Systems Medicine, Redoxomics and Type 2 Diabetes

Subjects: Medicine, General & Internal

Contributor: Stephanie N. Alu , Evan A. Los , George A. Ford , William L. Stone

Medicine has largely utilized a reductionist approach in which disease states are generally reduced to a single organ or defect. Consequently, this approach often overlooks potential interactions between both intrinsic and extrinsic modulators and environmental risk factors. Alternatively, an integrative systems medicine approach is becoming increasingly favored. Redoxomics is a branch of systems medicine focusing on oxidative stress, reactive oxygen species, and antioxidants. Systems medicine, also referred to as precision or “P4” medicine, captures the power of omics technologies, such as genomics, epigenomics, proteomics, and metabolomics, and their interaction with environmental factors like nutrition and the gut microbiome.

redoxomics diabetes systems medicine oxidative stress

1. Introduction

Systems medicine, also referred to as precision or “P4” medicine, captures the power of omics technologies, such as genomics, epigenomics, proteomics, and metabolomics, and their interaction with environmental factors like nutrition and the gut microbiome [1][2][3][4][5]. The goal of P4 medicine is to provide an integrated healthcare approach that is “predictive, preventive, personalized and participatory” [6][7]. In short, systems medicine is interdisciplinary and utilizes omics data to reveal pathophysiological processes useful for predicting the inherent risk of an individual patient developing a disease such as diabetes and to assess the success likelihood of specific treatments [1][2][3][4]. Redoxomics is a branch of systems medicine focusing on “omics” data related to redox status. Systems medicine with a complementary emphasis on redoxomics can potentially optimize future healthcare strategies for adults and children with type 2 diabetes (T2D).

Considerable evidence supports the role of oxidative stress as an initial etiological factor for pediatric T2D. It follows that redoxomics would be of optimal clinical benefit while simultaneously providing detailed molecular insights into pathophysiology. A comprehensive application of redoxomics to either adult or youth-onset T2D is currently lacking. An early childhood study with multiple follow-up periods would be ideal since it might identify very early redoxomics biomarkers providing precision guidance for preventing or slowing future T2D development before irreversible pathology occurs. The potential of a generalized systems medicine approach to T2D will be reviewed and detail the ongoing contributions of omics technology to risk assessment, patient stratification, and predicting drug responsiveness. It was noted that existing omics data relevant to oxidative stress and T2D since this would help guide future redoxomic studies. These omics studies have mostly been limited to adults of Western European origin, with some newer additions from East Asian populations [8][9][10]. Genomic technology is quite

advanced, very comprehensive, cost-effective, and has overcome many regulatory hurdles for providing data analysis reports directly to adult consumers.

2. Genomics and T2D

T2D has a strong genetic predisposition and published genome-wide association studies (GWAS) have identified over 500 single nucleotide polymorphisms (SNPs) associated with susceptibility [8]. Nevertheless, these genetic variants have accounted for only about 10–20% of the heritability of T2D and some of these variants are also associated with obesity [10]. The relevant genetic risk factors can be combined into a polygenic T2D risk score with the potential to inform healthcare decisions, e.g., responding to an oral diabetic medication [11]. Very cost-effective commercial genotyping can currently provide an estimate of T2D risk development for adults. The 23andme company provides a T2D polygenic sore based on over 1000 genetic variants. About 20% of their research population has a T2D genetic risk equal to that of being overweight. Nevertheless, 23andme did not obtain Food and Drug Agency (FDA) clearance for the genetic risk score as it was characterized as a wellness product that does not make a diagnosis or provide medical advice. A genetic risk score for youth onset T2D has not been published but could potentially provide a sign to initiate early and robust lifestyle interventions.

2.1. Genomics and Stratification of Adult T2D Patients

A second major contribution of genomics to T2D lies in its potential to help categorize diabetes types and thereby provide more individualized healthcare. A controversial Swedish study recently proposed that adult diabetes be subdivided into five groups rather than the current two [12]. Six measures were utilized to assign a patient to a group: body BMI, age at diabetes diagnosis, HbA1C level, beta-cell functionality, insulin resistance, and the presence of diabetes-related autoantibodies. Significantly, the five types of DM categorized by these parameters were genetically distinct. These are very promising results and extending these studies to additional ethnic populations as well as the pediatric population could have enormous healthcare-related significance.

2.2. Genomics May Help Stratify Youth Onset T2D Patients

The possibility of using genomics to help stratify youth onset T2D is a high-priority future goal. In a consensus report, Nadeau et al. [13] reviewed the clinical evidence suggesting that youth-onset T2D is unique and distinct from T2D in adults. Youth-onset T2D is characterized by both a rapid beta-cell decline and an accelerated progression. The underlying pathophysiological mechanisms for these unique alterations are not well understood. The consensus report asserts that new and comprehensive strategies for treating youth-onset T2D “are urgently needed” [13]. A systems medicine approach will most likely contribute to future efforts at developing targeted treatments.

2.3. Genomics and Oxidative Stress

GWAS studies on oxidative stress in humans are still “a work in progress,” although studies in other organisms have provided a useful framework [14]. Variants in CAT, GPX4, and GSR (glutathione reductase) and the transcription factor nuclear factor-erythroid factor 2-related factor 2 (Nrf2) have been found to modulate human oxidative stress [15]. Despite their potential importance, biomarkers for oxidative stress in T2D are not clinically used to categorize DM or guide healthcare. Tabatabaei-Malazy et al. have reviewed the potential relevance of polymorphisms in antioxidant genes to T2D or its clinical complications [16]. These authors stress the need for additional studies focusing on epigenetic mechanisms regulating the expression of antioxidant enzymes. Future GWAS studies in the pediatric population could benefit from looking at the genetic variants contributing to POS, the development of pediatric insulin resistance, prediabetes, and T2D. Given the potential importance of mitochondria in T2D, it may prove useful to place more emphasis on mitochondrial DNA variants, as suggested by Wang et al. [17]. Mitochondrial DNA is particularly susceptible to oxidative stress-induced mutations and DNA damage [17]. Circulating mitochondrial DNA, thought to arise from stressed cells, may be a non-invasive biomarker for T2D [18].

3. Metabolomics, Oxidative Stress, and T2D

The potential clinical applications of metabolomics to oxidative stress-induced alterations in cytosolic, mitochondrial, and redox metabolites hold great promise [19]. It has been well documented, for example, that branched-chain amino acids (BCAAs) are elevated in T2D [20]. BCAAs include leucine, isoleucine and valine. In vitro and ex vivo experiments demonstrate that BCAAs promote endothelial dysfunction via increased mitochondrial ROS generation and increased formation of peroxynitrite and 3-nitro-tyrosine [21]. The induction of oxidative stress in endothelial cells is thought to be caused by activation of the mTORC1 pathway [21]. GWAS/metabolomic studies have confirmed a causal role between the level of insulin resistance and levels of circulating BCAAs [22].

In 2011, Wang et al. utilized a targeted metabolomic approach to evaluate the risk of developing T2D in adults [23]. In this study, a metabolic profile (over 60 metabolites) was measured in the fasting plasma of 2422 healthy, non-diabetic subjects. After a 12-year follow-up period, 201 individuals developed T2D. Quite significantly, plasma BCAAs levels (and that of two aromatic amino acids) had a significant association with future T2D development that was superior to BMI, dietary pattern, and fasting glucose [23].

Lipidomics is a subset of metabolomics looking only at lipid metabolites in a given biofluid/biosample. When fasting plasma is used, the lipids sampled will primarily represent lipids associated with lipoproteins and not cellular biomembranes. Recent research in a Swedish population shows that a “lipidomic risk,” based on a single mass spectrometric measurement in a plasma sample, can identify a subset of adult individuals at high risk for developing T2D. Moreover, the lipidomic risk score was largely independent of the polygenic risk score [24].

4. Proteomics and T2D

Chen and Gerszten have reviewed the potential of proteomics for advancing T2D healthcare [25]. These authors suggest that integrating circulating metabolomics and proteomics (i.e., multiomics) would be an optimum strategy. For large-scale population studies and future pediatric studies, the emphasis on plasma is realistic. Skeletal muscle mitochondrial alterations are likely to be of etiological significance for T2D [16], and plasma (or RBC) would not be as mechanistically informative as a skeletal muscle biopsy. Future mechanistic multiomic studies with skeletal muscle biopsies remain critical for advancing an in-depth understanding of T2D. For children, skeletal muscle biopsies are bioethically justified only with specific medical justification. Following tissue damage, tissue-specific proteins can leak into plasma but are usually present only in low abundance making their detection and quantification technologically challenging (more on this below).

4.1. Protein Glycation and Oxidation in T2D

Plasma and RBC samples can provide quantitative information on proteins that have been modified by glycation, AGE formation, or oxidative stress. A comprehensive list of glycated proteins from the plasma and RBCs of control and T2D subjects has been published, with several proteins being significantly more glycated in T2D subjects [26]. Interestingly, GPX3 (plasma glutathione peroxidase) was found to be glycated at four distinct peptide sequences. Carbonylated plasma proteins can be formed directly from ROS modifications of susceptible amino acid residues or by the covalent addition of adducts with carbonyl groups as they arise from glycation [27][28]. Carbonylated proteins are not, therefore, a good measure of ROS-mediated protein oxidation alone. Although lacking quantification, Bollineni et al. [28] looked at the presence of carbonylated plasma proteins in a small population of lean subjects and obese subjects with or without T2D. A unique set of carbonylated proteins were found only in the obese T2D subjects. These unique proteins need to be confirmed by additional studies (including pediatric subjects) but strongly suggest that carbonylated plasma proteins could provide biomarkers for obesity-induced T2D.

4.2. The Proximity Ligation Assay, T2D, and Metformin Response Stratification

Traditional proteomics utilizing highly specialized modern spectrometry equipment is well suited for basic research, exploratory clinical research, and proteome discovery. Fu et al. [29] have detailed the potential power of label-free quantitation for biomarker discovery in diabetes. The utility of the proximity ligation assay (PIA) for T2D precision medicine and biomarker discovery has recently been demonstrated in a modest cohort of healthy and T2D subjects [30].

PIA can be used for the detection of proteins, post-translational modifications (e.g., glycation) and protein-protein interactions [31][32]. In this assay, two complementary DNA-tagged antibodies bind to epitopes in close proximity to each other on the same target protein. DNA in the matched pair of tagged antibodies hybridize, is extended by DNA polymerase, and amplified by the quantitative polymerase chain reaction (qPCR) or next-generation sequencing (NGS). The amplified DNA is essentially a unique double-stranded “barcode” for a specific target protein and the number of readouts of that unique barcode is a quantitative measure of the target protein’s level in the sample. This assay can be multiplexed to quantify many proteins in a given sample.

Utilizing microliter amounts of fasting plasma, Zhong et al. could quantify about 1500 proteins (with NGS readout) in an adult Swedish population, including low abundance proteins [30]. They found that the plasma proteome significantly varied from one healthy individual to the next, but each had a unique profile that was stable over time. Two populations of T2D subjects were studied, i.e., obese and non-obese. Four proteins were found to have significantly altered expression between these two groups (one was leptin). They then examined the protein profiles of non-obese T2D patients with non-obese healthy patients and found 32 proteins with altered expression. The authors suggest these 32 proteins might serve to identify subjects at increased T2D risk despite not being obese. They next attempted to stratify T2D patients based on their responses to metformin treatment. A total of 40 T2D subjects were treated with metformin for three months and these were stratified into responders, non-responders, and an intermediate group. Significantly, 30 proteins in the plasma proteome measured at baseline (before the start of metformin intervention) could distinguish the responders from the non-responders. This result suggests that the panel of 30 proteins could be used to predict whether a Swedish adult T2D patient would respond well to metformin therapy.

In contrast to the overall positive responses of T2D adults to metformin alone or insulin treatment followed by metformin, youth-onset T2D shows no improvement in progressive beta-cell deterioration [33]. This again points to the uniqueness of youth-onset T2D and the speculation that redoxomics could help define relevant factors for preserving beta-cell function and preventing T2D progression.

Once a subset of proteins has been established to have clinical relevance, proteomics can shift from a discovery mode to a targeted mode in which only this subset is quantified. To be of practical use in systems medicine, targeted proteomic analyses need to be highly sensitive and specific with high throughput and long-term reproducibility. The PEA assay is very promising in this regard and could easily be expanded to look at relevant plasma-proteins covalently modified by glycation, AGE formation, and oxidative stress.

5. System Medicine, Nutrigenomics and T2D

Obesity, excess dietary calories, lack of exercise, and poor diet all contribute to T2D risk and progression [4,12]. Interventions aimed at correcting these lifestyle issues are central to individual care and relevant public health policies and programs. The American Diabetes Association supports “evidence-based nutrition standards for school meals and snacks, and other child nutrition programs” [34]. In addition to total calories, fat levels and type, fiber content, and glycemic index, it would also be useful to consider the levels of various dietary antioxidants and dietary AGEs [35]. Nutrients and dietary patterns are also known to influence gene expression in ways potentially relevant to the causes and development of T2D [36].

Nutrigenomics is emerging as an area possibly important in T2D prevention and treatment [37]. Nutrigenomics is a branch of systems medicine studying the interactions between genes and nutrients [38]. Many polyphenols, in addition to having intrinsic antioxidant properties, are also bioactive compounds that can potentially alter the expression of genes important to T2D [37]. Resveratrol, quercetin, genistein, catechins, and curcumin are bioactive dietary polyphenols that may play a role in T2D prevention/management [37][39][40]. Both GSH and ascorbate are

water-soluble antioxidants that may also play protective roles in T2D. Dietary ascorbate supplementation may improve glycemic control, but further clinical trials are necessary [41]. Similarly, a short-term pilot study with glycine and N-acetylcysteine supplementation (precursors of GSH) improves mitochondrial dysfunction and insulin resistance in adult T2D patients [42][43].

6. Conclusions

Adopting a systems medicine approach to T2D may require significant clinical and educational changes. It is important to note that much of the preliminary research into the systems medicine of diabetes has been done with adult populations of mostly Western European descent. There is a critical need to extend these studies to pediatric populations and ethnically diverse populations. Youth onset T2D may prove to have a genetic risk score with a unique set of gene variants compared to adult-onset T2D. Dietary-induced oxidative stress is likely an early initiating event for T2D progression and, therefore, of etiological significance to pediatric T2D. The comprehensive characterization of redox status provided by redoxomics holds great future promise in helping to evaluate the efficacy of lifestyle and nutritional interventions for T2D as well as the application of precision medicine. A multiomics approach that would utilize a targeted panel of genomic, metabolomic, and proteomic biomarkers is likely to be optimal.

References

1. Kussmann, M.; Morine, M.J.; Hager, J.; Sonderegger, B.; Kaput, J. Perspective: A systems approach to diabetes research. Front. Genet. 2013, 4, 205.
2. Gustafsson, M.; Nestor, C.E.; Zhang, H.; Barabási, A.L.; Baranzini, S.; Brunak, S.; Chung, K.F.; Federoff, H.J.; Gavin, A.C.; Meehan, R.R.; et al. Modules, networks and systems medicine for understanding disease and aiding diagnosis. Genome Med. 2014, 6, 82.
3. Mardinoglu, A.; Nielsen, J. Systems medicine and metabolic modelling. J. Intern. Med. 2012, 271, 142–154.
4. Olivier, M.; Asmis, R.; Hawkins, G.A.; Howard, T.D.; Cox, L.A. The Need for Multi-Omics Biomarker Signatures in Precision Medicine. Int. J. Mol. Sci. 2019, 20, 4781.
5. Apweiler, R.; Beissbarth, T.; Berthold, M.R.; Blüthgen, N.; Burmeister, Y.; Dammann, O.; Deutsch, A.; Feuerhake, F.; Franke, A.; Hasenauer, J.; et al. Whither systems medicine? Exp. Mol. Med. 2018, 50, e453.
6. Flores, M.; Glusman, G.; Brogaard, K.; Price, N.D.; Hood, L. P4 medicine: How systems medicine will transform the healthcare sector and society. Pers. Med. 2013, 10, 565–576.
7. Hood, L.; Flores, M. A personal view on systems medicine and the emergence of proactive P4 medicine: Predictive, preventive, personalized and participatory. New Biotechnol. 2012, 29, 613–

624.

8. Liu, Y.; Wang, Y.; Qin, S.; Jin, X.; Jin, L.; Gu, W.; Mu, Y. Insights Into Genome-Wide Association Study for Diabetes: A Bibliometric and Visual Analysis From 2001 to 2021. Front. Endocrinol. 2022, 13, 817620.
9. Polfus, L.M.; Darst, B.F.; Highland, H.; Sheng, X.; Ng, M.C.Y.; Below, J.E.; Petty, L.; Bien, S.; Sim, X.; Wang, W.; et al. Genetic discovery and risk characterization in type 2 diabetes across diverse populations. HGG Adv. 2021, 2, 100029.
10. Xue, A.; Wu, Y.; Zhu, Z.; Zhang, F.; Kemper, K.E.; Zheng, Z.; Yengo, L.; Lloyd-Jones, L.R.; Sidorenko, J.; McRae, A.F.; et al. Genome-wide association analyses identify 143 risk variants and putative regulatory mechanisms for type 2 diabetes. Nat. Commun. 2018, 9, 2941.
11. Udler, M.S.; McCarthy, M.I.; Florez, J.C.; Mahajan, A. Genetic Risk Scores for Diabetes Diagnosis and Precision Medicine. Endocr. Rev. 2019, 40, 1500–1520.
12. Ahlqvist, E.; Storm, P.; Käräjämäki, A.; Martinell, M.; Dorkhan, M.; Carlsson, A.; Vikman, P.; Prasad, R.B.; Aly, D.M.; Almgren, P.; et al. Novel subgroups of adult-onset diabetes and their association with outcomes: A data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol. 2018, 6, 361–369.
13. Nadeau, K.J.; Anderson, B.J.; Berg, E.G.; Chiang, J.L.; Chou, H.; Copeland, K.C.; Hannon, T.S.; Huang, T.T.; Lynch, J.L.; Powell, J.; et al. Youth-Onset Type 2 Diabetes Consensus Report: Current Status, Challenges, and Priorities. Diabetes Care 2016, 39, 1635–1642.
14. Weber, A.L.; Khan, G.F.; Magwire, M.M.; Tabor, C.L.; Mackay, T.F.; Anholt, R.R. Genome-wide association analysis of oxidative stress resistance in Drosophila melanogaster. PLoS ONE 2012, 7, e34745.
15. Zhan, M.; Wang, H.; Xu, S.W.; Yang, L.H.; Chen, W.; Zhao, S.X.; Shen, H.; Liu, Q.; Yang, R.M.; Wang, J. Variants in oxidative stress-related genes affect the chemosensitivity through Nrf2-mediated signaling pathway in biliary tract cancer. EBioMedicine 2019, 48, 143–160.
16. Tabatabaei-Malazy, O.; Khodaeian, M.; Bitarafan, F.; Larijani, B.; Amoli, M.M. Polymorphisms of Antioxidant Genes as a Target for Diabetes Management. Int. J. Mol. Cell Med. 2017, 6, 135–147.
17. Wang, P.W.; Lin, T.K.; Weng, S.W.; Liou, C.W. Mitochondrial DNA variants in the pathogenesis of type 2 diabetes—Relevance of asian population studies. Rev. Diabetes Stud. 2009, 6, 237–246.
18. Silzer, T.; Barber, R.; Sun, J.; Pathak, G.; Johnson, L.; O'Bryant, S.; Phillips, N. Circulating mitochondrial DNA: New indices of type 2 diabetes-related cognitive impairment in Mexican Americans. PLoS ONE 2019, 14, e0213527.
19. Liu, J.; Litt, L.; Segal, M.R.; Kelly, M.J.; Pelton, J.G.; Kim, M. Metabolomics of oxidative stress in recent studies of endogenous and exogenously administered intermediate metabolites. Int. J. Mol.

Sci. 2011, 12, 6469–6501.

20. Bloomgarden, Z. Diabetes and branched-chain amino acids: What is the link? J. Diabetes 2018, 10, 350–352.
21. Zhenyukh, O.; González-Amor, M.; Rodrigues-Diez, R.R.; Esteban, V.; Ruiz-Ortega, M.; Salaices, M.; Mas, S.; Briones, A.M.; Egido, J. Branched-chain amino acids promote endothelial dysfunction through increased reactive oxygen species generation and inflammation. J. Cell. Mol. Med. 2018, 22, 4948–4962.
22. Wang, Q.; Holmes, M.V.; Davey Smith, G.; Ala-Korpela, M. Genetic Support for a Causal Role of Insulin Resistance on Circulating Branched-Chain Amino Acids and Inflammation. Diabetes Care 2017, 40, 1779–1786.
23. Wang, T.J.; Larson, M.G.; Vasan, R.S.; Cheng, S.; Rhee, E.P.; McCabe, E.; Lewis, G.D.; Fox, C.S.; Jacques, P.F.; Fernandez, C.; et al. Metabolite profiles and the risk of developing diabetes. Nat. Med. 2011, 17, 448–453.
24. Lauber, C.; Gerl, M.J.; Klose, C.; Ottosson, F.; Melander, O.; Simons, K. Lipidomic risk scores are independent of polygenic risk scores and can predict incidence of diabetes and cardiovascular disease in a large population cohort. PLoS Biol. 2022, 20, e3001561.
25. Chen, Z.Z.; Gerszten, R.E. Metabolomics and Proteomics in Type 2 Diabetes. Circ. Res. 2020, 126, 1613–1627.
26. Zhang, Q.; Monroe, M.E.; Schepmoes, A.A.; Clauss, T.R.; Gritsenko, M.A.; Meng, D.; Petyuk, V.A.; Smith, R.D.; Metz, T.O. Comprehensive identification of glycated peptides and their glycation motifs in plasma and erythrocytes of control and diabetic subjects. J. Proteome Res. 2011, 10, 3076–3088.
27. Hecker, M.; Wagner, A.H. Role of protein carbonylation in diabetes. J. Inherit. Metab. Dis. 2018, 41, 29–38.
28. Bollineni, R.C.; Fedorova, M.; Blüher, M.; Hoffmann, R. Carbonylated plasma proteins as potential biomarkers of obesity induced type 2 diabetes mellitus. J. Proteome Res. 2014, 13, 5081–5093.
29. Fu, J.; Luo, Y.; Mou, M.; Zhang, H.; Tang, J.; Wang, Y.; Zhu, F. Advances in Current Diabetes Proteomics: From the Perspectives of Label- free Quantification and Biomarker Selection. Curr. Drug Targets 2020, 21, 34–54.
30. Zhong, W.; Edfors, F.; Gummesson, A.; Bergström, G.; Fagerberg, L.; Uhlén, M. Next generation plasma proteome profiling to monitor health and disease. Nat. Commun. 2021, 12, 2493.
31. Greenwood, C.; Ruff, D.; Kirvell, S.; Johnson, G.; Dhillon, H.S.; Bustin, S.A. Proximity assays for sensitive quantification of proteins. Biomol. Detect. Quantif. 2015, 4, 10–16.

32. Weibrecht, I.; Leuchowius, K.J.; Clausson, C.M.; Conze, T.; Jarvius, M.; Howell, W.M.; Kamali-Moghaddam, M.; Söderberg, O. Proximity ligation assays: A recent addition to the proteomics toolbox. Expert Rev. Proteom. 2010, 7, 401–409.
33. Consortium, R. Impact of Insulin and Metformin Versus Metformin Alone on β-Cell Function in Youth With Impaired Glucose Tolerance or Recently Diagnosed Type 2 Diabetes. Diabetes Care 2018, 41, 1717–1725.
34. American Diabetes Association. Supporting Healthier School Meals. Available online: www.diabetes.org/blog/supporting-healthier-school-meals (accessed on 20 April 2022).
35. Glycemic. What Is Glycemic Index? Available online: health.clevelandclinic.org/glycemic-index/ (accessed on 20 April 2022).
36. Berná, G.; Oliveras-López, M.J.; Jurado-Ruíz, E.; Tejedo, J.; Bedoya, F.; Soria, B.; Martín, F. Nutrigenetics and nutrigenomics insights into diabetes etiopathogenesis. Nutrients 2014, 6, 5338–5369.
37. Felisbino, K.; Granzotti, J.G.; Bello-Santos, L.; Guiloski, I.C. Nutrigenomics in Regulating the Expression of Genes Related to Type 2 Diabetes Mellitus. Front. Physiol. 2021, 12, 699220.
38. Kang, J.X. Nutrigenomics and systems biology. J. Nutr. Nutr. 2012, 5, I–II.
39. Shahwan, M.; Alhumaydhi, F.; Ashraf, G.M.; Hasan, P.M.Z.; Shamsi, A. Role of polyphenols in combating Type 2 Diabetes and insulin resistance. Int. J. Biol. Macromol. 2022, 206, 567–579.
40. Sun, L.; Miao, M. Dietary polyphenols modulate starch digestion and glycaemic level: A review. Crit. Rev. Food Sci. Nutr. 2020, 60, 541–555.
41. Mason, S.A.; Keske, M.A.; Wadley, G.D. Effects of Vitamin C Supplementation on Glycemic Control and Cardiovascular Risk Factors in People With Type 2 Diabetes: A GRADE-Assessed Systematic Review and Meta-analysis of Randomized Controlled Trials. Diabetes Care 2021, 44, 618–630.
42. Sekhar, R.V.; McKay, S.V.; Patel, S.G.; Guthikonda, A.P.; Reddy, V.T.; Balasubramanyam, A.; Jahoor, F. Glutathione synthesis is diminished in patients with uncontrolled diabetes and restored by dietary supplementation with cysteine and glycine. Diabetes Care 2011, 34, 162–167.
43. Sekhar, R.V. GlyNAC (Glycine and N-Acetylcysteine) Supplementation Improves Impaired Mitochondrial Fuel Oxidation and Lowers Insulin Resistance in Patients with Type 2 Diabetes: Results of a Pilot Study. Antioxidants 2022, 11, 154.