Scholars Academic Journal of Pharmacy
Abbreviated Key Title: Sch Acad J Pharm
ISSN 2347-9531 (Print) | ISSN 2320-4206 (Online)
Journal homepage: http://saspublishers.com

OPEN ACCESS

Pediatrics

Impacts of Diabetes Type 1 on the Heart of Children

Ahmad Mohammad Ahmad Shaban[1*], Saher Sharif Alrimawi[2]

[1]Specialist Pediatrician, Primary Health Care Corporation (PHCC), Qatar
[2]Consultant Pediatrician, Primary Health Care Corporation (PHCC), Qatar

DOI: 10.36347/sajp.2022.v11i11.001 | **Received:** 18.10.2022 | **Accepted:** 05.12.2022 | **Published:** 13.12.2022

***Corresponding author:** Ahmad Mohammad Ahmad Shaban
Specialist Pediatrician, Primary Health Care Corporation (PHCC), Qatar

Abstract **Review Article**

The current study conducted an in-depth analysis of the most recent findings to be published in the peer-reviewed scientific literature on the topic of the effects that having type 1 diabetes mellitus (T1DM) has on the hearts of young people. The authors conducted an in-depth analysis of the most recent articles that were released to the public. The findings of this study indicate that children who have type 1 diabetes are at a greater risk of developing cardiovascular events than children who do not have type 1 diabetes. It has been postulated that diabetic children have insulin resistance as well as an impaired lipid profile. This is a factor that raises the risk of cardiovascular events happening to the patient. Screening for cardiovascular changes is something that needs to be done for children who have type 1 diabetes as a part of the overall management of their diabetes.

Keywords: T1DM, children, cardiovascular events, insulin resistance, lipid profile.

1. INTRODUCTION

In the current study, the effects of diabetes type 1 on the cardiovascular problems that develop in diabetic children and adolescents were investigated. This article offers a concise overview of type 1 diabetes, cardiovascular events, and the links between these conditions.

2. An overview of type 1 diabetes

Type 1 diabetes was once called insulin-dependent diabetes (Khatib and Al'ash, 2021). Young-onset diabetes is characterized by a fundamental insulin shortage that requires daily insulin (Day, 2012). Type 1 diabetes requires insulin. Type 1 diabetes causes high blood sugar, gradual functional loss, and organ and tissue degradation. Type 1 diabetics lack insulin because their pancreatic islet cells are defective (Khatib and Al'ash, 2021). High blood glucose causes oxidative damage. Free radicals damage DNA, lipids, and proteins, causing stress. High hyperglycemia causes oxidative stress. In unhealthy persons, this can cause rapid hyperglycemia, non-enzymatic glycosylation, or protein and tissue damage (Khatib and Al'ash, 2021). Not in healthy persons. Type 1 diabetes involves increased urination, unsatisfied hunger and thirst, visual problems, intense tiredness, and weight loss (Chukwuma, 2018). Several epidemiological studies have verified the hallmarks of the disease, which include clinical disease in infancy and adolescence, and occasionally difficulty identifying type 1 diabetes from certain kinds of type 2 diabetes (T2DM) or autoimmune diabetes mellitus in adults (WHO, 2021). This is despite the fact that type 1 diabetes can affect persons of any age. In developed countries, most type 1 diabetics die quickly (Diaz-Valencia *et al*., 2015), either because they aren't well monitored or because they elude healthcare workers. Type 1 diabetes is a chronic, severe disease that affects children worldwide. In developed locations, children with type 1 diabetes have an eight- to tenfold higher chance of death than in less developed regions. According to what was apparently determined and reported, the internal gradient in T1DM incidence was reduced by 60% during epidemic periods. Epidemics also occurred. It's vital for the international exploration and characterization of type 1 diabetes, as well as morbidity, mortality, and healthcare. Diabetes economics, promotion, and the local and worldwide construction of training programs in diabetes epidemiology for prevention are also significant (WHO, 1990; Chukwuma, 1993; Day, 2012). The pathogenesis of type 1 diabetes in children is not well understood (Chukwuma, 1995). Type 1 diabetes in children has reached epidemic proportions worldwide, and this trend is anticipated to continue throughout the 21st century. Continuous evolution decreased the progression of type 1 diabetes-causing diseases. Understanding what causes

type 1 diabetes can help with treatment. In animal models, 1,3,4-thiadiazine-derived compounds reduced blood glucose, HbA1c, and insulin. These chemicals helped achieve the goal of eradicating diabetes-related problems. Type 1 diabetes may be categorized as a non-communicable illness in the future due to extensive study. It was designed as a model in the transition of the current global road regarding health and healthcare due to Europe and North America's rising illness load. With current information and understanding, it's impossible to stop. It's also impossible to describe and clarify the disease's burden, trends, prevalence rates, and implications in many nations (Day, 2012). Type 1 diabetes, caused by defective pancreatic beta cells, impairs autoimmune metabolism. Type 1 diabetes causes this. Insulin insufficiency and excessive blood glucose levels cause this problem. Environmental factors can hasten autoimmune disease signs in genetically predisposed children and adolescents. Type 1 diabetes has higher morbidity and mortality rates than type 2 but being less common. Studies show that type 1 diabetes is common (Gale, 2002). Despite being more common in children, 25% of type 1 diabetics are adults. Clinical features of type 1 diabetes include classic new onset, hyperglycemia in the absence of acidosis, a common symptom in childhood, diabetic ketoacidosis, and silent or asymptomatic detection, which occurs when some children are diagnosed with type 1 diabetes before the onset of clinical symptoms (Patterson *et al*., 2001). Diabetic ketoacidosis develops when glucose levels rise too high. Most type 1 diabetics have these symptoms (Khatib and Al'ash, 2021).

3. Epidemiology of diabetes

Type 1 (T1D) and type 2 (T2D) diabetes are spreading at an alarming rate worldwide, making public health a critical concern (Saeedi *et al*., 2019; Williams *et al*., 2020). Even among children and adolescents, type 1 and type 2 diabetes are developing rapidly. International Diabetes Federation estimates 128,900 new cases of type 1 diabetes in children and teens each year. More than 1,100,000 children and teens worldwide have type 1 diabetes. Researchers didn't question the notion that type 2 diabetes only affects adults until the early 1990s. The number of nations where youth are impacted by the sickness is rising alarmingly (Saeedi *et al*., 2019). These more prevalent dispositions can be attributed to a western-style lifestyle. Lack of physical exercise, increased calorie consumption, and reduced energy expenditure contribute to overweight and obesity in children (Lobstein *et al*., 2016). These difficulties affect practically all type 2 diabetic children and are particularly common in the juvenile population, where type 1 diabetes prevalence can approach 34% (Maffeis *et al*., 2018; Jones *et al*., 2019).

A total of 708 young people without diabetes tested positive for one of the circulating diabetes autoantibodies. According to the study (Ferrara-Cook *et al*., 2020), children with a high BMI and negative HLA haplotypes had a higher incidence of type 1 diabetes and numerous autoantibodies (BMI). Under-40 type 2 diabetics had impaired insulin secretion and detectable autoantibodies (Klingensmith *et al*., 2010). Children and adolescents with type 2 diabetes have a faster loss in beta-cell function than adults (Steinarsson *et al*., 2018).

4. Diabetes as a risk factor for developing cardiovascular events in children

Childhood and adolescence are important years for developing cardiovascular (CV) risk factors (Tanrikulu *et al*., 2017). The majority of diabetic children and adolescents already have cardiovascular risk factors when they are diagnosed (Jones *et al*., 2019). This shows that these factors are more common than expected among diabetes children and teens. According to this information, these risk factors may be present sooner than when diagnosed. Diabetes mellitus doubles the risk of cardiovascular disease, promotes early death from cardiovascular disease, and quadruples the mortality rate in young people (Svane *et al*., 2019). Obesity increases both specific and total mortality (Lindberg *et al*., 2020). Previous study on type 1 and type 2 diabetes has shown an increased risk for ischemic heart disease, macrovascular illnesses, and death, especially in type 2 diabetics aged 15 to 30 (Constantino et al., 2013). Longitudinal research of 6.840 people with type 1 diabetes and 1.518 people with type 2 diabetes found that 15- to 19-year-olds with type 2 diabetes had a higher risk of death (Reynolds *et al*., 2018). In type 1 diabetics, cardiovascular events and mortality have a negative connection with age of onset, suggesting the risk is higher the younger diabetes is detected (Rawshani *et al*., 2018). Cardiovascular events and mortality are negatively correlated with diabetes beginning age. The prevalence of two or more cardiovascular disease risk factors is larger in younger people with type 2 diabetes (92%) than with type 1 (14%), and it increases by 1.4% annually in type 2 patients, but not in type 1 patients (Kim *et al*., 2019). Younger people with type 2 diabetes are more likely to have cardiovascular disease risk factors (92% vs. 14%). This contradicts the finding that type 1 diabetes risk factors don't change over time. 72% of 272 young T2D patients acquired diabetes, compared to 32% of 1746 young T1D patients (Dabelea *et al*., 2017).

There are a variety of cardiovascular risk factors, some of which have been known for a long time and others of which we only recently learned, that can be targeted in juvenile diabetes patients (Pastore *et al*., 2020). First-symptom age and length of illness are unchangeable (Miller *et al*., 2019). In a large longitudinal study of 27.195 patients with type 1 diabetes and 135.178 controls, the age of initial diagnosis was inversely related to cardiovascular disease and overall mortality. It was confirmed. Women diagnosed before age 10 had a life expectancy 18 years

less than men (Rawshani *et al*., 2018). Younger type 2 diabetics are more likely to have micro- and macro-vascular complications (Dabelea *et al*., 2017). Younger patients with type 2 diabetes have a higher risk of cardiovascular disease. The length of the condition correlates with the prevalence of cardiovascular risk factors and the number of deaths from cardiovascular disease, myocardial infarction, revascularization, angina, and stroke (Kim *et al*., 2019). Recent research indicated similar CV risk rates in males and females (Peters *et al*., 2014). In the adult population, females have a reduced CV risk in pre-menopause. In contrast, adult females had a decreased CV risk post-menopause. In contrast to what has been reported for adult women, post-menopausal women had a lower risk of cardiovascular disease. Metabolism modulation is a modifiable risk factor for cardiovascular disease [30], and anthropometric parameters correlate with it. Children and adolescents with diabetes have high BMIs and waist circumferences, and high HbA1c levels are linked to macrovascular problems (Miller *et al*., 2019). Higher glucose variability, the quantity and amplitude of blood glucose variations, may be a cardiovascular disease risk factor (Lu *et al*., 2020). Glucose variability is more important than mean glycemia or HbA1c. Continuous subcutaneous insulin infusion and real-time continuous glucose monitoring can improve endothelial function in young type 1 diabetics (Jamiolkowska *et al*., 2016). Type 1 and type 2 diabetics both have insulin resistance. Pathophysiology of insulin resistance in juvenile type 1 diabetics differs from type 2 (Nadeau *et al*., 2010). Insulin-resistant type 1 diabetics have an increased cardiovascular risk (Khawandanah *et al*., 2019). Insulin resistance and type 1 diabetes can coexist, resulting in hybrid or double diabetes. Diabetes problems must be managed when they arise. Children with type 1 diabetes who had high systolic blood pressure also had thicker carotid intima-media (Schwab *et al*., 2010) demonstrates the importance of monitoring blood pressure. This finding implies a link between the two events. In young people with type 2 diabetes, microalbuminuria, another modifiable risk factor, increases proportionally with disease duration (Group *et al*., 2013). In young people with type 1 diabetes, this largely coincides with increasing arterial stiffness (Shah *et al*., 2015). A larger atherogenic lipid profile in diabetic children is linked to glycated hemoglobin, fasting glucose, age, disease duration, and insulin resistance (Flokas *et al*., 2020).

Miculis *et al*., (2012) conducted a study to determine if cardiorespiratory fitness (CRF) is linked to type 1 diabetic children's cardiovascular risk factors. Fifty diabetic children and adolescents ages 9 to 17 with 4.6 years of diabetes therapy participated in the study. Analyzed data included anthropometric, sexual maturation, and blood pressure. A 20-meter shuttle run was used to determine CRF level. Laboratory findings revealed glycated hemoglobin and fasting lipid levels. The statistical investigations used a 0.05 significance criterion, Pearson partial correlation, the t test, and one-way ANOVA. After accounting for body adiposity and sexual maturity, inverse relationships were found between CRF and TC, TG, TC/HDL-C, TG/HDL-C, non-HDL-C, and SBP. CRF and TC, TG, TC/HDL-C, and TG/HDL-C correlated. CRF and non-HDL-C cholesterol have similar connections. Gender correlated with weight Z score, BMI Z score, skinfold thickness, body fat percentage, and diastolic blood pressure. Boys' CRF was higher than girls. Both CRF and TC revealed substantial differences based on sexual maturity level. In children and adolescents with poorly treated Type 1 Diabetes (T1DM), CRF was inversely related to most lipid profile components and SBP. This connection existed despite increased body fat (Miculis *et al*., 2012).

People who suffer from diabetes mellitus type 1 have an increased risk of developing cardiovascular disease (CVD), which is the leading cause of death as well as the leading cause of morbidity (Laing *et al*., 2003). Individuals who do not have the condition are at a lower risk of developing cardiovascular issues, while those who do have the condition develop them at a younger age and experience them more frequently (Fornari *et al*., 2020). According to the findings of a large longitudinal study that was conducted in 2003 (Laing *et al*., 2003), patients who were diagnosed with type 1 diabetes had mortality rates that were higher than those for the general population across all age categories. This was the case regardless of the patient's age. Patients diagnosed with type 1 diabetes who experienced the onset of their condition before the age of 10 have a thirtyfold increased risk of developing coronary heart disease and acute myocardial infarction in their early adult years (Rawshani *et al*., 2018). This risk is due to the fact that patients with type 1 diabetes are more likely to have a higher cholesterol level. Up to the time when menopause begins, the overall incidence of cardiovascular events is lower in females than it is in males in the general population (Millstein *et al.*, 2018). On the other hand, among the population of persons who have diabetes type 1, it seems that the risk of cardiovascular disease is higher in females who have diabetes, particularly at younger ages (Millstein *et al*., 2018). However, the risk of cardiovascular disease is increased by a factor of two for men who have diabetes when compared with men who do not have diabetes (Sanjeevi *et al*., 2018). The risk of cardiovascular disease is increased by a factor of four for women who have diabetes when compared with women who do not have diabetes. There was a reduction in life expectancy of 17.7 years for women and 14.2 years for men when type 1 diabetes was diagnosed before the age of 10 in large cohort studies (Rawshani *et al*., 2018). These investigations also indicated that the standardized mortality ratio was higher for women than it was for males across all age ranges (Laing *et al*., 2003). It is possible that differences in long-term exposure to cardiovascular risk factors (CVRFs) between boys and girls beginning at a young age are the root cause of the

disparity in the risk of cardiovascular disease that exists between the sexes in the population of people with type 1 diabetes (Laing *et al*., 2003). The prevalence of diabetes-related microvascular problems is shown to be higher in adolescent girls than it is in teenage boys (Benitez-Aguirre *et al*., 2014). In addition, young women with type 1 diabetes who are between the ages of 20 and 29 have a mortality risk from ischemic heart disease that is 45 times higher than the mortality risk for women of the same age who do not have diabetes (Laing *et al*., 2003). It has been shown that diabetic females have less control over their blood sugar levels and have higher levels of glycated hemoglobin (HbA1c) than diabetes boys (Gerstl *et al*., 2008). No research has, as far as we are aware, been conducted to evaluate whether or not there are gender-related differences in the atherogenic dietary habits that could influence the risk of cardiovascular disease in children and adolescents who have type 1 diabetes. Higher levels of LDL-cholesterol (LDL-c), which is a significant indicator of the risk of cardiovascular disease, have been linked to a high-fat diet, particularly one that is abundant in saturated fatty acids (Toeller *et al*., 1999). This association has been made in connection with a high-fat diet that is particularly high in saturated fatty acids. There is evidence that children and adolescents who have type 1 diabetes consume a diet that is higher in fat and lower in fiber than what is advised (Powers *et al*., 2018). This evidence is consistent. In addition, there is consistent data that demonstrates that engaging in this practice results in poor glycemic control and an increased risk of death from cardiovascular events over the long run (Maffeis *et al*., 2020). It is generally agreed upon that diet is the CVRF that can be modified with the least amount of effort required. Therefore, it follows that it is essential to adhere to the dietary recommendations issued by the American Diabetes Association (ADA) and the International Society of Paediatric and Adolescents Diabetes (ISPAD), beginning with the beginning of one's diagnosis of diabetes and continuing throughout one's entire life, in order to lower one's risk of developing cardiovascular disease (Maahs *et al*., 2018).

5. CONCLUSIONS

There is a correlation between type 1 diabetes and the occurrence of cardiovascular events in children. There is a possibility that this condition was brought on by the development of insulin resistance as well as an impaired lipid profile that involved rising levels of cholesterol. Because of this, there is an increased risk of developing coronary diseases. The production of autoantibodies has also been linked to Type 1 Diabetes as well as atherosclerosis. We recommend that additional studies be carried out with the primary focus being placed on cardiovascular events in diabetic children and that screenings for cardiovascular issues be carried out on children as early as is practically possible.

REFERENCES

1. Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., ... & IDF Diabetes Atlas Committee. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes research and clinical practice*, *157*, 107843. doi: 10.1016/j.diabres.2019.107843.
2. Williams, R., Karuranga, S., Malanda, B., Saeedi, P., Basit, A., Besançon, S., ... & Colagiuri, S. (2020). Global and regional estimates and projections of diabetes-related health expenditure: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes research and clinical practice*, *162*, 108072. doi: 10.1016/j.diabres.2020.108072.
3. Lobstein, T., & Jackson-Leach, R. J. P. O. (2016). Planning for the worst: estimates of obesity and comorbidities in school-age children in 2025. *Pediatric obesity*, *11*(5), 321-325. doi: 10.1111/ijpo.12185.
4. Jones, S., Khanolkar, A. R., Gevers, E., Stephenson, T., & Amin, R. (2019). Cardiovascular risk factors from diagnosis in children with type 1 diabetes mellitus: a longitudinal cohort study. *BMJ Open Diabetes Research and Care*, *7*(1), e000625. doi: 10.1136/bmjdrc-2018-000625.
5. Maffeis, C., Birkebaek, N. H., Konstantinova, M., Schwandt, A., Vazeou, A., Casteels, K., ... & SWEET Study Group. (2018). Prevalence of underweight, overweight, and obesity in children and adolescents with type 1 diabetes: Data from the international SWEET registry. *Pediatric diabetes*, *19*(7), 1211-1220. doi: 10.1111/pedi.12730.
6. Ferrara-Cook, C., Geyer, S. M., Evans-Molina, C., Libman, I. M., Becker, D. J., Gitelman, S. E., ... & Type 1 Diabetes TrialNet Study Group. (2020). Excess BMI accelerates islet autoimmunity in older children and adolescents. *Diabetes Care*, *43*(3), 580-587. doi: 10.2337/dc19-1167.
7. Klingensmith, G. J., Pyle, L., Arslanian, S., Copeland, K. C., Cuttler, L., Kaufman, F., ... & TODAY Study Group. (2010). The presence of GAD and IA-2 antibodies in youth with a type 2 diabetes phenotype: results from the TODAY study. *Diabetes care*, *33*(9), 1970-1975. doi: 10.2337/dc10-0373.
8. Steinarsson, A. O., Rawshani, A., Gudbjörnsdottir, S., Franzén, S., Svensson, A. M., & Sattar, N. (2018). Short-term progression of cardiometabolic risk factors in relation to age at type 2 diabetes diagnosis: a longitudinal observational study of 100,606 individuals from the Swedish National Diabetes Register. *Diabetologia*, *61*(3), 599-606. doi: 10.1007/s00125-017-4532-8.
9. Tanrikulu, M. A., Agirbasli, M., & Berenson, G. (2016). Primordial prevention of cardiometabolic

risk in childhood. *Hypertension: from basic research to clinical practice*, 489-496.

10. Svane, J., Lynge, T. H., Pedersen-Bjergaard, U., Jespersen, T., Gislason, G. H., Risgaard, B., ... & Tfelt-Hansen, J. (2021). Cause-specific mortality in children and young adults with diabetes mellitus: a Danish nationwide cohort study. *European Journal of Preventive Cardiology*, *28*(2), 159-165. doi: 10.1177/2047487319836550.
11. Lindberg, L., Danielsson, P., Persson, M., Marcus, C., & Hagman, E. (2020). Association of childhood obesity with risk of early all-cause and cause-specific mortality: A Swedish prospective cohort study. *PLoS medicine*, *17*(3), e1003078. doi:10.1371/journal.pmed.1003078.
12. Constantino, M. I., Molyneaux, L., Limacher-Gisler, F., Al-Saeed, A., Luo, C., Wu, T., ... & Wong, J. (2013). Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. *Diabetes care*, *36*(12), 3863-3869. doi: 10.2337/dc12-2455.
13. Reynolds, K., Saydah, S. H., Isom, S., Divers, J., Lawrence, J. M., Dabelea, D., ... & Hamman, R. F. (2018). Mortality in youth-onset type 1 and type 2 diabetes: The SEARCH for Diabetes in Youth study. *Journal of diabetes and its complications*, *32*(6), 545-549. doi: 10.1016/j.jdiacomp.2018.03.015.
14. Rawshani, A., Sattar, N., Franzén, S., Rawshani, A., Hattersley, A. T., Svensson, A. M., ... & Gudbjörnsdottir, S. (2018). Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. *The Lancet*, *392*(10146), 477-486. doi: 10.1016/S0140-6736(18)31506-X.
15. Kim, G., Divers, J., Fino, N. F., Dabelea, D., Lawrence, J. M., Reynolds, K., ... & Liu, L. (2019). Trends in prevalence of cardiovascular risk factors from 2002 to 2012 among youth early in the course of type 1 and type 2 diabetes. The SEARCH for Diabetes in Youth Study. *Pediatric diabetes*, *20*(6), 693-701. doi: 10.1111/pedi.12846.
16. Dabelea, D., Stafford, J. M., Mayer-Davis, E. J., D'Agostino, R., Dolan, L., Imperatore, G., ... & SEARCH for Diabetes in Youth Research Group. (2017). Association of type 1 diabetes vs type 2 diabetes diagnosed during childhood and adolescence with complications during teenage years and young adulthood. *Jama*, *317*(8), 825-835. doi: 10.1001/jama.2017.0686.
17. Peters, S. A., Huxley, R. R., & Woodward, M. (2014). Diabetes as risk factor for incident coronary heart disease in women compared with men: a systematic review and meta-analysis of 64 cohorts including 858,507 individuals and 28,203 coronary events. *Diabetologia*, *57*(8), 1542-1551. doi: 10.1007/s00125-014-3260-6.
18. Pastore, I., Bolla, A. M., Montefusco, L., Lunati, M. E., Rossi, A., Assi, E., ... & Fiorina, P. (2020). The impact of diabetes mellitus on cardiovascular risk onset in children and adolescents. *International Journal of Molecular Sciences*, *21*(14), 4928. doi:10.3390/ijms21144928. PMID: 32664699; PMCID: PMC7403998.
19. Miller, R. G., Costacou, T., & Orchard, T. J. (2019). Risk factor modeling for cardiovascular disease in type 1 diabetes in the pittsburgh epidemiology of diabetes complications (EDC) study: a comparison with the diabetes control and complications trial/epidemiology of diabetes interventions and complications study (DCCT/EDIC). *Diabetes*, *68*(2), 409-419.
20. Lu, J., Ma, X., Shen, Y., Wu, Q., Wang, R., Zhang, L., ... & Zhou, J. (2020). Time in range is associated with carotid intima-media thickness in type 2 diabetes. *Diabetes technology & therapeutics*, *22*(2), 72-78. doi: 10.1089/dia.2019.0251.
21. Jamiołkowska, M., Jamiołkowska, I., Łuczyński, W., Tołwińska, J., Bossowski, A., & Głowińska Olszewska, B. (2016). Impact of real-time continuous glucose monitoring use on glucose variability and endothelial function in adolescents with type 1 diabetes: new technology—new possibility to decrease cardiovascular risk?. *Journal of Diabetes Research*, 2016, 4385312. doi: 10.1155/2016/4385312.
22. Nadeau, K. J., Regensteiner, J. G., Bauer, T. A., Brown, M. S., Dorosz, J. L., Hull, A., ... & Reusch, J. E. (2010). Insulin resistance in adolescents with type 1 diabetes and its relationship to cardiovascular function. *The Journal of Clinical Endocrinology & Metabolism*, *95*(2), 513-521. doi: 10.1210/jc.2009-1756.
23. Khawandanah, J. (2019). Double or hybrid diabetes: A systematic review on disease prevalence, characteristics and risk factors. *Nutrition & diabetes*, *9*(1), 1-9. doi: 10.1038/s41387-019-0101-1.
24. Schwab, K. O., Doerfer, J., Marg, W., Schober, E., Holl, R. W., & DPV Science Initiative and the Competence Network Diabetes mellitus. (2010). Characterization of 33 488 children and adolescents with type 1 diabetes based on the gender-specific increase of cardiovascular risk factors. *Pediatric diabetes*, *11*(5), 357-363. doi: 10.1111/j.1399-5448.2010.00665.x.
25. TODAY Study Group. (2013). Rapid rise in hypertension and nephropathy in youth with type 2 diabetes: the TODAY clinical trial. *Diabetes Care*, *36*(6), 1735-1741. doi: 10.2337/dc12-2420.
26. Shah, A. S., Wadwa, R. P., Dabelea, D., Hamman, R. F., D'Agostino Jr, R., Marcovina, S., ... & Urbina, E. M. (2015). Arterial stiffness in adolescents and young adults with and without type 1 diabetes: the SEARCH CVD study. *Pediatric diabetes*, *16*(5), 367-374. doi: 10.1111/pedi.12279.

27. Flokas, M. E., Zeymo, A., Mete, M., Anhalt, H., Rother, K. I., & Gourgari, E. (2020). Overweight and obese children with optimal control in the T1D Exchange Registry: How are they different from lean children with optimal control?. *Journal of Diabetes and its Complications*, *34*(4), 107513. doi: 10.1016/j.jdiacomp.2019.107513.
28. Miculis, C. P., de Campos, W., Gasparotto, G. S., Silva, M. P., Mascarenhas, L. P., & Boguszewski, M. C. (2012). Correlation of cardiorespiratory fitness with risk factors for cardiovascular disease in children with type 1 diabetes mellitus. *Journal of Diabetes and its Complications*, *26*(5), 419-423.
29. Laing, S. P. Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, Gatling W, Bingley PJ, Patterson CC. *Mortality from heart disease in a cohort of*, *23*, 760-765. https://doi.org/10.1007/s00125-003-1116-6.
30. Fornari, E., Piona, C., Rabbone, I., Cardella, F., Mozzillo, E., Predieri, B., ... & Maffeis, C. (2020). Cardiovascular risk factors in children and adolescents with type 1 diabetes in Italy: a multicentric observational study. *Pediatric diabetes*, *21*(8), 1546-1555. https://doi.org/10.1111/pedi.13123.
31. Millstein, R. J., Pyle, L. L., Bergman, B. C., Eckel, R. H., Maahs, D. M., Rewers, M. J., ... & Snell-Bergeon, J. K. (2018). Sex-specific differences in insulin resistance in type 1 diabetes: The CACTI cohort. *Journal of Diabetes and its Complications*, *32*(4), 418-423. https: //doi.org/10.1016/j.jdiacomp.2018.01.002.
32. Sanjeevi, N., Lipsky, L. M., & Nansel, T. R. (2018). Cardiovascular biomarkers in association with dietary intake in a longitudinal study of youth with type 1 diabetes. *nutrients*, *10*(10), 1552. https://doi.org/10.3390/nu10101552.
33. Benitez-Aguirre, P., Craig, M. E., Cass, H. G., Sugden, C. J., Jenkins, A. J., Wang, J. J., ... & Donaghue, K. C. (2015). Sex differences in retinal microvasculature through puberty in type 1 diabetes: are girls at greater risk of diabetic microvascular complications?. *Investigative ophthalmology & visual science*, *56*(1), 571-577. https://doi.org/10.1167/iovs.14-15147.
34. Gerstl, E. M., Rabl, W., Rosenbauer, J., Gröbe, H., Hofer, S. E., Krause, U., & Holl, R. W. (2008). Metabolic control as reflectet by HbA1c in children, adolescents and young adults with type-1 diabetes mellitus: combined longitudinal analysis including 27,035 patients from 207 centers in Germany and Austria during the last decade. *European journal of pediatrics*, *167*(4), 447-453. https://doi.org/10.1007/s00431-007-0586-9.
35. Toeller, M., Buyken, A. E., Heitkamp, G., Scherbaum, W. A., Krans, H. M. J., Fuller, J. H., & null the EURODIAB IDDM Complications Study Group. (1999). Associations of fat and cholesterol intake with serum lipid levels and cardiovascular disease: the EURODIAB IDDM Complications Study. *Experimental and clinical endocrinology & diabetes*, *107*(08), 512-521. https://doi.org/10.1055/s-0029-1232560.
36. Powers, M. A., Gal, R. L., Connor, C. G., Mangan, M., Maahs, D. M., Clements, M. A., & Mayer-Davis, E. J. (2018). Eating patterns and food intake of persons with type 1 diabetes within the T1D exchange. *Diabetes research and clinical practice*, *141*, 217-228. https://doi.org/10.1016/j.diabres.2018.05. 011.
37. Maffeis, C., Tomasselli, F., Tommasi, M., Bresadola, I., Trandev, T., Fornari, E., ... & Piona, C. (2020). Nutrition habits of children and adolescents with type 1 diabetes changed in a 10 years span. *Pediatric Diabetes*, *21*(6), 960-968. https://doi.org/10.1111/pedi.13053.
38. Chiang, J. L., Maahs, D. M., Garvey, K. C., Hood, K. K., Laffel, L. M., Weinzimer, S. A., ... & Schatz, D. (2018). Type 1 diabetes in children and adolescents: a position statement by the American Diabetes Association. *Diabetes care*, *41*(9), 2026-2044. https://doi.org/10.2337/dci18-0023.
39. Khatib, A. J., & Ali Al'ash, F. A. A. (2021). Diabetes types: Different etiology and similar therapeutic strategies complicate the clinical situation and worsen the outputs management. *J RNA Genomics*, 17(S1), 11-15.
40. Day, A. (2012). HbA1c and diagnosis of diabetes. The test has finally come of age. *Annals of clinical biochemistry*, *49*(1), 7-8.
41. Chukwuma Sr, C. (2018). Type 1 diabetes mellitus: issues, challenges and opportunities. *Journal: Edelweiss Applied Science and Technology*, 290-297.
42. WHO. (2021). Diabetes. World Health Organization.
43. Diaz-Valencia, P. A., Bougnères, P., & Valleron, A. J. (2015). Global epidemiology of type 1 diabetes in young adults and adults: a systematic review. *BMC public health*, *15*(1), 1-15.
44. WHO. (1990). Multinational project for childhood diabetes. WHO diamond project group. *Diabetes Care*, 13, 1062-1068.
45. Chukwuma Sr, C. (1993). Type I diabetic nephropathy: Clinical characteristics and economic impact. *Journal of diabetes and its complications*, *7*(1), 15-27.
46. Chukwuma Sr, C. (1995). Type II diabetic nephropathy in perspective. *Journal of Diabetes and its Complications*, *9*(1), 55-67.
47. Gale, E. A. (2002). The rise of childhood type 1 diabetes in the 20th century. *Diabetes*, *51*(12), 3353-3361.
48. Patterson, C. C., Dahlquist, G., Soltész, G., & Green, A. (2001). Is childhood-onset type I diabetes a wealth-related disease? An ecological analysis of European incidence rates. *Diabetologia*, *44*(3), B9-B16.