Explore The Effect of SLC30A8 Gene on Lipid Profile and Anthropometric Parameters in T2DM Patients In AL-Najaf Population.

Huda Abd Alrazaq Muneam[1]*, Asst. Prof. Dr. Haider Farhan Salman Alzubaidy[2], Lecturer Dr. Roaa Hameed Alwaidh[3]
[1]*MSc, College of Pharmacy, University of Kufa, Najaf, Iraq
[2].PhD in Molecular Clinical Chemistry, Department of clinical laboratory science, Faculty of Pharmacy, Kufa University, Najaf, Iraq
[3].Lecturer Dr in Department of pathology and forensic medicine, Faculty of medicine, Kufa University, Najaf, Iraq
*Corresponding Author
Email: hudaa.alkhanani@student.uokufa.edu.iq
Email: hayderf.salman@uokufa.edu.iq
Email: roaah.alwaidh@uokufa.edu.iq

Abstract
Background: Diabetes mellitus is a collection of chronic endocrine disorders marked by persistent hyperglycemia caused by insulin production, insulin action, or both. The importance of insulin as an anabolic hormone leads to a metabolic deficit in carbs, lipids, and proteins. Various genome-wide association studies have identified several single nucleotide polymorphisms associated with type 2 Diabetes, as they were found to alter lipid metabolism, insulin secretion, glucose metabolism, and insulin receptor signaling, and the rs13266634 found in (the solute carrier family 30 member 8) SLC30A8 gene is one of the consistently reported risk factor single nucleotide polymorphism for type 2 Diabetes. Study Objective: Explore the effect of SLC30A8 gene on lipid profile and anthropometric parameters in T2DM patients in AL-Najaf populations. Methods: This case-control study enrolled 100 type 2 Diabetes mellitus patients and 100 controls who fulfilled the inclusion criteria. Blood samples were collected from all participants and were used for the rs13266634 single nucleotide polymorphism genotyping by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) technique. Outcomes: Two-hundred case-control studies with 100 cases and 100 controls were included for SLC30A8 and type 2 Diabetes mellitus. The comparison of results of parameters (triglyceride, total-cholesterol, very low density lipoprotein cholesterol, low density lipoprotein cholesterol, and body mass index) exhibited significant ($p<0.0001$) increases in the patient's group when compared with the group of controls. Yet, high density lipoprotein cholesterol levels exhibited significant elevated ($P= 0.0132$) in type 2 diabetes mellitus patients when compared with the controls group. Genotyping result of single nucleotide polymorphism (rs13266634 C/T) of Type 2 Diabetes mellitus as well as control persons under the co-dominant model showed that patients of heterozygous genotypes (CT) significantly elevated (OR = 2.56, 95% CI = 1.33 - 4.67, P = 0.0049) with respect to the control group. The dominant model indicated that patients of (CT+TT) genotypes increased significantly (OR=1.87, CI 95%=1.04 - 3.30, P=0.0434) with respect to the controls, and the single nucleotide polymorphism (rs13266634 C/T) of SLC30A8 not associated with of phenotypic parameter analysis. Conclusion: The rs13266634 is single nucleotide polymorphism significantly associated with type 2 Diabetes mellitus susceptibility among AL-Najaf Population and this gene not associated with lipid profile and anthropometric parameters. Recommends: A large sample size is required to investigate the correlation between rs13266634 SNP of SLC30A8 gene and occurrence of disease and further studies in the future should be done on different SNPs of SLC30A8 gene in AL_Najaf population. These studies can discover which SNPs are more common in this governorate that involved in the pathogenesis of T2DM.
Keywords: SLC30A8 gene, single nucleotide polymorphism, Type 2 diabetes mellitus, lipid profile, anthropometric parameters.

1. Introduction

Diabetes mellitus is a collection of chronic endocrine disorders marked by persistent hyperglycemia caused by insulin production, insulin action, or both. The importance of insulin as an anabolic hormone leads to a metabolic deficit in carbs, lipids, and proteins. These metabolic disorders are caused by low insulin levels and/or insulin resistance in target tissues, primarily skeletal muscles, adipose tissue, and to a lesser extent, liver, at the level of insulin receptors, signal transduction systems, and/or effector enzymes or gene (Kazi et al .,2019).

The major DM types are as follows

doi.org/10.31838/hiv23.03.19 Received: 18.10.22, Revised: 12.11.22, Accepted: 24.12.22

1.Type 1 diabetes mellitus (T1DM) is a chronic autoimmune illness defined by elevated blood glucose levels (hyperglycemia) caused by insulin insufficiency caused by the death of pancreatic islet cells (Katsarou et al. ,2017).

2. Type 2 diabetes (also known as non-insulin dependent diabetes) is defined by a dysregulation of carbohydrate, lipid, and protein metabolism, which can be caused by decreased insulin production, insulin resistance, or a combination of the two (Reed et al., 2021).

Various genome-wide association studies (GWAS) have identified several single nucleotide polymorphisms (SNPs) associated with T2DM (Imamura et al., 2021), as they were found to alter lipid metabolism, insulin secretion, glucose metabolism, and insulin receptor signaling, and the rs13266634 found in the SLC30A8 gene is one of the consistently reported risk factor SNP for T2DM.The SLC30A8 (solute carrier family 30 member 8) gene is found at 8q24.11 on the long (q) arm of human chromosome 8. The zinc transporter protein member-8 (ZnT-8) gene encodes a 369-amino-acid protein (Thirunavukkarasu et al., 2019).

Iraq is a multi-ethnic country with a population of 40,222,493 million people in 2021. The entire adult population is 19,914,400 million, including 1,505,000 million adults suffering from diabetes (Falih et al., 2021).

In type 2 diabetes, there is a strong inheritable genetic link; having type 2 DM relative particularly first degree relatives significantly increase the risk of acquiring type 2 DM (Virginia et al., 2022).

SLC30A8 (The zinc transporter protein member-8 (ZnT-8) gene encodes a 369-amino-acid protein. ZnT-8 regulates zinc homeostasis in pancreatic beta cell and is essential for the stability, storage, and release of insulin and other genes that have role on type 2 diabetes (Blumer et al. ,2022) . Obesity (an independent risk factor for type 2 diabetes) is also significantly inherited (Ligthart et al., 2021).

Pathophysiology of T2DM is the result of two metabolic disorders: insulin resistance (Stožer et al., 2022), b-dysfunction(Mao et al., 2022).

Gene report that the solute carrier family 30 member 8 (SLC30A8) gene located on the chromosome 8q24.11, contains 13 exons encoding 369 amino acids (Li et al., 2018) ,The total length of the SLC30A8 gene is 226,442 bases (Abu Seman et al. ,2015).

Approved symbol: SLC30A8 (www.ncbi.nlm.nih.gov.2022)

Approved name: solute carrier family 30 member 8 (www.ncbi.nlm.nih.gov.2022)

GENE type: protein coding (www.ncbi.nlm.nih.gov.2022)

HGNC ID: 20303(www.ncbi.nlm.nih.gov.2022)

Chromosomal location: 8q24.11 (www.ncbi.nlm.nih.gov.2022)

Gene ID: 169026 (www.ncbi.nlm.nih.gov.2022)

OMIM: 611145 (www.omim.org)

Organism: Homo sapiens (www.ncbi.nlm.nih.gov.2022)

Previous studies in Iranian population study founded that SNP of SLC30A8 gene associated with T2DM risk, genotypic frequency of SNPs variants was analyzed from the blood samples patients and non-diabetic individuals from the Iranian population. The genotypic frequencies of the homozygous (C/C), heterozygous(C/T), and homozygous (T/T) variants of the rs13266634 (T/C) significantly (P value<0.001). However, patients with C/T and C/C genotypes significantly indicated high risk of T2DM in comparison with T/T genotype. This study demonstrated that there is a significant correlation ($p<0.05$) between T2DM patients and control groups with certain clinical parameters, including BMI, LDL, HDL, TG, FBS and HbA1c (Yazdi et al., 2020).

Study objective: Explore the effect of SLC30A8 gene on lipid profile and anthropometric parameters in T2DM patients in AL-Najaf populations.

Hypothesis of the study: Explore the effect of SLC30A8 gene on lipid profile and anthropometric parameters in T2DM patients in AL-Najaf population.

2. Materials and Methods

Study design: A case-control study has been utilized on 200 participants. They were divided into two groups, type 2 diabetic patients (100) and a healthy individual group (100). The period of the study was from November 2020 till November 2022.The study was done in the Postgraduate Laboratory Department of Biochemistry/University of Kufa/Faculty of pharmacy.

Patients group: with 100 T2DM patients, the ages ranged from 20- 66 year with a M±SD of 49.41 ± 9.43 year. They were selected from the Diabetes Center in Teaching Hospital (AL-Sadder) in Al-Najaf Al-Ashraf, province. They have been observed and diagnosed by specialist physicians for the measures of inclusion.

Inclusion criteria: include, patients with T2DM and The level of fasting blood sugar was 7.0mmol/l (> 126 mg/dl) with diabetes manifestation of (nocturia, polyuria, weight decrease and polyphagia).

Exclusion criteria: include, Patients with T1DM, T2DM on antihyperlipidemic therapy, patients have other diseases as cardiovascular diseases, kidney dysfunction patient, cancer patients, hypertension patients and glucocorticoid dependency, also patient with thyroids and patients take insulin therapy.

Control group of 100 volunteers include the ages ranged from 22-67 year with a M±SD of 46.5 ± 11.67 year. They were relatives, friends, and medical staff. Any participant who had a disease, for instance DM, hypertension, heart disease, cardiovascular disease, renal disease, or other persons suspected to have any diseases had been excluded from the current study.

The Ethical Committee Approval: Approval

from the Ethical Committee (in the Faculty of Pharmacy /Kufa University) was taken for the protocol of the study.

Samples collection: after an overnight fast, each participant had a blood sample of five milliliters collected via a peripheral vein puncture. Two components of the blood sample were separated. Part one involved placing 3ml of blood in a plain tube and allowing it to coagulate for around 15 minutes at 37°C before centrifuging it for 10-15 minutes at 2000 xg. The collected sera were separated and stored at -20°C for phenotypic parameter assessment. That include lipid profile. Part two was a tube containing two milliliters of blood mixed with EDTA for gene analysis.

Genotype measurements: DNA is extracted from blood using a DNA purification kit (Add bio). SLC30A8 polymorphisms (rs13266634) were genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), then cheeked on an agarose gel using electrophoresis linked to the PCR product. In addition, each SNP's amplification technique was carried out using appropriate primers and master mixture. Furthermore, restriction enzyme types (Promega kit) were used to digest the PCR results, and the digested products were extracted on a 2 percent agarose gel.

Statistical analysis: The student t-test was used to examine the differences in means (mean ± SD) between the healthy individuals and patients group, using (SPSS.v.25.0 software) SPSS Inc. Chicago, IL, the mean levels of each characteristic via genotype were compared using the Student t-test and ANOVA. The chi-square test was also used to examine categorical data (alleles and genotypes). A significance level of less than 0.05 was used in all statistical analyses. Multinominal logistic regression analysis for verifications of genotype and frequencies of allele impact on T2DM via several inheritance models, such as a recessive, co-dominant, dominant, and additive model, as well as the Allelic model, SPSS.v.25.0 software was used. The results were expressed as a P-value, an odds ratio (OR), and a confidence interval (CI 95%).

3. Study results

Table 1: phenotype parameters values of T2DM and control groups.

Parameters	T2DM group (N=100)	control group (N=100)	P value
NO (M/F)	(60/40)	(42/58)	
Age (years), Mean ± SD	49.41 ± 9.43	46.5 ± 11.67	0.06
BMI (kg/m2), Mean ± SD	30.63 ± 5.678	25.13 ± 4.115	<0.0001****
TG (mg/dl), Mean ± SD	152.7 ± 57.93	121 ± 50.41	<0.0001****
TC (mg/dl), Mean ± SD	169.7 ± 34.86	144.7 ± 26.86	<0.0001****
VLDL-C (mg/dl), Mean ± SD	31.39 ± 12.38	24.01 ± 10.37	<0.0001****
LDL-C (mg/dl), Mean ± SD	104.4 ± 33.82	84.78 ± 24.88	<0.0001****
HDL-C (mg/dl), Mean ± SD	39.38 ± 9.377	36.14 ± 8.819	0.0132*
Note: * = mean that a significant result.			

Table (1) shows that the normally distributed data like (age, TG, TC, VLDL-C, LDL-C, BMI and HDL-C) tested with unpaired t- test and explained with mean ± SD. The comparison of results of ages values in the patients group versus the controls group revealed insignificant variations according to the P value (0.06). Other parameters were found to change in T2DM patients when compared with healthy individuals. Levels of TG, TC, VLDL-C, LDL-C, and BMI exhibited significant ($p<0.0001$) increases in the patient's group when compared with the group of controls. Yet, HDL-C levels exhibited significant elevated (P= 0.0132) in T2DM patients when compared with the controls group.

Table (2): DNA Purity and Concentration

	Mean±SD
DNA purity	1.98 ± 0.31
DNA concentration (µg/ml)	92.34 ± 48.75

Table (2) shows that the A260/A280 ratio was calculated to measure DNA purity and concentration. Displays the purity and concentration of the extracted DNA samples.

Table (3): Genotype and allele frequency results of SNP rs13266634 C/T SLC30A8 gene in T2DM and control subjects.

rs13266634 C/T	Patient group (N= 100)		control group (N= 100)		OR(CI%)	P value
	NO.	%	NO.	%		
Genotyping						
Codominant						
CC	50	42.74	67	57.26	Reference group	
CT	42	65.63	22	34.38	2.56(1.33 - 4.67)	0.0049**
TT	8	42.11	11	57.89	0.97(0.36 - 2.65)	>0.99
Dominant						
CC	50	43.70	67	56.30	Reference group	
CT+TT	50	59.26	33	40.74	1.87(1.04 - 3.30)	0.0434*
Recessive						
CC+CT	92	50.83	89	49.17	Reference group	
TT	8	42.11	11	57.89	0.70(0.27 - 1.82)	0.63
Frequency						
C	142	47.65	156	52.35	Reference group	
T	58	56.86	44	43.14	1.44(0.92 - 2.27)	0.13
Total	200		200		400	

Table (3) shows that The results of SNP (rs13266634 C/T) of T2DM as well as control persons with numerous inheritance models are shown in table 3.4. The codominant model showed that patients of heterozygous genotypes (CT) significantly elevated (OR = 2.56, 95% CI = 1.33 - 4.67, P = 0.0049) with respect to the control group. Patients with the homozygous genotype (TT) insignificantly decreased (OR=0.97, CI 95%= 0.36 - 2.65, P=0.99) relative to the control group. The dominant model indicated that patients of (CT+TT) genotypes increased significantly (OR=1.87, CI 95%=1.04 - 3.30, P=0.0434) with respect to the controls. Recessive model showed that patients of TT genotypes insignificantly declined (OR =0.70, 95% CI = 0.27 - 1.82, P =0.63) with respect to the controls groups. Frequency of (T) in patient group insignificantly increased (OR= 1.44, CI 95%= 0.92 - 2.27, P=0.13) with respect to the controls group.

Table (4): Results of phenotypic parameters of diabetic patients analyzed in relevance to the rs13266634 C/T under the co-dominant model.

Parameters	CC(N=50) Mean ± SD	CT(N=42) Mean ± SD	TT(N=8) Mean ± SD	P value
BMI (kg/m2)	30.05 ± 5.69	31.24 ± 5.78	31.47 ± 4.69	0.57
TG (mg/dl)	160.6 ± 70.7	159.4 ± 53.23	151 ± 52.83	0.96
TC (mg/dl)	173.8 ± 44.14	176.4 ± 43.36	166.3 ± 10.53	0.88
VLDL-C (mg/dl)	32.06 ± 14.14	31.83 ± 10.65	25.55 ± 14.21	0.61
LDL-C (mg/dl)	102.8 ± 34.2	106.4 ± 35.07	103.2 ± 11.65	0.87
HDL-C (mg/dl)	40.61 ± 9.78	38.59 ± 8.68	37.6 ± 6.26	0.51

Table (4) shows that Analysis for BMI, VLDL-C, TG, TC, VLDL-C, LDL-C, HDL-C values was conducted by the ANOVA test in relation to genotypes of the studied SNP rs13266634 C/T of SlC30A8 gene. For the SNP rs13266634 C/T genotypes, the co-dominant model revealed insignificant relationship for phenotypic parameter analysis, means did not show significant modifications in relevance to the rs13266634 C/T under the dominant model

Table (5): Results of phenotypic parameters of diabetic patients analyze

Parameters	CC(N=50) Mean ± SD	CT + TT(N=50) Mean ± SD	P value
BMI (kg/m2)	30.05 ± 5.69	31.26 ± 5.65	0.29
TG (mg/dl)	160.6 ± 70.70	167.7 ± 74.79	0.62
TC (mg/dl)	173.8 ± 44.14	175.5 ± 41.66	0.84
VLDL-C (mg/dl)	32.06 ± 14.14	33.44 ± 15.04	0.64
LDL-C (mg/dl)	102.8 ± 34.20	106.2 ± 33.69	0.62
HDL-C (mg/dl)	40.61 ± 9.783	38.51 ± 8.46	0.25

Table (5): shows that under the dominant pattern, BMI, TG, TC, VLDL-C, LDL-C, and HDL-C showed insignificant alterations relevant to the variant allele.

4. Discussion

Nowadays, diabetes mellitus is a disorder with multiple genetic and environmental contributing elements. The complicated illness known as type 2 diabetes mellitus (T2DM) is brought on by the combination of genetic and environmental variables. Studying the origins and effects of T2DM in humans has primarily been done to lessen its impact on the health care system because it is expensive, time-consuming, and detrimental to community vitality.

The SLC30A8 gene was identified as one of the risky T2DM genes, and as a result, its effects on T2DM risk (Du et al., 2018). However, the results are still underestimate. The potential importance of defective zinc signaling in T2DM has recently increased our understanding of the condition.

In this work, anthropometric and biochemical feature assessment are tested for their comparisons between patients with T2DM group and controls group, in a case-control approach conducted according to previous studies. The result of BMI of patients significant elevated than healthy individuals that mean strong association between obesity and worse glycemic control, so excess body weight has a well-established link with decreased insulin sensitivity, elevated insulin resistance, which in turn is a correlate of risk type 2 diabetes (T2D) and other disease like cardiovascular. Also general obesity has been measured using BMI (kg/m2). Reduced glucose tolerance, modifications to the glucose-insulin balance, lower metabolic clearance of insulin, and impaired insulin-stimulated glucose disposal have all been associated with central obesity. In fact, the primary mechanism triggering the activation of pro-inflammatory pathways known to impair insulin signaling and result in insulin resistance is obesity-induced adipose tissue inflammation. However, activation of inflammatory pathways in adipocytes reduces triglyceride storage and increases the release of free fatty acids (FFAs), too much of which is known to cause IR in the liver and muscles. The current findings are consistent with previous study (Boye et al., 2021; Reddy et al., 2015).Yet , elevated body weight escalates the pathogenesis of T2DM through stimulation of insulin resistance (Wondmkun., 2020).

The results of lipid profile in this research, which includes TG, TC, LDL and VLDL significantly excess in patients than controls group and The causes of

high fat in diabetic patients is unknown at first, but it is possible that one of the reasons is the lack of control of the disease, unhealthy food that contains fat, genetic factor and weight gain or increase of BMI, as well as the defect in metabolic process all these reasons may be explain the elevated of fat in T2DM patients and also the elevated of fat that accumulate in pancreas led to beta cell dysfunction. This result is consistent with a previous study showing the association of patients with type 2 diabetes with elevated fat and accumulate in the liver and pancreas (Bozzetto et al., 2011). Another study in Iranian population explain that elevated lipid profile was associated with onset of T2DM (Sadeghi et al., 2020).

The HDL_C parameter in this study significantly increase in patients with type 2 DM than controls because those patients under oral antidiabetic treatment that increase level of HDL_C like Pioglitazone , glibenclimide, liraglutide, dapagliflozin, acarbose, this study is consistent with a previous study (Rosenblit., 2016). Also, these patients were diagnosed long ago with this disease, so they underwent treatment and are not at the beginning of their diagnosis, which is why we notice an increase in HDL-C.

The analysis of the data of SNP rs13266634 C/T under the codominant demonstrated that patients of heterozygous genotypes CT significantly elevated than controls with odds ratios of more than 1. This finding suggests that CT allele is associated with diabetes risk and or/development of T2DM in the studied sample, i.e., AL_Najaf population. The current finding is consistent with past study (Du et al., 2018) which represented that heterozygous CT genotype were at higher risk of T2DM occurrence while the patients with the homozygous genotype TT under codominant demonstrated insignificantly decreased relative to the controls group with odds ratios of less than 1 and This indicates that there is no relationship between homozygous genotype TT and development/ or risk of T2DM and this consistent with previous study (Faghih et al., 2014) shows that there is no relationship with the development of T2DM with homozygous genotype TT.

5. Conclusions

1.The rs13266634 SNP of SLC30A8 gene is implicated in the pathogenesis of T2DM in AL_Najaf population.

2. According to the allele frequency the presence of heterogeneous CT genotype responsible to develop T2DM in AL_Najaf population.

3.There is no association between rs13266634 SNP of SLC30A8 gene and lipid profile and anthropometric parameters .

6. Recommendations

1. A large sample size is required to investigate the correlation between rs13266634 SNP of SLC30A8 gene and occurrence of disease.

2. Further studies in the future should be done on different SNPs of SLC30A8 gene in AL_Najaf population. These studies can discover which SNPs are more common in this governorate that involved in the pathogenesis of T2DM.

Limitation of the study: The presented work has some restrictions. In general, the individuals' family histories were not examined in relation to their genetics. Patients with diabetes may use medications that impact IR and insulin secretory function in addition to antihyperglycaemic drugs. The length of T2DM is not taken into account, however it could be an additional component that worsens the metabolic effects of prolonged hyperglycemia. Therefore, more large-scale study is important for validating the association between SLC30A8 polymorphism and T2DM in the AL-Najaf population as well as for illuminating the basic mechanism behind the impact of genetic polymorphism on metabolic imbalances and diabetes.

Funding: No funding was received for this study.

Conflicts of interest: Authors declare no conflict of interest.

7. Acknowledgement

The authors are grateful to all patients involved in the study.

References

Abu Seman, Norhashimah, Wan Nazaimoon Wan Mohamud, Claes Göran Östenson, Kerstin Brismar, and Harvest F. Gu. 2015. "Increased Dna Methylation of the Slc30a8 Gene Promoter Is Associated with Type 2 Diabetes in a Malay Population." Clinical Epigenetics 7 (1): 7–30. https://doi.org/10.1186/s13148-015-0049-5.

Blumer, Moritz, Tom Brown, Mariella Bontempo Freitas, Ana Luiza Destro, Juraci A. Oliveira, Ariadna E. Morales, Tilman Schell, et al. 2022. "Gene Losses in the Common Vampire Bat Illuminate Molecular Adaptations to Blood Feeding." Science Advances 8 (12). https://doi.org/10.1126/sciadv.abm6494.

Boye, Kristina S., Maureen J. Lage, Vivian Thieu, Shraddha Shinde, Shivanie Dhamija, and Jay Patrick Bae. 2021. "Obesity and Glycemic Control among People with Type 2 Diabetes in the United States: A Retrospective Cohort Study Using Insurance Claims Data." Journal of Diabetes and Its Complications 35 (9): 107975. https://doi.org/10.1016/j.jdiacomp.2021.107975.

Bozzetto, Lutgarda, Anna Prinster, Marcello Mancini, Rosalba Giacco, Claudia De Natale, Marco Salvatore, Gabriele Riccardi, Angela A. Rivellese, and Giovanni Annuzzi. 2011. "Liver Fat in Obesity: Role of Type 2 Diabetes Mellitus and Adipose Tissue Distribution." European Journal of Clinical Investigation 41 (1): 39–44. https://doi.org/10.1111/j.1365-2362.2010.02372.x.

Du, Xiu Ben, Ke Hui Zhu, Xiao Jing Chen, Jing Wu,

Dan Dan Liu, Zi Hao Wen, Xiao Qian Zou, et al. 2018. "Association between SLC30A8 Rs13266634 Polymorphism and Risk of T2DM and IGR in Chinese Population: A Systematic Review and Meta-Analysis." Frontiers in Endocrinology 9 (SEP). https://doi.org/10.3389/fendo.2018.00564.

Faghih, Hossein, Saied Reza Khatami, Negar Azarpira, and Ali Mohammad Foroughmand. 2014. "SLC30A8 Gene Polymorphism (Rs13266634 C/T) and Type 2 Diabetes Mellitus in South Iranian Population." Molecular Biology Reports 41 (5): 2709–15. https://doi.org/10.1007/s11033-014-3158-x.

Falih, Zubaida, and Mizil Alzubaidi. 2021. "Association of Calpain-10 Gene Polymorphism with Type 2 Diabetes Mellitus in Iraqi Patients."

Imamura, Minako, Atsushi Takahashi, Masatoshi Matsunami, Momoko Horikoshi, Minoru Iwata, Shin Ichi Araki, Masao Toyoda, et al. 2021. "Genome-Wide Association Studies Identify Two Novel Loci Conferring Susceptibility to Diabetic Retinopathy in Japanese Patients with Type 2 Diabetes." Human Molecular Genetics 30 (8): 716–26. https://doi.org/10.1093/hmg/ddab044.

Katsarou, Anastasia, Soffia Gudbjörnsdottir, Araz Rawshani, Dana Dabelea, Ezio Bonifacio, Barbara J. Anderson, Laura M. Jacobsen, Desmond A. Schatz, and Ake Lernmark. 2017. "Type 1 Diabetes Mellitus." Nature Reviews Disease Primers 3 (May 2020): 1–18. https://doi.org/10.1038/nrdp.2017.16.

Kazi, A. A., and L. Blonde. 2019. Classification of Diabetes Mellitus. Clinics in Laboratory Medicine. Vol. 21. https://doi.org/10.5005/jp/books/12855_84.

Li, Yan Yan, Xin Zheng Lu, Hui Wang, Xin Xing Yang, Hong Yu Geng, Ge Gong, Yi Yang Zhan, Hyun Jun Kim, and Zhi Jian Yang. 2018. "Solute Carrier Family 30 Member 8 Gene 807C/T Polymorphism and Type 2 Diabetes Mellitus in the Chinese Population: A Meta-Analysis Including 6,942 Subjects." Frontiers in Endocrinology 9 (MAY): 1–9. https://doi.org/10.3389/fendo.2018.00263.

Ligthart, Symen, Natalie R. Hasbani, Fariba Ahmadizar, Thijs T.W. van Herpt, Maarten J.G. Leening, André G. Uitterlinden, Eric J.G. Sijbrands, et al. 2021. "Genetic Susceptibility, Obesity and Lifetime Risk of Type 2 Diabetes: The ARIC Study and Rotterdam Study." Diabetic Medicine 38 (10): 1–10. https://doi.org/10.1111/dme.14639.

Mao, Yiping, Jacob Schoenborn, Zhihong Wang, Xinqian Chen, Katy Matson, Ramkumar Mohan, Shungang Zhang, et al. 2022. "Transgenic Overexpression of MicroRNA-30d in Pancreatic Beta-Cells Progressively Regulates Beta-Cell Function and Identity." Scientific Reports 12 (1): 1–12. https://doi.org/10.1038/s41598-022-16174-7.

Reddy, C Tirupathi, B Suryanarayana, R Siddeswari, B Sudarsi, and S Manohar. 2015. "A Study of Correlation of Body Mass Index , Waist Hip Ratio and Lipid Profile in Type II Diabetes Mellitus Subjects." International Journal of Scientific and Research Publications 5 (4): 1–4.

Reed, Josh, Stephen Bain, and Venkateswarlu Kanamarlapudi. 2021. "A Review of Current Trends with Type 2 Diabetes Epidemiology, Aetiology, Pathogenesis, Treatments and Future Perspectives." Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 14: 3567–3602. https://doi.org/10.2147/DMSO.S319895.

Rosenblit, Paul D. 2016. "Common Medications Used by Patients with Type 2 Diabetes Mellitus: What Are Their Effects on the Lipid Profile?" Cardiovascular Diabetology 15 (1): 1–13. https://doi.org/10.1186/s12933-016-0412-7.

Sadeghi, Erfan, Sayed Mohsen Hosseini, Mehrdad Vossoughi, Ashraf Aminorroaya, and Massoud Amini. 2020. "Association of Lipid Profile with Type 2 Diabetes in First-Degree Relatives: A 14-Year Follow-up Study in Iran." Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 13: 2743–50. https://doi.org/10.2147/DMSO.S259697.

Stožer, Andraž, Marko Šterk, Eva Paradiž Leitgeb, Rene Markovič, Maša Skelin Klemen, Cara E. Ellis, Lidija Križančić Bombek, Jurij Dolenšek, Patrick E. MacDonald, and Marko Gosak. 2022. "From Isles of Königsberg to Islets of Langerhans: Examining the Function of the Endocrine Pancreas Through Network Science." Frontiers in Endocrinology 13 (June): 1–28. https://doi.org/10.3389/fendo.2022.922640.

Thirunavukkarasu, Ramasamy, Arthur Joseph Asirvatham, Ayyappan Chitra, and Mariakuttikan Jayalakshmi. 2019. "SLC30A8 Gene Rs13266634 C/T Polymorphism in Children with Type 1 Diabetes in Tamil Nadu, India." JCRPE Journal of Clinical Research in Pediatric Endocrinology 11 (1): 55–60. https://doi.org/10.4274/jcrpe.galenos.2018.2018.0195.

Virginia, Dita Maria, Iwan Dwiprahasto, Mae Sri Hartati Wahyuningsih, and Dwi Aris Agung Nugrahaningsih. 2022. "The Effect of PRKAA2 Variation on Type 2 Diabetes Mellitus in the Asian Population: A Systematic Review and Meta-Analysis." Malaysian Journal of Medical Sciences 29 (3): 5–16. https://doi.org/10.21315/mjms2022.29.3.2.

Wondmkun, Yohannes Tsegyie. 2020. "Obesity, Insulin Resistance, and Type 2 Diabetes: Associations and Therapeutic Implications." Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 13: 3611–16. https://doi.org/10.2147/DMSO.S275898.

Yazdi, Kazem Vatankhah, Seyed Mehdi Kalantar, Massoud Houshmand, Masoud Rahmanian, Masoud Reza Manaviat, Mohammad Reza Jahani, Behnam Kamalidehghan, and Amir Almasi-Hashiani. 2020. "Slc30a8, Cdkal1, Tcf7l2, Kcnq1 and Igf2bp2 Are Associated with Type 2 Diabetes Mellitus in Iranian Patients." Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 13: 897–906. https://doi.org/10.2147/DMSO.S225968.