Review Article

Ascorbic and Dehydroascorbic Acid- Connections to Type 1 Diabetes

Johnny Ludvigsson*

Senior Professor of Pediatrics, Crown Princess Victoria Children´s Hospital and Division of Pediatrics, Department of Biomedical and Clinical Sciences, Linköping university, Linköping, Sweden

***Corresponding author:** Professor Johnny Ludvigsson, Crown Princess Victoria Children´s Hospital and Div of Pediatrics, Dept of Biomedical and Clinical Sciences, Linköping university, Linköping , Sweden, Tel: +46 0706 577 234

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Abstract

The etiology of Type 1 diabetes (T1D) is unknown. While especially B- and D-vitamins have been to some extent studied in relation to development of Type 1 diabetes, Vitamin C has been ignored despite its important effects as an antioxidant protecting against oxidative stress, its influence on the immune function including autoimmunity, and the possible direct effects on the pancreatic beta cells. Recently the demonstration of increased dehydroascorbic acid before the development of autoantibodies in serum of children with genetic risk for T1D has drawn some attention to the ascorbic and dehydroascorbic acids, which decades ago have been linked to effects on the pancreatic beta cells. As long as there is no safe, efficacious and practical way of preventing Type 1 diabetes there are reasons to resume the interest for vitamins, including Vitamin C.

Keywords: Type 1 diabetes; Vitamin C; Ascorbic acid; Dehydroascorbic acid; Autoimmunity; Type 2 diabetes; Beta cell function

1. Introduction

The etiology of Type 1 diabetes (T1D) is unknown. Genetic factors are important [1] as well as environmental [2]. Autoimmunity is common with autoantibodies against multiple autoantigens preceding the clinically manifest disease usually for many years. Depending on the initial appearance of

the two most common autoantibodies, against insulin (IAA) or against Glutamic Acid Decarboxylase (GADA), and the difference in HLA association, it has been proposed that we may deal with different endotypes of the disease [3-5]. We still do not know why the autoimmune process starts, even though virus is one common hypothesis [6-8]. Nutritional agents such as cow´s milk proteins and gluten introduction early in life has had a strong position, but after the failure of the TRIGR study [(9] the cow´s milk hypothesis has lost power, while gluten is still regarded as reasonably plausible as contributing cause of T1D [10]. This short review reminds about the possible role of vitamins, here concentrating on AA, not only as antioxidant, but via different possible mechanisms that could influence beta cell autoimmunity.

2. Vitamins and Type 1 Diabetes

Even though vitamins are extremely important for the body function, they seldom seem to get enough status in diabetes research. Periodically attention has been focused on Nicotinamide, with a peak interest when Nicotinamide was used to prevent T1D, but when this effort failed [11] the interest decreased again. Vitamin D has also been noticed as there are studies indicating that vitamin D has effects on the immune system which might decrease the risk of T1D [12] and there are epidemiological studies which suggest that lack of vitamin D might increase the risk of getting T1D [13]. Finally there has been some interest in the antioxidant effect of several vitamins, which have therefore been tried to protect beta cells and preserve beta cell function, but with limited or no effect [14, 15].

Recent studies have made AA more interesting. It is known that certain metabolic changes seem to occur already before the development of autoantibodies, such as increasing amounts of glutamate and changes in lipids [16, 17]. However, interestingly another substance found to be increased very early in the process is DHAA [18], which suggests a possible role for AA in the disease process leading to T1D.

3. Vitamin C/Ascorbic acid (AA) and Dehydro-Ascorbic Acid (DHAA)

Vitamin C or ascorbic acid (AA) is an essential nutrient which has to be supplied via the diet [19]. Normal diet contains also dehydroascorbic acid (DHAA), which is also generated from ascorbic acid in the gut. DHAA is absorbed from the small intestine and reduced to AA, which then circulates in the blood. The water soluble AA cannot be stored long time but is quite rapidly depleted after only about a week of insufficient intake [20]. Considering the individual variability in healthy subjects, a daily intake of AA from 100 to 400 mg is supposed to give full bioavailability with a steady state of plasma concentration, usually with a maximum concentration of ca 70-80 µmol/L [21, 22]. When 500-1000 mg of AA is taken orally, the uptake is maximal, while the urine excretion of the vitamin gradually increases [23]. There seems to be a balance in uptake and excretion which has led to a recommended dietary allowance (RDA) for AA, which varies among countries. In the USA and Canada 90 mg/day for adult men and 75 mg/day for adult women is recommended [24], while in Sweden the recommendation is 75 mg for adults, 50 mg for children 10-13 years old and 100 mg for pregnant women [25]. Several factors can modify AA requirements, including gender, age, smoking, pregnancy, and lactation [26]. Furthermore, in children the RDAs for AA, derived from adult needs,

are usually adjusted for body mass [27-29]. When AA is used as an antioxidant and enzyme cofactor it is oxidized to DHAA. DHAA increases with AA deficiency, while high doses of AA leads to a decrease of DHAA. Both insulin and insulin-like growth factor I (IGF-1) influence the DHAA-AA balance, which is also influenced by oxidative stress and by diabetes.

4. Vitamin C/AA and Immune Function

AA plays an important role for the immune system [30]. It was proposed by, among others, Linus Pauling that large doses of AA are useful against common colds. According to Pauling, a daily AA intake of 1000 mg can reduce the incidence of common colds by about 45% and the optimal daily intake of AA for a healthy life should be at least 2-3 g [31, 32]. Encouraged by Linus Pauling´s ideas we performed two double-blind, randomized trials in altogether 800 school children and found that 1000 mg AA per day for some months might shorten the duration of common colds, but did not decrease the incidence of common colds [33]. The result was similar in another study [34]. The conclusion of a large review of published studies [35], was that AA supplementation may decrease the common colds by about 50% in people, at least under physical stress.

And recently, it was shown in a large randomized, double-blind, placebo-controlled trial in 1,444 Korean soldiers, 695 of whom received high doses of AA (6 g/day) for 30 days that the AA group had a 0.80-fold lower risk of getting a common cold compared to the placebo group (n = 749) [36]. As another example of AA effect on infections there are recent reports during the corona pandemic suggesting that AA might give some benefit in the treatment of Covid19 [37, 38].

Thus during infections AA is consumed, while DHAA increases. AA influences the leukocyte function [39]. It contributes to protection of the neutrophils from oxidative stress during the early stages of an immune response, when neutrophils activate phagocytosis and produce reactive oxygen species (ROS) to destroy antigens [40, 41]. When the phagocytic capacity is exhausted and neutrophils start to die, AA seems to regulate the immune process in favor of apoptosis, as AA activates a caspase-dependent cascade, inhibits necrosis, which contributes to resolution of inflammation [42]. AA is also involved in the migration of neutrophils and macrophages toward the infection sites [43].

Further, AA may induce a shift of immune responses from Th2 to Th1 [44], and the vitamin might affect the production of antibodies [45-48]. AA seems to reduce the concentrion of pro-inflammatory leukocyte-derived cytokines (e.g., TNFα and IL-6) [49, 50]. Finally, AA seems to increase the activity of epigenetic enzymes, including the ten-eleven translocation (TET) proteins [51, 52].

5. Vitamin C/AA and Diabetes

It is reasonable that AA is related to the process leading to T1D in case virus infections are involved. But in addition AA has several other connections to diabetes.

5.1 Type 1 diabetes

AA and glucose are structurally similar, and transport and accumulation of AA in the beta cells may affect glucose-induced insulin release. The presence of the AA-dependent enzyme peptidylglycine a-amidating monooxygenase in the islets of Langerhans [53-56] indicates that AA has a function in the islet cells. The

balance between the concentration of AA and DHAA is influenced by the concentration of AA as mentioned above but also by the glucose concentration [57]. In healthy individuals mainly ascorbic acid is found, but no or minimal dehydroascorbic acid. However, diabetic patients, and actually also their non-diabetic close relatives, have been found to have remarkably high DHAA concentrations [58]. It was proposed long time ago that DHAA might damage beta cells [59] although studies have given diverging results [60]. It has been shown that elevated DHAA inhibits insulin secretion in mice [61-63], and exposure of isolated mouse islets to DHAA can reduce the responsiveness of the islets (65) or lead to decreased insulin secretion [63, 64]. Impaired recycling of AA as a result of increased glucose metabolism may have implications for the role of AA /DHAA in insulin secretion in diabetes and might be on part of the glucose toxicity in beta cells [65].

Interestingly it has recently been noticed that there is increased concentrations of dehydroascorbic acid in individuals already before the development of islet autoantibodies, both before development of IAA and before GADA [66]. In a follow-up study in the TEDDY project it was found that infants with low plasma AA got IAA as their first autoantibody. Plasma AA and 25 (OH)-D (vitamin D) at infancy were lower in HLA-DR3/DR4 children among those with IAA [67]. In agreement with this another study found that childhood plasma AA was inversely associated with islet autoimmunity risk starting with insulin autoantibodies, but not starting with GADA. Although, there was no relation to risk of T1D, the authors concluded that high plasma ascorbic acid levels may protect against islet autoimmunity in children genetically at risk for T1D [68].

5.2 Type 2 diabetes

Patients with T2D seem to have low plasma concentrations of AA [69]. There are different possible explanations such as increased urinary excretion [70] or an increase of oxidative stress consuming AA [71, 72]. Large doses of AA supplementation is shown to reduce CRP, IL-6, fasting blood glucose and triglycerides in patients with diabetes [73]. In addition, supplementation with larger doses of AA (200 to 1,000 mg per day) during at least 4 weeks seems to reduce fasting blood glucose in patients with T2D according to a meta-analysis [74]. These later effects of AA may have some relation to the mechanisms of development of T1D.

5.3 Microangiopathy

In addition to the interest of AA for the development of diabetes, there is research suggesting that diabetic microangiopathy is associated with oxidative damage caused by increased free radicals, and AA is an effective free radical scavenger. Diabetic patients may be less able to prevent oxidative damage due to their lower AA concentrations, which therefore might increase the risk for microangiopathy [75]. These findings need to be further investigated. So far AA is not generally recommended to prevent diabetic microangiopathy.

6. Nutrition, Vitamin C/AA and Development of T1D

AA can be synthesized from glucose by most animals, but not by Homo sapiens, where the necessary enzyme is lacking. Instead humans have to get AA via food intake. Food with high concentration of vitamin

C is eg potatoes, vegetables, citrus fruits, paprika, and strawberries. If lack of AA and perhaps corresponding increase of DHAA may cause toxic effects on the beta cells, contributing to the development of islet autoimmunity, decreased beta cell function and perhaps later development of T1D, one might expect to find some support for protective effect of food containing AA. However there are no solid data supporting this connection and some studies on early nutrition or nutrition during pregnancy give divergent results.

The Diabetes Autoimmunity Study in the Young (DAISY) analyzed the effect of early nutrition on development of autoantibodies [76]. Adjusting for duration of breast-feeding, age at first cereal introduction, ethnicity, HLA, family history of type 1 diabetes, and total caloric intake, they found that higher maternal intake of potatoes was the only part of the nutrition associated with a delayed time to onset of islet autoimmunity. Potatoes contain rather much AA, but the result is no strong support for the importance of AA.

In the All Babies in Southeast Sweden (ABIS) study daily vegetable intake during pregnancy was negatively associated to islet autoimmunity in the offspring [77]. AA was not measured, but it cannot be excluded that vitamins, including AA played a role for the result.

The Finnish Type 1 Diabetes Prediction and Prevention (DIPP) prospective birth cohort includes children genetically at risk for type 1 diabetes. The diet of mothers in late pregnancy was assessed with a validated food frequency questionnaire. Consumption of AA was not found to be associated with the risk of neither islet autoimmunity nor type 1 Diabetes [78].

7. Conclusions

The etiology of T1D is unknown. While especially B- and D-vitamins have been to some extent studied in relation to development of T1D, it may be time to take a closer look at AA. Both AA and its oxidized form DHAA may have a role in the development of T1D, both via mechanisms related to defense against infections, effects on the immune function and even direct effects on the beta cell function.

Disclosure

The author has nothing to disclose in relation to the paper.

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References

1. Pociot F, Lernmark Å. Genetic risk factors for type 1 diabetes. Lancet 387 (2016): 2331-2339.
2. Rewers M, Ludvigsson J. Environmental risk factors for type 1 diabetes. Lancet 387 (2016): 2340-2348.
3. Leete P, Oram RA, McDonald TJ, Shields BM, Ziller C. TIGI study team, Hattersley AT, Richardson SJ, Morgan NG. Studies of insulin and proinsulin in pancreas and serum

support the existence of aetiopathological endotypes of type 1 Diabetes associated with age at diagnosis. Diabetologia 63 (2020): 1258-1267.

4. Smith MJ, Cambier JC, Gottlieb PA. Endotypes in T1D: B lymphocytes and early onset. Curr Opin Endocrinol Diabetes Obes 27 (2020): 225-230.
5. Redondo MJ, Hagopian WA, Oram R, Steck AK, Vehik K, et al. The clinical consequences of heterogeneity within and between different diabetes types. Diabetologia 63 (2020): 2040-2048.
6. Hyöty H. Viruses in type 1 diabetes. Pediatr Diabetes22 (2016): 56-64.
7. Dunne JL, Richardson SJ, Atkinson MA, Craig ME, Dahl-Jørgensen K, et al. Rationale for enteroviral vaccination and antiviral therapies in human type 1 diabetes. Diabetologia 62 (2019): 744-753.
8. Craig ME, Kim KW, Isaacs SR, Penno MA, Hamilton-Williams EE, et al. Early-life factors contributing to type 1 diabetes. Diabetologia 62 (2019): 1823-1834.
9. Writing Group for the TRIGR Study Group, Knip M, Åkerblom HK, Al Taji E, Becker D, Bruining J, et al. Effect of Hydrolyzed Infant Formula vs Conventional Formula on Risk of Type 1 Diabetes: The TRIGR Randomized Clinical Trial. JAMA 319 (2018): 38-48.
10. Antvorskov JC, Josefsen K, Engkilde K, Funda DP, Buschard K. Dietary gluten and the development of type 1 diabetes. Diabetologia 57 (2014): 1770-1780.
11. Gale EA, Bingley PJ, Emmett CL, Collier T; European Nicotinamide Diabetes Intervention Trial (ENDIT) Group. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. Lancet 363 (2004): 925-931.
12. Mathieu C, Gysemans C, Giulietti A, et al. Vitamin D and diabetes. Diabetologia 48 (2005): 1247-1257.
13. Zipitis CS, Akobeng AK. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. Arch Dis Child 93 (2008): 512-517.
14. Ludvigsson J, Samuelsson U, Johansson C, Stenhammar L. Treatment with antioxidants at onset of type 1 diabetes in children: a randomized, double-blind placebo-controlled study. Diabetes Metab Res Rev 17 (2001): 131-136.
15. Crinò A, Schiaffini R, Manfrini S, Mesturino C, Visalli N, et al. A randomized trial of nicotinamide and vitamin E in children with recent onset type 1 diabetes (IMDIAB IX). Eur J Endocrinol 150 (2004): 719-724.
16. Orešič M, Simell S, Sysi-Aho M, et al. Dysregulation of lipid and amino acid metabolism precedes islet autoimmunity in children who later progress to type 1 diabetes. J Exp Med 205 (2008): 2975-2984.
17. Pflueger M, Seppänen-Laakso T, Suortti T, et al. Age- and islet autoimmunity-associated differences in amino acid and lipid metabolites in children at risk for type 1 diabetes. Diabetes 60 (2011): 2740-2747.
18. Li Q, Parikh H, Butterworth MD, Lernmark Å, Hagopian W, et al. TEDDY Study Group. Longitudinal Metabolome-Wide Signals Prior to the Appearance of a First Islet

Autoantibody in Children Participating in the TEDDY Study. Diabetes 69 (2020): 465-476.

19. Linster CL, Van Schaftingen E. Vitamin C. Biosynthesis, recycling and degradation in mammals. FEBS J 274 (2007): 1-22.
20. Kim H, Bae S, Yu Y, Kim Y, Kim H-R, et al. The Analysis of Vitamin C Concentration in Organs of Gulo -/- Mice upon Vitamin C Withdrawal. Immune Netw 12 (2012): 18-26.
21. Frei B, Birlouez-Aragon I, Lykkesfeldt J. Authors' perspective: What is the optimum intake of vitamin C in humans? Crit Rev Food Sci Nutr 52 (2012): 815-829.
22. Levine M, Padayatty SJ, Espey MG. Vitamin C. A Concentration-Function Approach Yields Pharmacology and Therapeutic Discoveries. Adv Nutr 2 (2011): 78-88.
23. Levine M, Conry-Cantilena C, Wang Y, Welch RW, Washko PW, et al. Vitamin C pharmacokinetics in healthy volunteers: Evidence for a recommended dietary allowance. Proc Natl Acad Sci USA 93 (1996): 3704-3709.
24. Bechthold A. New reference values for Vitamin C intake. Ann Nutr Metab 67 (2015): 13-20.
25. https://www.livsmedelsverket.se/näringsämne/C-vitamin.
26. Carr AC, Lykkesfeldt J. Discrepancies in global vitamin C recommendations: a review of RDA criteria and underlying health perspectives. Crit Rev Food Sci Nutr (2020): 1-14.
27. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) Scientific Opinion on Dietary Reference Values for vitamin C. EFSA J 11 (2013): 3418.
28. German Nutrition Society New Reference Values for Vitamin C Intake. Ann Nutr Metab 67 (2015): 13-20.
29. Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. Washington (DC): National Academies Press (US) (2000).
30. Carr AC, Maggini S, Vitamin C. and immune function. Nutrients 9 (2017): 1211.
31. Pauling L. Evolution and the need for ascorbic acid. Proc Natl Acad Sci USA 67 (1970): 1643-1648.
32. Pauling L. The significance of the evidence about ascorbic acid and the common cold. Proc Natl Acad Sci USA 68 (1971): 2678-26781.
33. Ludvigsson J, Hansson LO, Tibbling G. Vitamin C as a preventive medicine against common colds in children. Scand J Infect Dis 9 (1977): 91-98.
34. Elwood PC, Hughes SJ, Leger St AS. A randomized controlled trial of the therapeutic effect of vitamin C in the common cold. Practitioner 218 (1977): 133-137.
35. Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev (2013): CD000980.
36. Kim TK, Lim HR, Byun JS. Vitamin C supplementation reduces the odds of developing a common cold in Republic of Korea Army recruits: randomised controlled trial. BMJ Mil Heal (2020).

37. Hernández A, Papadakos PJ, Torres A, González DA, Vives M, et al. Two known therapies could be useful as adjuvant therapy in critical patients infected by COVID-19. Rev Esp Anestesiol Reanim 67 (2020): 245-252.
38. Matthay MA, Aldrich JM, Gotts JE. Treatment for severe acute respiratory distress syndrome from COVID-19. Lancet Respir Med 8 (2020): 433-434.
39. Ludvigsson J, Hansson LO, Stendahl O. The effect of large doses of vitamin C on leukocyte function and some laboratory parameters. Int J Vitam Nutr Res 49 (1979): 160-165.
40. Winterbourn CC, Vissers MCM. Changes in ascorbate levels on stimulation of human neutrophils. BBA - Mol Cell Res 763 (1983): 175-179.
41. Oberritter H, Glatthaar B, Moser U, Schmidt KH. Effect of functional stimulation on ascorbate content in phagocytes under physiological and pathological conditions. Int Arch Allergy Appl Immunol 81 (1986): 46-50.
42. Vissers MCM, Wilkie RP. Ascorbate deficiency results in impaired neutrophil apoptosis and clearance and is associated with up-regulation of hypoxia-inducible factor 1α. J Leukoc Biol 8 (2007): 1236-1244.
43. Goldschmidt MC. Reduced bactericidal activity in neutrophils from scorbutic animals and the effect of ascorbic acid on these target bacteria in vivo and in vitro. Am J Clin Nutr 54 (1991): 1214S-1220S.
44. Van Gorkom GNY, Klein Wolterink RGJ, Van Elssen CHMJ, Wieten L, Germeraad WTV, et al. Influence of Vitamin C on lymphocytes: An overview. Antioxidants 7 (2018): 41.
45. Vallance S. Relationships between ascorbic acid and serum proteins of the immune system. Br Med J 2 (1977): 437-438.
46. Anderson R, Oosthuizen R, Maritz R, Theron A, Van Rensburg AJ. The effects of increasing weekly doses of ascorbate on certain cellular and humoral immune functions in normal volunteers. Am J Clin Nutr 33 (1980): 71-76.
47. Prinz W, Bloch J, Gilich G, Mitchell G. A systematic study of the effect of vitamin C supplementation on the humoral immune response in ascorbate-dependent mammals. I. The antibody response to sheep red blood cells (a T-dependent antigen) in guinea pigs. Int J Vitam Nutr Res 50 (1980): 294-300.
48. Feigen GA, Smith BH, Dix CE, Flynn CJ, Peterson NS, et al. Enhancement of antibody production and protection against systemic anaphylaxis by large doses of vitamin C. Res Commun Chem Pathol Pharmacol 38 (1982): 313-333.
49. Carr AC, Rosengrave PC, Bayer S, Chambers S, Mehrtens J, et al. Hypovitaminosis C and vitamin C deficiency in critically ill patients despite recommended enteral and parenteral intakes. Crit Care 21 (2017): 200.
50. Bonham MJD, Abu-Zidan FM, Simovic MO, Sluis KB, Wilkinson A, et al. Early ascorbic acid depletion is related to the severity of

acute pancreatitis. Br J Surg 86 (1999): 1296-12301.

51. Lee Chong T, Ahearn EL, Cimmino L. Reprogramming the Epigenome With Vitamin C. Front Cell Dev Biol 7 (2019): 128.
52. Blaschke K, Ebata KT, Karimi MM, Zepeda-Martínez JA, Goyal P, et al. Vitamin C induces Tet-dependent DNA demethylation and a blastocyst-like state in ES cells. Nature 500 (2013): 222-226.
53. Ouafik LH, Dutour A, Salem P, Giraud P, Boudoureeque F, et al. Evidence for high peptide a-amidation activity in hte neonatal rat pancreas. Biochem. Biophys. Res. Commun 138 (1986): 179-184.
54. Mackin RB, Flacker EM, Mackin JA, Noe BD. Peptidyl-glycine α-amidating monooxygenase is present in islet secretory granules of the anglerfish, Lophius americanus. Gen. Comp. Endocrinol 67 (1987): 263-269.
55. Scharfmann R, Leduque P, Aratan-Spire S, Dubois I, Basmaciogullari A, et al. Persistence of peptidylglycine α-amidating monooxygenase activity and elevated thyrotropin- releasing hormone concentrations in fetal rat islets in culture. Endocrinology 123 (1988): 1329-1334.
56. Maltese JY, Giraud P, Kowalski C, Ouafik LH, Salem P, et al. Ontogenetic expression of peptidyl-glycine α-amidating monooxygenase mRNA in the rat pancreas. Biochem. Biophys. Res. Commun 168 (1989): 244-250.
57. Vera JC, Rivas CI, Fischbarg J, Golde DW. Mammalian facilitative hexose transporters mediate the transport of dehydroascorbic acid. Nature 364 (1993): 79-82.
58. A Banerjee Blood dehydroascorbic acid and diabetes mellitus in human beings Ann Clin Biochem 19 (1982): 65-70.
59. Patterson JW. The diabetogenic effect of dehydroascorbic and dehydroisoascorbic acids. J. Bwl. Chem 183 (195): 8148.
60. Domke I, Weis W. Reinvestigation of the diabetogenic effect of dehydroascorbic acid. Int J Vitam Nutr Res 53 (1983): 51-60.
61. Behrens WA, Madere R. Vitamin C and vitamin E status in the spontaneously diabetic BB rat before the onset of diabetes. Metabolism 40 (1991): 72-76.
62. Senmaru T, Yamazaki M, Okada H, et al. Pancreatic insulin release in vitamin C-deficient senescence marker protein-30/gluconolactonase knockout mice. J Clin Biochem Nutr 50 (2012): 114-118.
63. Bergsten P, Moura AS, Atwater I, Levine M. Ascorbic acid and insulin secretion in pancreatic islets. J Biol Chem 269 (1994): 1041-1045.
64. Pence LA, Mennear JH. Inhibition effect of dehydroascorbic acid on insulin secretion from mouse pancreatic islets. Toxicol Appl Pharmacol 50 (1979): 57-65.
65. Steffner RJ, Wu L, Powers AC, et al. Ascorbic acid recycling by cultured beta cells: effects of increased glucose metabolism. Free Radic Biol Med 37 (2004): 1612-1621.
66. Li Q, Parikh H, Butterworth MD, Lernmark Å, Hagopian W, et al. TEDDY Study Group. Longitudinal Metabolome-Wide Signals Prior to the Appearance of a First Islet

Autoantibody in Children Participating in the TEDDY Study. Diabetes 69 (2020): 465-476.

67. Li Q, Liu X, Yang J, Erlund I, Lernmark Å, et al. TEDDY Study Group. Plasma Metabolome and Circulating Vitamins Stratified Onset Age of an Initial Islet Autoantibody and Progression to Type 1 Diabetes: The TEDDY Study. Diabetes 70 (2021): 282-292.
68. Mattila M, Erlund I, Lee HS, Niinistö S, Uusitalo U, et al. TEDDY Study Group. Plasma ascorbic acid and the risk of islet autoimmunity and type 1 diabetes: the TEDDY study. Diabetologia 63 (2020): 278-286.
69. Wilson R, Willis J, Gearry R, Skidmore P, Fleming E, et al. Inadequate vitamin C status in prediabetes and type 2 diabetes mellitus: Associations with glycaemic control, obesity, and smoking. Nutrients 9 (2017): 997.
70. Seghieri G, Martinoli L, Miceli M, Ciuti M, D'Alessandri G, et al. Renal excretion of ascorbic acid in insulin dependent diabetes mellitus. Int J Vitam Nutr Res 64 (1994): 119-124.
71. Sinclair AJ, Taylor PB, Lunec J, Girling AJ, Barnett AH. Low Plasma Ascorbate Levels in Patients with Type 2 Diabetes Mellitus Consuming Adequate Dietary Vitamin C. Diabetes Med 11 (1994): 893-898.
72. Luc K, Schramm-Luc A, Guzik TJ, Mikolajczyk TP. Oxidative stress and inflammatory markers in prediabetes and diabetes. J Physiol Pharmacol 70 (2019).
73. Ellulu MS, Rahmat A, Ismail P, Khaza'ai H, Abed Y. Effect of vitamin C on inflammation and metabolic markers in hypertensive and/or diabetic obese adults: a randomized controlled trial. Drug Des Devel Ther 9 (2015): 3405-3412.
74. Ashor AW, Werner AD, Lara J, Willis ND, Mathers JC, et al. Effects of Vitamin C supplementation on glycaemic control: A systematic review and meta-analysis of randomised controlled trials. Eur J Clin Nutr 71 (2017): 1371-1380.
75. Jennings PE, Chirico S, Jones AF, Lunec J, Barnett AH. Vitamin C metabolites and microangiopathy in diabetes mellitus. Diabetes Res 6 (1987): 151-154.
76. Lamb MM, Myers MA, Barriga K, Zimmet PZ, Rewers M, et al. Maternal diet during pregnancy and islet autoimmunity in offspring. Pediatr Diabetes 9 (2008): 135-141.
77. Brekke HK, Ludvigsson J. Pediatr Diabetes 11 (2010): 244-250.
78. Mattila M, Hakola L, Niinistö S, Tapanainen H, Takkinen HM, et al. Maternal Vitamin C and Iron Intake during Pregnancy and the Risk of Islet Autoimmunity and Type 1 Diabetes in Children: A Birth Cohort Study. Nutrients 13 (2021): 928.