International Journal on Science and Technology (IJSAT)
E-ISSN: 2229-7677 ● Website: www.ijsat.org ● Email: editor@ijsat.org

Genetic Predictors of Response to Medical Nutrition Therapy in Type 2 Diabetes: A Focus on TCF7L2 and Nutrigenetic Interactions

Sara F. Alrashed[1], Rana S. Alzahrani[2], Sara H. Alamri[3], Ayidh M. Alqarni[4], Mohammed A. Alyahya[5]

Abstract:
Background: Single nucleotide polymorphisms in the TCF7L2 gene have been linked to variations in β-cell function and peripheral insulin sensitivity, raising the possibility that such genetic variability may moderate the effect of medical nutrition therapy (MNT) in patients with Type 2 Diabetes Mellitus (T2DM).
Objective: This study aimed to evaluate the association between TCF7L2 genetic polymorphisms and the glycemic response to a standardized MNT regimen in adults with T2DM within a tertiary-care context in Riyadh.
Methods: We conducted a prospective cohort study enrolling 112 adults with T2DM. Participants were genotyped for the TCF7L2 rs7903146 polymorphism and classified into wild-type, heterozygous, and homozygous at-risk genotypic categories. All patients received a custom, carbohydrate-moderate MNT intervention for 6 months. Changes in glycemic and metabolic endpoints were analyzed across genotype strata.
Results: All genotype groups experienced significant reductions in HbA1c and fasting plasma glucose; however, the magnitude of decline was significantly larger in the wild-type group compared to at-risk carriers ($p < 0.001$ for both endpoints). Multivariable regression confirmed genotype as an independent predictor of the magnitude of glycemic change after adjusting for baseline values and relevant covariates.
Conclusion: The presence of the TCF7L2 risk allele modulates glycemic improvement following MNT in T2DM, suggesting that nutrigenetic assessment could be a valuable component of personalized dietary strategies in clinical diabetes management.

Keywords: Type 2 Diabetes Mellitus, TCF7L2, Nutrigenetics, Medical Nutrition Therapy, Personalized Nutrition, Gene–Diet Interaction.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) continues to rank among the foremost global causes of morbidity, mortality, and strain on health-care systems, a trend particularly pronounced in countries, including Saudi Arabia, undergoing rapid urbanization and dietary transition. While lifestyle modification and dietary therapy constitute fundamental components of glycemic management, individual responses to medical nutrition therapy (MNT) exhibit considerable heterogeneity. Recent findings indicate that this phenotypic variability may, in part, be attributable to genetic determinants, specifically single nucleotide polymorphisms (SNPs) that modulate insulin sensitivity, appetite control, and nutrient handling (Tanisawa & Higuchi, 2019).

Notably, polymorphisms at the Transcription Factor 7-Like 2 (TCF7L2) locus, with rs7903146 and rs12255372 serving as the most thoroughly investigated, demonstrate a robust link to heightened T2DM susceptibility and differential metabolic adaptation to high-carbohydrate regimens (Corella et al., 2016). These SNPs exert modulatory effects on insulin secretion and β-cell responsiveness, while concurrently influencing the efficacy of dietary interventions, thereby establishing TCF7L2 as a prominent candidate for

the implementation of nutrigenetic stratification in the therapeutic management of diabetes (Berná et al., 2014).

Nutrigenetics, which operates under the broader umbrella of nutrigenomics, strives to tailor nutritional interventions according to the genomic blueprint of the individual. By aligning nutrient distributions with inherited susceptibilities, this approach is poised to refine therapeutic efficacy in type 2 diabetes mellitus (T2DM). Investigations of gene–diet interplay have highlighted that heterozygous and homozygous carriers of the TCF7L2 susceptibility alleles exhibit differential metabolic outcomes contingent upon carbohydrate load, thereby indicating a possible locus-specific moderation of macronutrient effects (Vesnina et al., 2020). Nonetheless, the prevailing literature is predominantly derived from homogeneous cohorts, and gene–diet linkage data from the Middle Eastern demographic, notably Saudi Arabia, is still limited.

Within the Saudi context—characterised by one of the highest national T2DM burdens globally—embedding hereditary predisposition data into dietary management protocols could elevate precision and long-term adherence. An ethnically stratified dissertation conducted in the Kingdom reaffirmed the role of TCF7L2 allelic variation, alongside several cardiometabolic loci, in shaping individual adaptive responses to lifestyle modification (Alsulami, 2021). Such outcomes reinforce the imperative to translate genomic knowledge into culturally relevant medical nutrition therapy (MNT).

This investigative work is designed to delineate how polymorphic variation at the TCF7L2 locus drives heterogeneity in clinical response to MNT in Saudi adults with established T2DM. By appraising the extant literature and prospectively delineating pragmatic clinical pathways, the study will lay the groundwork for embedding genotype-informed dietary guidance into the routine management of diabetes in Middle Eastern populations.

LITERATURE REVIEW

Nutrigenetics—how variation in DNA sequences modulates the effects of diet—has emerged as a promising tool for tailoring interventions in chronic conditions, most notably Type 2 Diabetes Mellitus (T2DM). By integrating genomic information, clinicians aim to refine dietary prescriptions according to allelic variants that may dictate metabolic pathways for macro-nutrient oxidation, energy expenditure, and food-derived bioactive compounds. A focal locus in the current literature is Transcription Factor 7-Like 2 (TCF7L2), whose polymorphisms consistently correlate with T2DM incidence and progression in heterogeneous ethnic cohorts (Berná et al., 2014).

Situated within the Wnt signaling cascade, TCF7L2 modulates β-cell maturation, insulin release kinetics, and hepatic glucose production. Among its variants, the rs7903146 single-nucleotide polymorphism embodies the most robust genetic predictor of T2DM. Notably, carriers of the risk allele demonstrate divergent glycemic responses to variations in carbohydrate density and soluble fiber content, a differential that may, in future personalized protocols, guide optimization of macronutrient ratios during dietary counseling (Corella et al., 2016).

Gene–diet interaction studies are beginning to clarify the mechanistic role of TCF7L2 variants in modulating the response to medical nutrition therapy. Within the extensive PREDIMED trial, a significant interaction was observed whereby carriers of the TCF7L2 risk alleles derived a diminished benefit from the Mediterranean diet, particularly when contrasted with the standard high-fiber, low-fat regimen, relative to non-carriers Corella et al., 2016. This observation reinforces the imperative that clinical dietary interventions integrate genetic predisposition to enhance therapeutic outcomes.

The clinical relevance of TCF7L2 polymorphisms has been further interrogated within frameworks aimed at personalizing nutritional prescriptions. Vesnina et al. (2020) incorporated TCF7L2 and PPARG variants into

a multivariable nutritional algorithm, demonstrating that genetic-guided meal structuring yielded superior glycemic and lipid control compared to a uniform dietary regimen. Their findings lend support to the integration of nutrigenetic diagnostics as a strategic adjunct for tailoring macronutrient ratios in T2DM management.

The proactive application of nutrigenetic principles to aging populations is gaining traction. An integrative review that focused on geriatric patients with T2DM underscored that TCF7L2 risk alleles are predictive not only of earlier disease emergence but also of attenuated therapeutic response to dietary modification in later life Nicholas-Okpara et al.. Collectively, these data underscore the necessity for dietary protocols that are calibrated across the lifespan, particularly in the context of diabetes management.

In Saudi Arabia, Alsulami (2021) examined how lifestyle factors and genetic variants, notably TCF7L2, jointly affect cardiometabolic traits across a heterogeneous population. This doctoral work emphasized an emerging awareness of gene–environment interplay within the Arabian Peninsula and articulated the feasibility of embedding genotype-informed dietary interventions into the nation's public diabetes management protocols (Alsulami, 2021).

Collectively, existing studies affirm a significant link between TCF7L2 genetic variations and differential responsiveness to dietary interventions. Nonetheless, focused investigations within Arab and other under-sampled groups remain essential to translate these associations into actionable, population-specific frameworks for personalized dietary management of type 2 diabetes mellitus.

METHODOLOGY

Study Design and Setting

This investigation utilized a prospective cohort methodological framework and spanned 12 months, a principal academic referral institution located in Riyadh, Saudi Arabia. Approval was granted by the hospital's Institutional Review Board, and written informed consent was obtained from each participant prior to enrollment.

Participants

The study cohort comprised 120 adult individuals, aged 30 to 65 years, with a substantiated diagnosis of Type 2 Diabetes Mellitus (T2DM). Subjects were recruited from the hospital's outpatient endocrinology and clinical nutrition clinics. Inclusion criteria mandated stability in glycemic pharmacotherapy for no fewer than 3 months, an HbA1c concentration between 7.0% and 9.5%, and no recent modifications in dietary management. Participants were excluded if they had type 1 diabetes mellitus, ongoing malignancy, advanced chronic kidney disease, were pregnant, or were involved in concurrent dietary intervention trials.

Genotyping

Peripheral blood was obtained in EDTA tubes and processed in the hospital's genetics laboratory. Genomic DNA was isolated using the QIAamp DNA Blood Mini Kit. Genotyping of two TCF7L2 single-nucleotide polymorphisms, rs7903146 (C>T) and rs12255372 (G>T), was accomplished by real-time polymerase chain reaction using TaqMan assays. The obtained genotype distributions were validated to conform to Hardy-Weinberg equilibrium.

Participants were divided into three genetic strata:

- Homozygous wild-type genotype
- Heterozygous genotype
- Homozygous risk allele genotype

Nutritional Intervention

All subjects engaged in tailored medical nutrition therapy delivered by a registered dietitian nutritionist. Dietary prescriptions adhered to American Diabetes Association standards, with caloric and macronutrient distributions calibrated to individual weight status and specific metabolic endpoints.

The MNT paradigm was calorically neutral and prescribed a moderate carbohydrate composition of 40–45% of total energy. Adherence was tracked by 3-day dietary recalls and biweekly motivational interviewing sessions. Modifications to pharmacologic treatment were disallowed, barring urgent medical necessity; such instances prompted participant exclusion from subsequent analysis.

Outcome Measures

Primary Outcome:

• Absolute change in glycated hemoglobin (HbA1c) in percentage from enrollment to 6 months

Secondary Outcomes:

• Alterations in fasting plasma glucose, insulin concentration, and HOMA insulin resistance index
• Body weight and body mass index (BMI)
• Compliance with prescribed dietary regimen (derived from food diaries)
• Patient-reported satisfaction and intervention acceptability (assessed through a structured questionnaire)
• Feasibility of implementation (evaluated by questionnaire)

Data Analysis

Data were analyzed with SPSS version 26.0. Descriptive statistics for continuous measures are presented as mean ± standard deviation. Comparisons of baseline to 6-month outcomes employed paired t-tests or repeated-measures analysis of variance as appropriate; categorical distributions were examined with chi-square tests. Multiple linear regression models addressed interactions between TCF7L2 genotype and changes in glycemic indices. A two-tailed significance threshold was set at $p < 0.05$.

RESULTS

Participant Characteristics

Of the 120 participants who were enrolled, 112 fulfilled the protocol to completion. The analysis ultimately comprised 40 homozygous wild-type (WT), 46 heterozygous (HT), and 26 homozygous at-risk allele carriers (RA) of the TCF7L2 rs7903146 single-nucleotide variant. Baseline characteristics were statistically similar among the three genotype strata.

Table 1. Baseline Characteristics by TCF7L2 Genotype

Characteristic	WT (n=40)	HT (n=46)	RA (n=26)	*p*-value
Age (years)	52.1 ± 8.4	50.9 ± 7.7	51.4 ± 9.1	0.72
Gender (M/F)	18 / 22	22 / 24	13 / 13	0.88
BMI (kg/m²)	30.6 ± 3.8	31.1 ± 4.1	30.9 ± 3.5	0.64
HbA1c (%)	8.2 ± 0.5	8.1 ± 0.6	8.2 ± 0.4	0.90
Fasting glucose (mg/dL)	166.5 ± 12.3	169.2 ± 13.7	167.8 ± 11.9	0.81

There were **no significant baseline differences** in age, sex, BMI, or glycemic parameters among genotype groups.

Glycemic Response to Medical Nutrition Therapy

After 6 months of standardized MNT:

- All groups showed significant reductions in **HbA1c and fasting glucose**, but the **magnitude of improvement varied by genotype**.
- The **wild-type group had the greatest improvement**, followed by heterozygotes.
- Risk allele carriers showed **attenuated glycemic response**.

Table 2. Glycemic Outcomes After 6 Months of MNT

Outcome	WT (n=40)	HT (n=46)	RA (n=26)	*p*-value (ANOVA)
Δ HbA1c (%)	–1.2 ± 0.4	–0.9 ± 0.3	–0.6 ± 0.3	**<0.001**

Outcome	WT (n=40)	HT (n=46)	RA (n=26)	*p*-value (ANOVA)
Δ Fasting glucose (mg/dL)	–28.5 ± 9.8	–21.1 ± 10.2	–14.3 ± 11.0	**<0.001**
Δ HOMA-IR	–1.9 ± 0.6	–1.5 ± 0.5	–1.0 ± 0.4	0.003

Risk allele carriers demonstrated **significantly lower reductions** in HbA1c and insulin resistance indices compared to WT and HT groups.

Adherence and Weight Loss

- Dietary adherence was high (>80%) across all groups.
- All groups experienced modest but significant weight loss, with **no statistical difference** between genotypes.

Table 3. Secondary Outcomes

Outcome	WT	HT	RA	*p*-value
Δ Body weight (kg)	–2.4 ± 0.9	–2.2 ± 1.0	–2.0 ± 0.8	0.28
Dietary adherence (%)	88.2 ± 6.1	87.4 ± 5.7	85.9 ± 6.9	0.45
Satisfaction score (1–10)	8.7 ± 1.2	8.4 ± 1.3	8.2 ± 1.1	0.41

REGRESSION ANALYSIS

A multiple linear regression adjusting for age, sex, BMI, and baseline HbA1c showed that **TCF7L2 genotype was an independent predictor of glycemic response** to MNT ($\beta = 0.41$, $p < 0.001$).

DISCUSSION

This investigation assessed how TCF7L2 genetic variants modulate glycemic outcomes following medical nutrition therapy (MNT) in adults with Type 2 Diabetes Mellitus (T2DM) attending a tertiary hospital in Riyadh. Our data reveal that the common rs7903146 single-nucleotide polymorphism at the TCF7L2 locus markedly altered the effectiveness of prescribed dietary regimens.

Subjects who carried the T risk allele attained smaller reductions in both HbA1c and fasting plasma glucose than non-carriers, despite comparable dietary adherence and degree of weight loss. These observations support existing evidence that TCF7L2 polymorphisms disrupt pancreatic β-cell response and insulin secretion, consequently attenuating the dietary-induced glycemic improvements achievable with carbohydrate-moderated regimens (Corella et al., 2016; Berná et al., 2014).

The impaired glycemic response in T risk allele carriers resonates with extensive gene–diet interaction analyses, including the PREDIMED investigation, which documented reduced Mediterranean diet-induced benefits among individuals possessing the TCF7L2 risk allele (Corella et al., 2016). These consistent data imply that individualized genetic profiling may enhance the efficacy of MNT, especially in cohorts like ours where the frequency of TCF7L2 risk variants is elevated.

Notably, every subject achieved a small degree of body-weight reduction and rated their adherence to the dietary protocol as high, independent of genotype. This uniformity in body composition and self-reported compliance, paired with contrasting metabolic phenotypes, suggests that genetic determinants, rather than behavioural ones, are primarily responsible for differential physiological adaptation. Such results bolster the hypothesis that allelic variation, while inert to adherence dynamics, can selectively influence metabolic endpoints (Vesnina et al. 2020).

The present analysis also fills an important gap in the regional literature. In a previous thesis, Alsulami (2021) documented that cardiometabolic risk in Saudi cohorts is jointly shaped by genetic predispositions and

lifestyle exposures. Our work builds upon that foundation by demonstrating that, even within genetically and culturally distinct Saudi subgroups, forward-looking genetic screening can serve as a partial predictor of individual clinical response to normatively designed nutritional intervention.

STRENGTHS AND LIMITATIONS

The principal strength of this investigation arises from its execution within a community-based clinical environment and the collaborative involvement of multidisciplinary fields, including clinical nutrition, genomics, and pharmaceutical sciences. The prospective design, combined with objective monitoring of adherence via electronic diaries and biochemical indicators, fortified the veracity of the outcome measures. Notwithstanding, a number of limitations merit consideration. Primarily, the examination concentrated exclusively on a single polymorphism within the TCF7L2 locus, while the aetiology of type 2 diabetes mellitus manifests as a polygenic, multifactorial disorder. Although the number of enrolled participants was sufficient to identify genotype-driven variances in clinical endpoints, the sample may remain underpowered for detecting more intricate gene–gene and gene–environment interactions that could further delineate heterogeneity in metabolic phenotypes. Additionally, the absence of postprandial glucometabolic and incretin secretory profiles constrains the resolution of the specific physiological pathways that the observed dietary responses may engage.

IMPLICATIONS FOR PRACTICE

The results advocate for the integration of genetic interrogation within the framework of medical nutrition therapy for type 2 diabetes mellitus. In the context of the ongoing shift toward precision-oriented healthcare, genotype-driven counselling may yield more favourable glycaemic trajectories and sustain dietary adherence over extended periods. For healthcare infrastructures within the Gulf Cooperation Council, where the burden of diabetes is among the highest globally, the adoption of such tailored interventions promises to attenuate population-level morbidity and to optimise longitudinal clinical outcomes.

CONCLUSION

The present investigation establishes that variation within the TCF7L2 locus modulates the glycemic response to medical nutrition therapy in adults with Type 2 Diabetes. Although adherence to prescribed regimens and magnitude of weight loss did not differ among genotype strata, carriers of the risk alleles manifested smaller reductions in HbA1c and diminished enhancement of insulin sensitivity. These results endorse the incorporation of nutrigenetic testing into standard dietary prescription workflows, thereby facilitating the translation of genomic insights into tailored clinical interventions. Such an approach is of particular relevance in high-prevalence settings, including the Kingdom of Saudi Arabia, where optimizing resource allocation and clinical outcomes is imperative.

REFERENCES:

1. Alsulami, S. (2021). *A nutrigenetic approach to investigate the effect of genetic and lifestyle factors on cardiometabolic-disease related traits in ethnically diverse populations* [Doctoral dissertation, University of Reading]. CentAUR. https://centaur.reading.ac.uk/105704/
2. Berná, G., Oliveras-López, M. J., Jurado-Ruíz, E., & Tejedo, J. (2014). Nutrigenetics and nutrigenomics insights into diabetes etiopathogenesis. *Nutrients, 6*(11), 5338–5369. https://www.mdpi.com/2072-6643/6/11/5338/pdf
3. Corella, D., Coltell, O., Sorli, J. V., Estruch, R., & Quiles, L. (2016). *TCF7L2* interacts with obesity on type-2 diabetes in the PREDIMED study emphasizing the heterogeneity of genetic variants in type-2 diabetes risk prediction. *Nutrients, 8*(12), 793. https://www.mdpi.com/2072-6643/8/12/793
4. Nicholas-Okpara, V. A., Utazi, I. A., Ezeanyanaso, C. S., & Ita, B. (n.d.). Current trend of nutrigenomics of geriatric type 2 diabetes. *ResearchGate*. https://www.researchgate.net/publication/354851689_Current_Trend_of_Nutrigenomics_of_Geriatric_Type_2_Diabetes

5. Tanisawa, K., & Higuchi, M. (2019). Nutrigenomics and personalized nutrition for the prevention of hyperglycemia and type 2 diabetes mellitus. In F. De Meester, R. R. Watson, & V. R. Preedy (Eds.), *Handbook of nutrition, diet, and epigenetics* (pp. 1–14). Academic Press. https://www.sciencedirect.com/science/article/pii/B9780128498866000094
6. Vesnina, A., Prosekov, A., Kozlova, O., & Atuchin, V. (2020). Genes and eating preferences: Their roles in personalized nutrition. *Genes, 11*(4), 357. https://www.mdpi.com/2073-4425/11/4/357