Investigating the effect of ApoE gene variation on diabetes risk

Aakifa Abdullah[1], Ria Weston[2]

[1]The University of Manchester

[2]Centre for Bioscience, Department of Life Science, Manchester Metropolitan University, M1 5GD

Introduction

- Type 2 diabetes (T2D), a complex metabolic condition accounts for over 90% of diabetic cases. Vascular complications frequently arise, creating a significant burden on healthcare services which cost the NHS over £14 billion a year *(Kayyali et al., 2019)*. Despite increased knowledge of T2D risk factors, the prevalence continues to increase. Lipoprotein abnormalities are common in T2D patients, and recent studies have implicated certain ApoE gene isoforms with increased T2D risk. There are 3 key isoforms highlighted in figure 1.

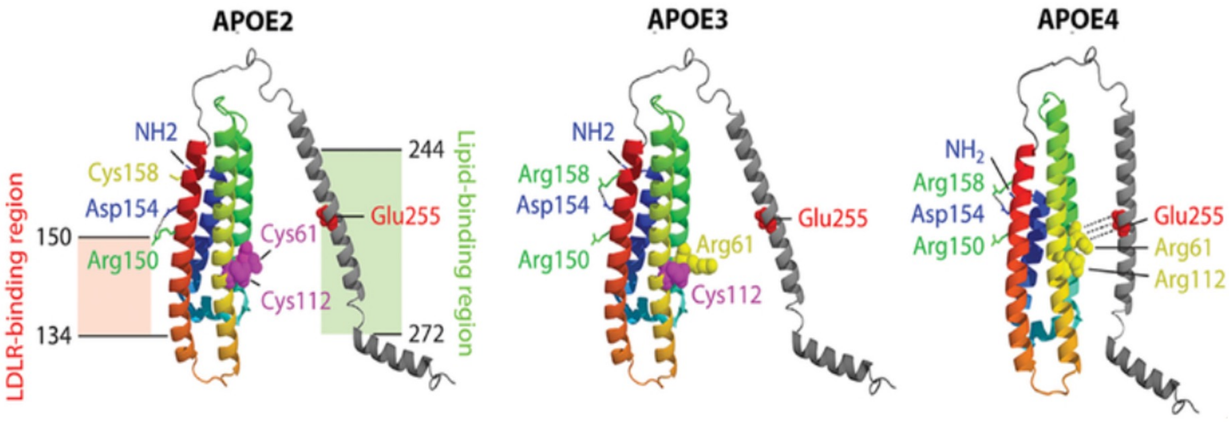


Figure 1. Structural models of the three key polymorphisms of the *APOE* gene with *ApoE2*, *ApoE3* and *ApoE4* isoforms encoded by alleles ε2, ε3, ε4 respectively. Two structural domains are present within *APOE* gene, N-terminal domain which consists of LDLR-binding region and C-terminal domain containing the lipid-binding region attached by a hinge region. *(Belloy et al., 2019).*

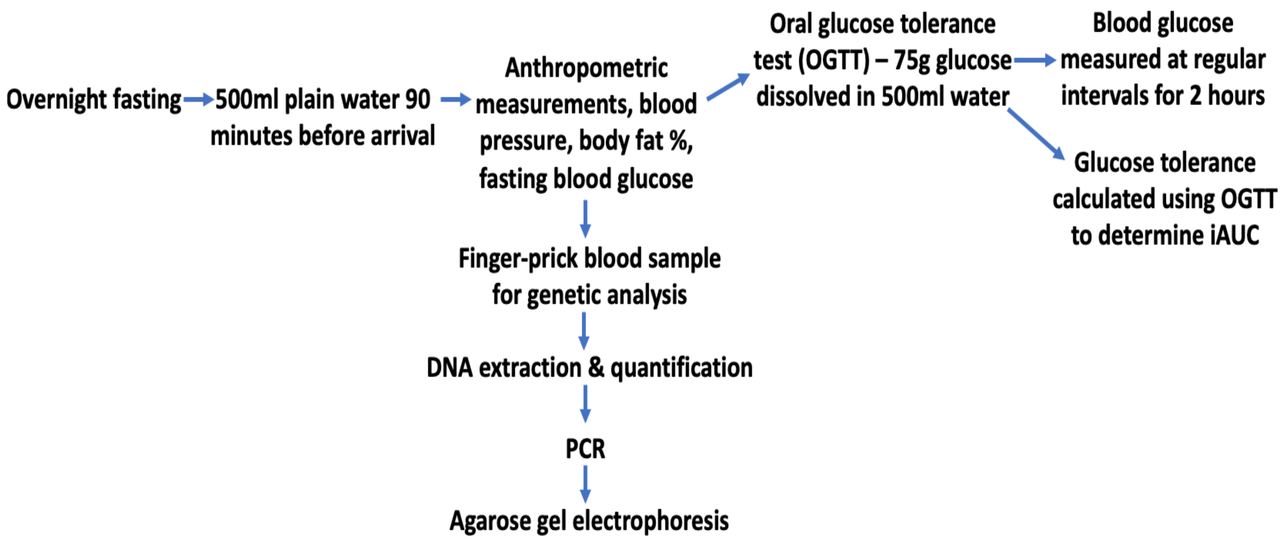
- Around 75% of patients with diabetes present with dyslipidaemia *(Athyros et al., 2018)*. ApoE variants are related to dyslipidaemia as different isoforms disturb triglyceride rich lipoproteins metabolic pathways with *ApoE4* and *ApoE2* having greater variation of lipoproteins in humans *(Tudorache et al., 2017)*. *ApoE4* increases LDL-C, increasing CVD risk whereas *ApoE2* decreases LDL-C levels *(Khalil et al., 2021)* which is important as high LDL-C levels are associated with higher risk of diabetes *(Janghorbani et al., 2018)*, constituting a probable association between *ApoE* isoforms and diabetes risk.

Aim

- To investigate the impact of ApoE isoforms on blood glucose response in a younger, healthy adult population who are less likely to have developed T2D.
- To determine if a specific ApoE allelic variation is prevalent in those at increased risk of developing T2D.

Methods

- 50 healthy individuals between the ages of 18-40 were recruited.



Results

Table 1. Baseline subject characteristics.

(*n* = 48)	
Gender (male/female)	19/29
Age (years)	21.0 (19.0 -26.0)
Height (cm)	171.14 ± 10.00
Weight (kg)	71.33 ± 17.15
BMI (kg/m^2)	24.21 ± 4.72
BP systolic (mmHg)	118.42 ± 13.10
BP diastolic (mmHg)	74.68 ± 8.09
Body fat (%)	29.94 ± 8.73
Hip (cm)	99.39 ± 10.34
Waist (cm)	79.92 ± 11.71
Waist:Hip ratio	0.80 ± 0.08
Baseline glucose concentration (mmol/L)	5.35 (2.60 – 6.20)

Table 2. ApoE genotype distribution.

Sample genotype	
ε2ε2	1
ε2ε3	5
ε3ε3	29
ε3ε4	10
ε4ε4	3

- *ApoE* ε3ε3 was the most common genotype in this study.
- A strong positive correlation was observed between BMI and glucose tolerance in genotypes ε2ε3 and ε4ε4, and between waist:hip ratio and glucose tolerance in genotype ε2ε3.

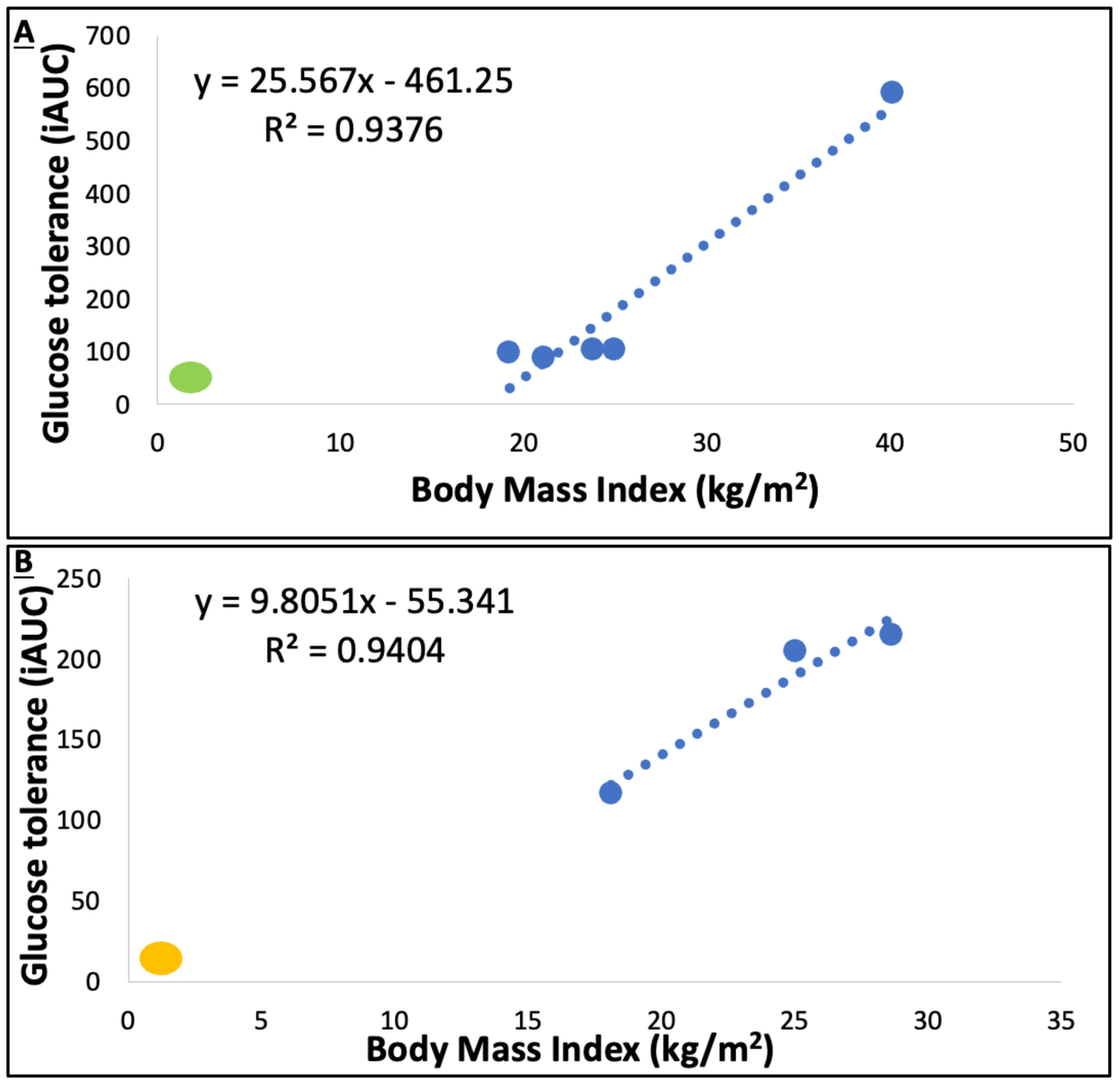


Figure 2. Relationship between BMI (kg/m^2) and glucose tolerance (iAUC) in ApoE genotypes, with R^2 value recorded. A: Genotype ε2ε3, B: Genotype ε4ε4.

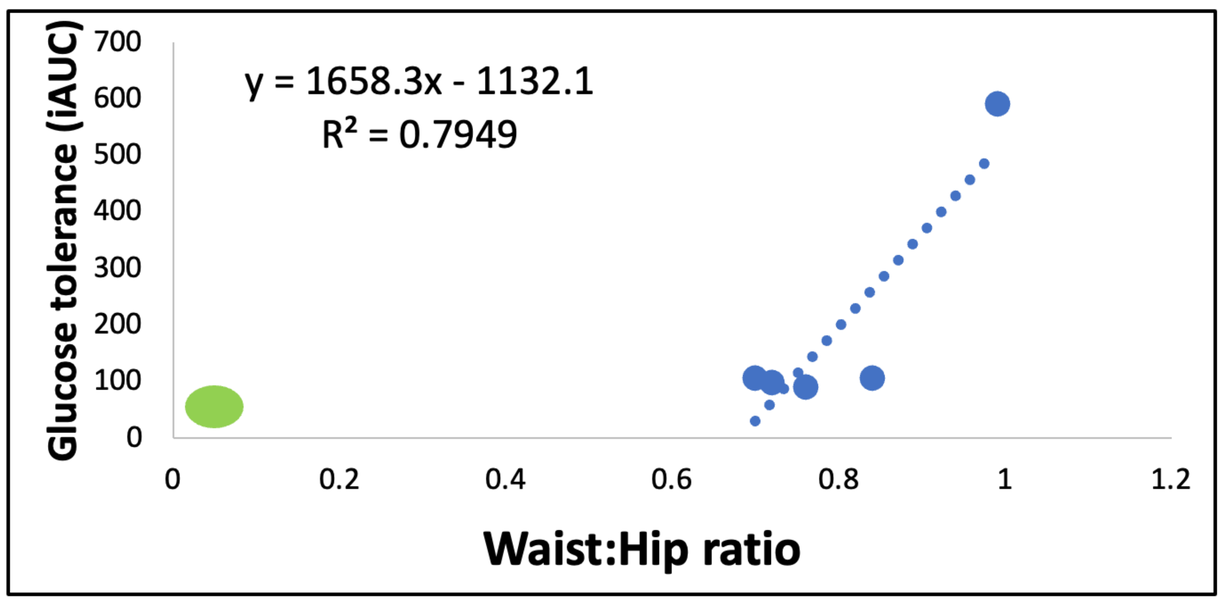


Figure 3. Relationship between Waist:Hip ratio and glucose tolerance (iAUC) in participants with ApoE ε2ε3 genotype, with R^2 value recorded.

Conclusion and future studies

- ApoE gene polymorphisms associate with BMI and glucose tolerance, specifically *ApoE* ε 4 ε 4 genotype. As obesity is a prominent risk factor for T2D, a higher BMI in those with an at-risk genotype could increase the risk of T2D, but these findings request validation in a greater representative population.
- Additional research is required to further understand the links between ApoE isoforms, particularly ε4 and ε2, and T2D risk. Early screening of high-risk individuals and educating high-risk genotype carriers on the importance of blood glucose supervision could allow lifestyle interventions to prevent the development of T2D, thus reducing the economic burden on the NHS, as well as improving individuals' quality of life.

References and Acknowledgements

- Athyros, V. G., Doumas, M., Imprialos, K. P., Stavropoulos, K., Georgianou, E., Katsimardou, A. and Karagiannis, A. (2018) 'Diabetes and lipid metabolism.' *Hormones (Athens)*, 17(1), pp. 61-67.
- Belloy, M. E., Napolioni, V. and Greicius, M. D. (2019) 'A Quarter Century of APOE and Alzheimer's Disease: Progress to Date and the Path Forward.' *Neuron*, 101(5), pp. 820-838.
- Janghorbani, M., Soltanian, N., Amini, M. and Aminorroaya, A. (2018) 'Low-density lipoprotein cholesterol and risk of type 2 diabetes: The Isfahan diabetes prevention study.' *Diabetes Metab Syndr*, 12(5), pp. 715-719.
- Kayyali, R., Slater, N., Sahi, A., Mepani, D., Lalji, K. and Abdallah, A. (2019) 'Type 2 Diabetes: how informed are the general public? A cross-sectional study investigating disease awareness and barriers to communicating knowledge in high-risk populations in London.' *BMC Public Health*, 19(1), p. 138.
- Khalil, Y. A., Rabes, J. P., Boileau, C. and Varret, M. (2021) 'APOE gene variants in primary dyslipidemia.' *Atherosclerosis*, 328, pp. 11-22.
- Tudorache, I. F., Trusca, V. G. and Gafencu, A. V. (2017) 'Apolipoprotein E - A Multifunctional Protein with Implications in Various Pathologies as a Result of Its Structural Features.' *Comput Struct Biotechnol J*, 15, pp. 359-365.