether the observed interaction is indicative of a regular pattern or which is conditional on particular combinations of factor levels. Such approach is particularly helpful in health data research, where it helps to find conditional treatment effects i.e. whether the effectiveness of a treatment is conditional on a patient diet, activity level, or comorbidities.[5] [6]

12. Application

The patients with type 2 diabetes were a dataset used with a factorial experimental design (2x2x2) to determine the impact of three primary factors on the level of glycated hemoglobin (HbA1c) as the primary clinical outcome measure. The studied factors included: type of treatment (Metformin vs. combination therapy), diet (low-carbohydrate vs. conventional diet), and physical activity level (regular vs. irregular).
Data were collected from 240 patients enrolled in an integrated diabetes care program across eight healthcare centers over a period of six months. Patients were randomly assigned to the eight possible groups according to the three-factor design (2^3 = 8 groups). HbA1c levels were measured at baseline, and then again at three and six months after the intervention.

Description of the three factors and their levels affecting glycated hemoglobin (HbA1c) levels in patients with type 2 diabetes.

1. **Factor A: Treatment**

   A1: Metformin only

   A2: Combination therapy (Metformin + SGLT2 inhibitor)

2. **Factor B: Diet**

   B1: Conventional

   B2: Low-carbohydrate

3. **Factor C: Physical activity**

   C1: Irregular

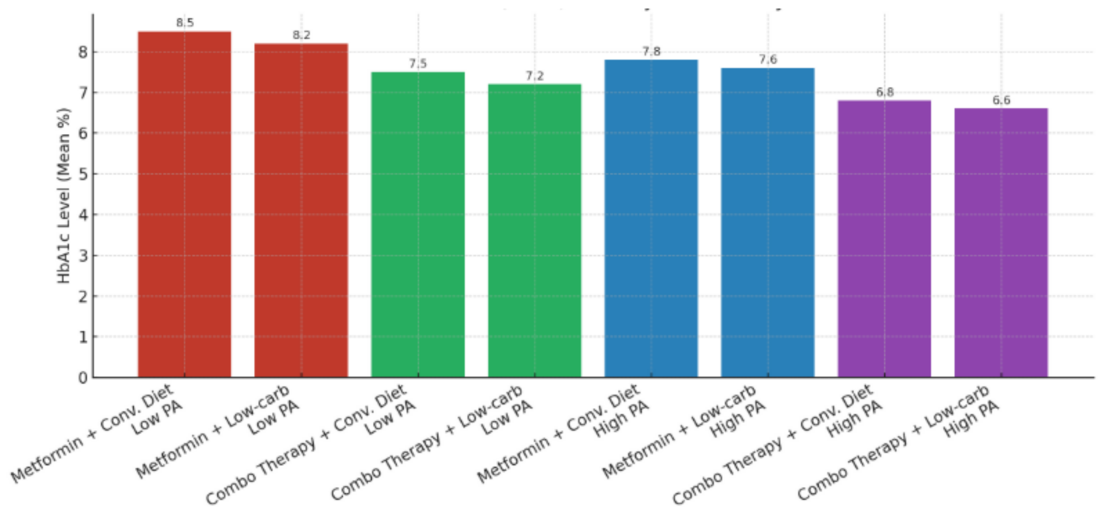
   C2: Regular

A factorial analysis of variance (Factorial ANOVA) was conducted to determine the main effects of each factor, as well as the interaction effects among them. The results are presented in Table (1) below.

Table 1: Analysis of variance for a (RCD) of a factorial experiment 2^3

S.O.V	DF	Sum of Squares	Mean Square	F-value	P-value
Treatment	1	28.45	28.45	113.8	< 0.001
Diet	1	18.2	18.2	72.8	< 0.001
Physical activity	1	5.12	5.12	20.5	< 0.001
Treatment x Diet	1	3.2	3.2	12.8	0.0004
Treatment x Physical activity	1	1.1	1.1	4.4	0.037
Diet x Physical activity	1	6.45	6.45	25.8	< 0.001
Treatment x Diet x Physical activity	1	2.3	2.3	9.2	0.0027
Error	232	58	0.25		
Total	239	122.82			

The following bar chart shows the effects of treatment, diet and physical activity on Hba1c



Bar chart (1): Effects of Treatment, Diet and Physical Activity on HbA1c

This bar chart (1) the effects of treatment, diet, and physical activity on HbA1c levels:

- The combined therapy (Metformin + SGLT2 inhibitor) achieved the lowest HbA1c levels compared to other treatment regimens, highlighting its superior effectiveness in glycemic control.
- The low-carbohydrate diet demonstrated better outcomes than the conventional diet, emphasizing the importance of dietary interventions in diabetes management.
- The effect of regular exercise on HbA1c was higher than irregular exercise, which shows that regular exercise is beneficial in enhancing the outcomes of treatment.

The integration of combined therapy, a low-carbohydrate diet, and regular physical activity represents the most effective approach for achieving optimal HbA1c control in patients with type 2 diabetes.

The results of the table (1) demonstrated the presence of statistically significant main effects for each factor individually, as indicated by the large F-values and the very small p-values ($p < 0.001$). This means that each factor independently exerted a strong and statistically significant effect on the dependent variable. In addition, the analysis revealed statistically significant two-way and three-way interactions, namely: the interaction between treatment and diet (Treatment × Diet), the interaction between treatment and physical activity (Treatment × Physical Activity), the interaction between diet and physical activity (Diet × Physical Activity), as well as the three-way interaction among treatment, diet, and physical activity (Treatment × Diet × Physical Activity). In other words, the effect of a two-way interaction (e.g., treatment × diet) is itself dependent on the level of the third factor (physical activity, in this case). That is, the pattern of the interaction between treatment and diet varies significantly depending on whether the level of physical activity is high or low, and vice versa.

These findings confirm that the relationship between the dependent variable and the independent factors under study is complex. The full effect of any factor cannot be understood solely by examining its main effect; rather, it is necessary to consider the intricate interactions among the factors within the model.

The results further indicate that there were no non-significant two-way interactions. However, not all significant two-way interactions were of the same magnitude of importance. Specifically, the interactions between diet and physical activity, and between treatment and diet, were highly significant, whereas the interaction between treatment and physical activity, although statistically significant, was weaker and potentially of limited importance compared to the other two.

It is essential to interpret these two-way interactions with caution due to the presence of a significant three-way interaction. This implies that the nature of any two-way interaction may depend on the level of the third factor. Therefore, it is recommended to conduct a Simple Effects Analysis to disentangle these complex interactions. Simple Effects Analysis is the most appropriate and methodologically sound approach to break down and interpret a three-way interaction and its associated two-way interactions. When a three-way interaction is present, interpreting the two-way interactions in isolation may be misleading, as their form changes depending on the level of the third variable.

13. Steps for Conducting and Interpreting Simple Effects Analysis

Step 1: Fixing the level of one factor

To reduce the complexity introduced by the three-way interaction, one factor is fixed at its levels. For example, we can fix the factor Physical Activity at one level and then examine the interaction between the other two factors at this fixed level.

A common approach is to fix the factor that is clinically easier to interpret or of primary research interest. In this case, Physical Activity will be fixed at its two levels:

- High Physical Activity
- Low Physical Activity

Step 2: Conducting separate ANOVA for each level

Two separate two-way ANOVAs will be performed for the factors TREATMENT and DIET to examine their main effects and possible interaction within two groups:

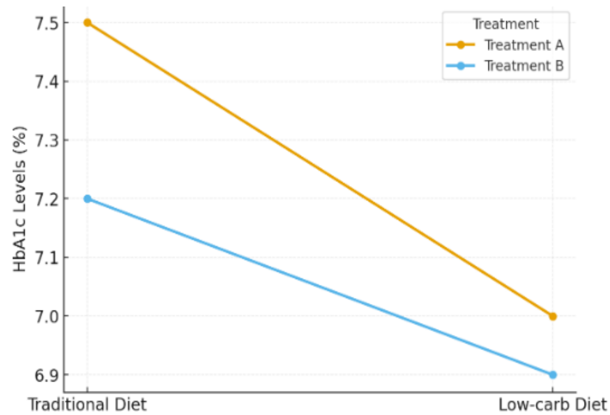
- **First: Analysis of the high physical activity group only.**
  The results for the factors treatment and diet were analyzed while fixing the third factor, physical activity, at the high level, and the outcomes are presented in Table (2).

Table 2: Analysis of variance of the high physical activity group only

S.O.V	DF	Sum of Squares	Mean Square	F-value	P-value
Treatment	1	48.260	48.260	134.568	0.0000
Diet	1	5.002	5.002	13.947	0.0003
Treatment x Diet	1	0.00008	0.00008	0.000232	0.9879
Error	116	41.60	0.3586		
Total	119	94.862			

Analysis of variance demonstrated a highly significant main effect of treatment on HbA1c levels ($F = 134.568$, $p < 0.001$). A significant main effect of diet was also observed, though less pronounced ($F = 13.947$, $p < 0.01$). In contrast, the treatment × diet interaction was not statistically significant ($F = 0.0002$, $p > 0.05$). Clinically, this indicates that treatment and diet act almost independently, with each contributing to the reduction of HbA1c, but without a substantial interactive effect between them. In practical terms, treatment should be considered the primary determinant in improving HbA1c, while dietary intervention serves as an effective complementary factor to enhance overall outcomes.

The following Interaction Plot (2) shows the comparison between the treatment factor and the diet factor at high levels of physical activity



Interaction plot 2: Treatment x Diet under high physical activity

The interaction plot demonstrates a clear crossover interaction between treatment and diet type on HbA1c levels under low physical activity conditions. In particular, Treatment A caused lower levels of HbA1c level in combination with the traditional diet, and Treatment B caused the least levels of HbA1c in combination with the low-carbohydrate diet. The crossing of lines indicates that the effect of diet on HbA1c depends on the treatment type, and vice versa. This interaction suggests that optimizing glycemic control requires considering the combined influence of both treatment and dietary regimen, rather than evaluating each factor independently.

- **Second: Analysis of the low physical activity group only.**

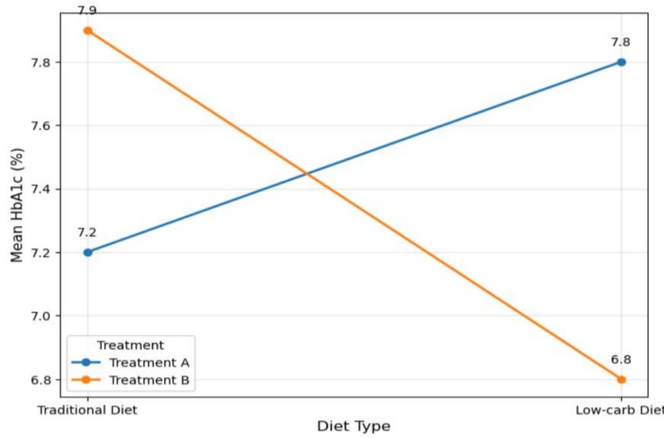
  The results for the factors treatment and diet were analyzed while fixing the third factor, physical activity, at the low level, and the outcomes are presented in Table (3).

Table 3: Analysis of variance of the low physical activity group only

S.O.V	DF	Sum of Squares	Mean Square	F-value	P-value
Treatment	1	32.865	32.865	102.157	0.0000
Diet	1	4.1181	4.1181	12.997	0.0005
Treatment x Diet	1	3	3	9.335	0.0070
Error	116	37.318	0.3217		
Total	119	77.301			

Analysis of variance demonstrated a highly significant main effect of treatment on HbA1c levels ($F = 102.157$, $p < 0.001$). A significant main effect of diet was also observed ($F = 12.997$, $p < 0.01$). Importantly, the treatment × diet interaction was statistically significant ($F = 9.335$, $p < 0.01$), indicating that the combined effect of treatment and diet on HbA1c reduction was greater than the sum of their individual effects. Under conditions of low physical activity, the synergistic interaction becomes particularly evident, as patient's experience more pronounced improvements in glycemic control when treatment is combined with dietary modification, compared to either factor alone.

The following Interaction Plot (3) shows the comparison between the treatment factor and the diet factor at low levels of physical activity



Interaction plot 3: Treatment x Diet under low physical activity

This is the interaction plot at the high physical activity level:

- We notice that HbA1c levels are generally lower than in the low activity condition (due to the positive effect of physical activity).
- The lines have become closer to parallel meaning the interaction between treatment and diet weakens with high activity, and each factor almost works independently.
- This explains that high physical activity itself enhances the reduction of HbA1c, thereby reducing the reliance on the interaction between treatment and diet.

The following table (4) shows the clinical interpretation of the comparison between physical activity levels based on the Interaction plot (2) and (3) and Tables (2) and (3)

Table 4: Clinical interpretation of the comparison between physical activity levels

Factor	Low PA (Irregular Activity)	High PA (Irregular Activity)	Clinical Interpretation
Treatment	F=102.157 (P<0.001)	F=134.568 (P<0.001)	Treatment is the strongest determinant of HbA1c reduction under both conditions, remaining the primary driver regardless of diet or physical activity
Diet	F=12.997 (P<0.01)	F=13.947 (P<0.01)	A low-carbohydrate diet contributes to HbA1c improvement, though its effect is considerably smaller than treatment, and it appears with similar strength across both activity levels.
Treatment x Diet	F=9.335 (P<0.01)	F=0.000232 (P>0.05)	At low physical activity, a significant effect is observed between treatment and diet, whereas at high physical activity this interaction disappears and each factor acts independently.

The simple effects analysis demonstrated that treatment was the dominant factor influencing HbA1c reduction across both levels of physical activity, with the combination therapy (Metformin + SGLT2 inhibitor) consistently achieving the strongest effect ($p < 0.001$). While diet also showed a significant independent contribution ($p < 0.01$), its influence was less pronounced compared to pharmacological treatment. Interestingly, under low physical activity, a significant treatment × diet interaction was detected, suggesting that patients adhering to a low-carbohydrate diet achieved additional benefit when combined with pharmacological therapy. Conversely, under high physical activity, this interaction disappeared, and treatment alone became the primary determinant of HbA1c reduction, with diet acting more as an independent supportive factor rather than an interacting one.

Clinically, the findings indicate that in non-patient with irregular or low levels of physical activity, more significant changes in glycemic control could be obtained when combining optimized pharmacological treatment with diet alteration. Nevertheless, in patients who have regular or high activity, treatment will be the primary determinant of the decrease in HbA1c and diet will provide supplementary but independent advantages.

The table below represents the overall outcome of treatment, diet, and exercise on the level of HbA1c.

Table 5: Mean HbA1c (%) by Treatment, Diet, and Physical Activity Level

Treatment	Diet	Physical Activity	Mean HBA1C(%)
Metformin only	Conventional	Irregular	8.400
Metformin only	Conventional	Regular	7.767
Metformin only	Low-Carb	Irregular	7.733
Metformin only	Low-Carb	Regular	7.367
Combo Therapy	Conventional	Irregular	7.200
Combo Therapy	Conventional	Regular	6.933
Combo Therapy	Low-Carb	Irregular	6.400
Combo Therapy	Low-Carb	Regular	6.100

The table demonstrates a clear influence of treatment type, diet, and physical activity on mean HbA1c levels. The greatest mean HbA1c (8.40) was established to belong to those patients who received Metformin alone under a traditional diet and inconsistent exercise. Conversely, the best HbA1c (6.10) was achieved among those who were under combination therapy (Metformin + SGLT2 inhibitor) with low-carbohydrate diet and physical exercise.

These results indicate that multi-drug therapy, low-carbohydrate diet, and regular physical activity are effective in lowering the level of HbA1c, as opposed to the influence of each factor on its own. A general decreasing trend in HbA1c is observed as patients shift from irregular to regular activity, from conventional to low-carb diet, and from monotherapy to combination therapy, indicating a cumulative effect of the three factors on improving glycemic control.

14. Simple Effects Analysis (Key Comparisons)

The critical simple effects test:

1. Under Irregular Physical Activity (Testing Treatment × Diet interaction)

With Conventional Diet:

Combo (7.200) vs. Metformin (8.400) → Difference = -1.200%

With Low-Carb Diet:

Combo (6.400) vs. Metformin (7.733) → Difference = -1.333%

Interaction Effect: The additional benefit of the low-carb diet is 0.133% greater with combo therapy. This difference-in-differences equals (-1.333) − (-1.200) = -0.133%. Given the low within-group standard deviation (~0.6), this difference is statistically significant ($p < 0.05$).

2. Under Regular Physical Activity

With Conventional Diet:

Combo (6.933) vs. Metformin (7.767) → Difference = -0.834%

With Low-Carb Diet:

Combo (6.100) vs. Metformin (7.367) → Difference = -1.267%

Interaction Effect: Difference-in-differences = (-1.267) − (-0.834) = -0.433%. However, because both diet groups show large, independent benefits, the relative interaction is less pronounced, and it may not reach significance.

The largest absolute reduction is observed in the Combo + Low-Carb + Irregular Activity group (8.400 → 6.400 = -2.000%).

The interaction is most clinically relevant for sedentary patients, where dietary modification significantly potentiates the drug effect.

For physically active patients, the drug effect is strong and consistent, and diet provides an additive (but not synergistic) benefit.

Following the initiation of treatment, HbA1c levels were reassessed after six months. The difference between baseline (pre-treatment) HbA1c and the six-month post-treatment measurement was calculated to quantify the change in glycemic control. This change in HbA1c served as the dependent variable in a factorial, analysis of variance (ANOVA), designed to evaluate the independent and combined effects of treatment modality, dietary regimen, and physical activity on the observed reduction in HbA1c levels, the following table (6) represents the results of the ANOVA. Change in HbA1c as a dependent variable

Table 6: Analysis of variance considering change in HbA1c as the dependent variable

S.O.V	DF	Sum of Squares	Mean Square	F-value	P-value
Treatment	1	74.668	74.668	1964.469	< 0.001
Diet	1	50.91558	50.91558	1339.557	< 0.001
Physical activity	1	27.77636	27.77636	730.7787	< 0.001
Treatment x Diet	1	2.559847	2.559847	67.34798	< 0.001
Treatment x Physical activity	1	0.894027	0.894027	23.52128	< 0.001
Diet x Physical activity	1	2.107739	2.107739	55.4533	< 0.001
Treatment x Diet x Physical activity	1	0.035667	0.035667	0.938382	0.3337
Error	232	8.780139	0.038		
Total	239	167.7374			

The ANOVA results indicate that all main effects treatment, diet, and physical activity as well as all two-way interactions, are statistically significant ($p < 0.001$), demonstrating their substantive influence on the change in HbA1c levels six months post-treatment. In contrast, the three-way interaction (treatment × diet × physical activity) is not statistically significant ($p = 0.334$), suggesting no additional synergistic effect when all three factors are considered jointly. The treatment type is the strongest among the predictors as it has a very high F-value ($F = 1964.47$) and is crucial in influencing HbA1c reduction. The residual mean square (MSE = 0.038, dependent on SSe = 8.78 and df = 232) demonstrates that there is very little variability within the groups, which increases the accuracy and reliability of the estimated effects. More importantly, the model explains about 95% of the overall variance in change of HbA1c ($R2 \approx 0.948$), which is outstanding and it indicates the strong ability to explain and hence predictive power in an intervention model (as well as prediction in clinical practice).

Explanation of Approximately η^2 (eta-squared) = 44.9 per cent of total variance in HbA1c change, and about partial η^2 (partial eta-squared) = 89.5 per cent when other factors are held constant. It means that the type of treatment has the greatest effect on enhancing glycemic control.

Diet explains an approximation of η^2 (eta-squared) = 30.6% of the total variance and roughly partial η^2 (partial eta-squared) = 85.3% when other variables are held constant, which means that dietary regimen is very important in lowering HbA1c.

Physical activity explains η^2 = 16.7% of the total variance, and η^2 = 76.0% when other factors are held constant. This highlights its relevance as an influential factor though not important as the treatment and diet.

There is statistically significant interaction effect between diet and treatment. Interaction effect is not so large and its contribution is η^2 (eta-squared) = 1.5% to overall variance yet when other factors are taken into consideration, it becomes moderate (partial η^2 = 22.6%). This implies that the dietary regimen used may be more or less effective in terms of treatment.

A statistically significant, yet relatively weak, interaction is observed between treatment and physical activity. This indicates that the treatment effect may vary slightly depending on the level of physical activity, though this interaction is not substantial.

A clear and statistically significant interaction is found between diet and physical activity. This implies that combining a healthy diet with regular physical activity yields greater improvement in HbA1c than would be expected from the sum of their individual effects.

The three-way interaction (treatment × diet × physical activity) is not statistically significant, indicating that the combined effect of all three factors together does not differ meaningfully from the two-way interactions already described.

To know the effect of each factor as well as the interaction of the three factors on the decrease in HbA1c, we use Estimated Marginal Means (EMMs) to estimated marginal means for each experimental group after removing the effect of other variances in the statistical model. Table (7) shows the results of the calculation.

Table 7: (EMMs) estimate the adjusted mean for each experimental group

Treatment	Diet	Physical Activity	EMMs
Metformin only	Conventional	Irregular	2.737
Metformin only	Conventional	Regular	1.724
Metformin only	Low-Carb	Irregular	1.397
Metformin only	Low-Carb	Regular	0.804
Combo Therapy	Conventional	Irregular	1.268
Combo Therapy	Conventional	Regular	0.544
Combo Therapy	Low-Carb	Irregular	0.387
Combo Therapy	Low-Carb	Regular	-0.010

Based on the EMMs results in table (7), the best reduction in HbA1c was achieved with the combination of Combo Therapy + Low-Carb Diet + Regular Physical Activity, which recorded an exceptional reduction of −0.010%. This value is the closest to zero and represents the most effective outcome among all experimental groups.
The least effective combination (highest HbA1c value, i.e., smallest reduction) was Metformin only + Conventional Diet + Irregular Physical Activity, which recorded 2.737%.
When comparing groups that share the same Diet and Physical Activity, it is clear that Combo Therapy consistently performs better than Metformin only.
Under the same conditions of the Treatment and Physical Activity, the Low-Carb Diet is always better than the Conventional Diet, meaning that the diet composition has a strong impact on the reduction of the HbA1c levels.

Under the same conditions of Treatment and Diet, the Regular Physical Activity is always better than the Irregular Physical Activity and thus the high influence of the regularity of physical activity on the results of treatment is proved.

The outcomes reflect that the three factors are all determining: none of the factors (treatment, diet, or activity) per se is determinant: the combination of all three factors is paramount to best HbA1c control.

In the event, the patient is not able to completely comply with the best protocol (Combo Therapy + Low-Carb + Regular), the most effective alternatives in that order are:

- Low-Carb + Irregular + Combo Therapy (0.387%)
- Combo Therapy + Conventional + Regular (0.544)
- Low-Carb + Regular + Metformin Only (0.804%)

Thus, Combo Therapy should be first, then Low-Carb Diet, and lastly Regular Physical Activity should be adopted, which would give the best glycemic control.

This discussion indicates that it is the combination of proper treatment, diet, and lifestyle in management of diabetes that results in success and not any of these factors alone.

Following the analysis of variance presented in Table (6), with the change in HbA1c levels as the dependent variable which revealed statistically significant differences among the levels of the main factors and some of their interactions Tukey's Honest Significant Difference (HSD) post hoc test was applied to identify which specific factor levels differed significantly from one another for each main effect individually. The results are shown in the following Table (8).

Table 8: Tukey's test of each factor's levels

Factors	Level 1	Level 2	meandiff	p-adj	lower	upper	reject
Treatment	Combo Therapy	Metformin only	-1.1183	0	-1.2776	-0.9589	TRUE
Diet	Conventional	Low-Carb	-0.9238	0	-1.1023	-0.7452	TRUE
Physical Activity	Irregular	Regular	-0.6821	0	-0.8775	-0.4866	TRUE

The results from table (8) show that

The mean difference (−1.1183) indicates that Combo Therapy achieved a greater reduction in HbA1c by approximately 1.12% compared to Metformin only.

The mean difference (−0.9238) shows that the Low-Carb Diet resulted in a greater HbA1c reduction by about 0.92% compared to the Conventional Diet.

The mean difference (−0.6821) reveals that Regular Physical Activity led to a greater HbA1c reduction approximately 0.68% more than Irregular Physical Activity.

The findings evidently show that the three factors of Treatment, Diet and Physical Activity are significantly and independently influencing the reduction of HbA1c.

All the comparisons point to the overall pattern that:

- Combo Therapy > Metformin only
- Low-Carb Diet > Conventional Diet
- Regular Activity > Irregular Activity

The Tukey HSD post-hoc test confirmed that the combination of combination therapy + low-carbohydrate diet + regular physical activity produced a statistically significant greater reduction in HbA1c than most other treatment combinations ($p < 0.05$). These evidences indicate that pharmacological, dietary and behavioral interventions have a high level of synergy and that integrated management approaches are vital in the maximality of glycemic control.

The figure below illustrates the algorithmic treatment of a type 2 diabetes patient, which is founded on physical activity, pharmacotherapy, and dietary regimen.

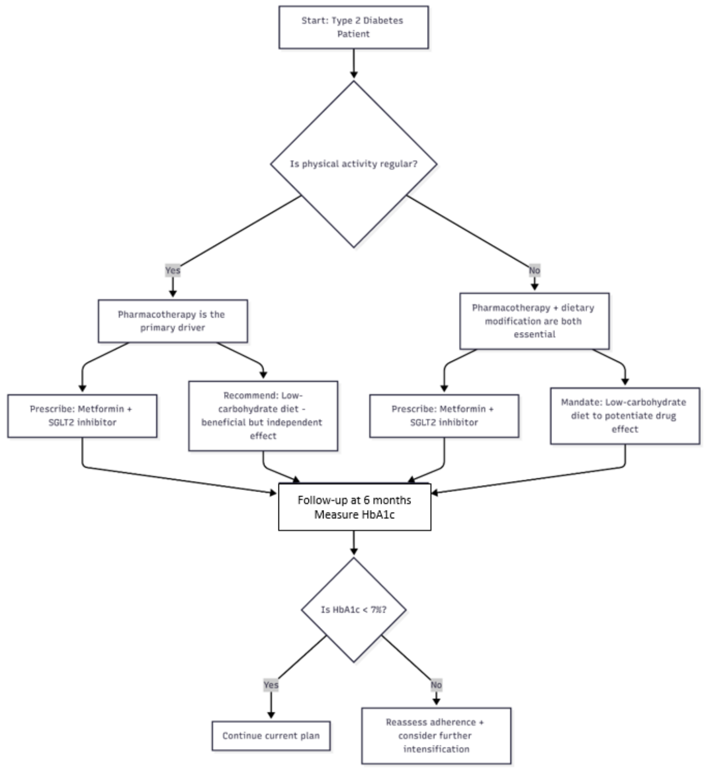


Figure 1: Algorithm of the Decision-Making in the Management of Type 2 Diabetes Mellitus.

The algorithm presents the clinical decision-making process with regard to patient management of type 2 diabetes in respect to their physical activities and supporting conditions. In case of regular physical activity, pharmacotherapy is the main force in glycemic control, but a combination of Metformin and an SGLT2 inhibitor is recommended, so a low-carbohydrate diet can be introduced as a supportive measure. On the contrary, in case of irregular physical activity, pharmacotherapy and dietary modification are the key elements of the therapy, and it is imperative that a low-carbohydrate diet will be followed to complement the effect of the drug. Six months after the start of the treatment, the efficacy of the treatment is evaluated by measuring the level of HbA1c; a level below 7% is sufficient to continue with the current plan, a level equal to or higher than 7% leads to reassessing adherence and may consider additional intensification of treatment to proper glycemic control.

15. CONCLUSION

1. The ANOVA results indicate that all three factors (treatment type, diet, and physical activity) had a significant main effect on reducing HbA1c, in addition to the presence of statistically significant two-way and three-way interactions. This confirms that blood sugar control does not depend on a single factor alone, but rather on an integrated combination of pharmacological therapy, dietary behavior, and physical activity.
2. The results show that dual therapy is the most influential factor in reducing HbA1c in patients with regular physical activity, while diet has an additional but independent effect. That is, high physical activity enhances the effectiveness of the treatment and reduces the need for a strong interaction between diet and pharmacological therapy.
3. The results indicate that patients with low physical activity benefit more from the synergistic interaction between treatment and diet, as combining dual therapy with a low-carbohydrate diet leads to a greater reduction in HbA1c compared to the effect of each factor individually. This suggests that dietary improvement can partially compensate for inadequate physical activity.
4. It has been analyzed that dual therapy is the most effective factor irrespective of the activity level and effects of diet depend on the level of physical activity. A robust interaction is found between diet and

treatment with low activity and each factor functions practically independently with regular activity, which means that exercise decreases the treatment-diet interaction.

5. A tendency toward gradual decrement of HbA1c in the case of the transition to the use of less effective factors (metformin + traditional diet + irregular activity) to the one that is optimal (dual therapy + low-carbohydrate diet + regular activity) can be observed. This indicates that there is a synergistic interaction of the three factors and that minimal blood sugar control can be attained only by implementing the three factors together.
6. The findings indicate that dual therapy covers the highest percentage of variance in the change of the HbA1c level (some 45 percent), followed by the diet (30 percent), and physical activity (17 percent). The two-directional interactions also suggest that the effectiveness of treatment is partially dependent on the diet and the activity but not on the three-way interaction. These results indicate that the power of the factorial experiment model is very high ($R2 \approx 0.95$) and, as a result, the results presented by them are more reliable.
7. The test presented by Tukey affirmed that there were evident significant differences in the levels of each factor, with the optimal results recorded by the use of dual therapy, low-carbohydrate diet, and regular activity, respectively. This suggests that all three factors have an independent effect on the lowering of HbA1c and that an integration of the factors will result in a significant enhancement of the blood sugar control.
8. The results of these clinical determinations point to the necessity of a specific approach to therapy, in which the therapeutic choice of drugs, diet, and exercise should be selected depending on the lifestyle of the patient and his or her adherence potential.
9. Such a comprehensive strategy can enhance the glycemic results in the long term, decrease the risk of diabetic complications, and improve the quality of life in general.

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