Environmental Triggers and Epigenetic Regulation in Type 1 Diabetes: A Review

Fuxin Chai

Department of Statistics and Probability, College of Natural Science, Michigan State University, East Lansing, Michigan, United States

fuxinchai@hotmail.com

Abstract. Type 1 diabetes (T1D) arises from autoimmune destruction of pancreatic β-cells, yet genetic predisposition alone cannot fully account for its onset. Environmental triggers and epigenetic regulation have emerged as contributors bridging external exposures with immune and metabolic dysfunction. This review synthesizes current evidence on three major non-genetic domains influencing T1D pathogenesis. The Environmental Triggers section focuses on vitamin D and enterovirus. Vitamin D is discussed for its potential role in immune tolerance, while enterovirus represents a well-supported infectious trigger associated with β-cell autoimmunity. The Epigenetic Regulation section highlights how epigenetic and multi-omics studies reveal and associate with biological mechanisms and T1D onset, via DNA methylation, histone modification, and non-coding RNA pathways. Collectively, these perspectives illustrate how environmental exposures can influence immune and transcriptional networks beyond genetic susceptibility. The review concludes by outlining future research priorities, including longitudinal multi-omics studies and the identification of modifiable epigenetic biomarkers, which may provide new insights in exploring disease mechanisms and foster the development of targeted prevention and therapeutic strategies for T1D.

Keywords: Type 1 Diabetes; Vitamin D; Enterovirus Infection; Epidemiology.

1. Introduction

Type 1 diabetes is a chronic autoimmune disorder characterized by immune-mediated destruction of pancreatic β-cells, resulting in insulin dependence. Over the past fifty years, research on HLA gene associations has laid the foundation for our understanding of T1D genetic risk [1]. The HLA region remains the strongest known genetic contributor [2][3]. However, even among monozygotic twins, disease discordance is frequently observed [4], indicating that non-genetic factors play a key role in disease initiation and progression.

Large-scale prospective efforts systematically evaluate early-life environmental exposures and their relationships with islet autoimmunity and the onset of type 1 diabetes (T1D) [5]. Among these environmental candidates, vitamin D status and enteroviral infection are the two triggers that have been intensively studied. Vitamin D has been linked in numerous observational studies to the risk of T1D, yet causality remains debated. In contrast, enteroviruses get more consistent epidemiological and pathological support as instigators of islet autoimmunity, potentially via well-defined mechanisms. These two factors thus represent complementary vantage points, one reflecting uncertainty in mechanism, the other elucidating a stronger mechanistic hypothesis.

Despite substantial effort into environmental association studies, the bridge from external exposures to immune-regulating remains largely speculative. To understand how environmental factors contribute to autoimmunity and β-cell injury, epigenetic regulation offers a compelling interface. DNA methylation, histone modifications, and non-coding RNAs mediate how environmental inputs can stably modulate gene expression without altering the DNA sequence. As argued by Minniakhmetov et al. [6], a modern view of T1D etiology necessarily integrates both genetic and epigenetic dimensions, highlighting that epigenetic remodeling may act as a mediator of environmental influence. The multi-omics approaches link the genome, epigenome, transcriptome, and metabolome.

In light of these considerations, this review aims to synthesize the current evidence on non-genetic determinants of T1D by focusing on three principal domains: Vitamin D, representing a widespread

but mechanistically uncertain environmental factor; Enterovirus, typifying a clear infectious trigger with unclear mechanistic pathways; Epigenetic and omics approaches, bridging environmental exposure with gene regulation and immune response. This review examines how environmental and epigenetic factors may converge to influence T1D susceptibility, thereby laying the groundwork for mechanistically informed prevention and intervention strategies through a comparative discussion of these themes.

2. Environmental Triggers and Epigenetic Regulation in Type 1 Diabetes

2.1 Vitamin D

Vitamin D has been proposed as a potential environmental factor influencing the development of type 1 diabetes. Vitamin D status is often low in children with T1D. Across cross-sectional and case–control studies, patients with type 1 diabetes consistently show lower circulating 25(OH)D than healthy peers. A meta-analysis reports a high prevalence of deficiency among pediatric T1D cohorts, with approximately half of participants affected [7]. Daskalopoulou et al. [8] systematically reviewed cohort, case–control, and cross-sectional studies involving children and adolescents (≤ 15 years) and found that most studies reported significantly lower serum 25(OH)D levels in those who developed T1D, particularly among genetically predisposed individuals. Collectively, these findings suggest a potential epidemiological association between low vitamin D levels and an increased susceptibility to T1D.

However, the strength and causality of this relationship remain debated, as other studies do not support a strong causal relationship between vitamin D status and T1D incidence. Nascimento et al. [9] filtered studies through a systematic review and quality assessment, finding that 50% of studies yielded a positive result in evaluating the effect of vitamin D supplementation on HbA1c. However, only one trial was rated as having positive methodological quality, with inconsistent overall evidence for glycemic control benefits. Manousaki et al [10] indicate no strong causal effect of genetically determined 25(OH)D on T1D risk, by using a two-sample Mendelian randomization analysis with single-nucleotide polymorphisms (SNPs) that relate to 25(OH)D levels in a large vitamin D genome-wide association study. Durá-Travé and Gallinas-Victoriano [11] conducted a comprehensive review of clinical and experimental studies assessing vitamin D supplementation in patients with T1D. They summarized data from randomized and observational trials, showing that supplementation often led to transient improvements in insulin sensitivity or HbA1c; however, results remained inconsistent due to small sample sizes, variable dosing, and heterogeneous study designs. Therefore, although vitamin D deficiency is prevalent among individuals with T1D, current evidence supports an epidemiological association rather than a direct causal relationship between vitamin D status and disease onset.

While epidemiological studies provide important clues, understanding the biological mechanisms by which vitamin D influences T1D pathogenesis is critical for developing targeted interventions. Several lines of evidence have elucidated potential immunological and molecular pathways. At the cellular immune level, He et al. [12] proposed that vitamin D may attenuate inflammation and oxidative stress by downregulating cathepsin G (CatG), thereby reducing $CD4^+$ T-cell activation and promoting a shift towards Th2/Treg responses while suppressing Th1/Th17 activity, ultimately protecting pancreatic β-cell integrity and intervening in the occurrence of type I diabetes. At the epigenetic level, Mazur et al. [13] reviewed vitamin D as a nutri-epigenetic factor, capable of shaping immune tolerance and inflammatory networks through DNA methylation, histone modifications, and regulation of non-coding RNAs (miRNAs and lncRNAs). Moreover, Cristelo et al. [14] explored the role of cathelicidin expression in T1D susceptibility. On promoting inflammation, β-cell injury can release self-DNA, which complexes with cathelicidin to activate Toll-like receptor 9 (TLR9) in macrophages and dendritic cells, triggering IFN-α production and amplifying inflammation. On the protective side, cathelicidin, induced by vitamin D, supports gut barrier integrity, maintains

microbiota homeostasis, and modulates immune responses, collectively contributing to β-cell preservation.

These mechanistic findings highlight that vitamin D's role in T1D extends beyond statistical associations. Current evidence supports a modulatory rather than a causal role for vitamin D, primarily through its influence on immune and epigenetic regulatory pathways. Rather than focusing solely on whether vitamin D deficiency directly causes T1D, future research should pay more attention on elucidating the underlying epigenetic mechanisms that mediate its immunomodulatory effects. Such an approach may provide a more comprehensive framework for understanding the disease mechanism and identifying new insights and strategies.

2.2 Enterovirus

Although the role and mechanisms of vitamin D in type 1 diabetes remain to be clarified, enteroviruses have been more consistently implicated as candidates for initiating islet autoimmunity and leading to T1D. As highlighted by Hyöty et al. [15], EVs stand out among environmental triggers due to the large amount of coherent evidence linking them to the early stages of autoimmunity. Epidemiological and pathological studies have repeatedly shown that exposure to EV is significantly associated with the initiation of IA and clinical T1D, making EV the most likely environmental trigger of T1D. Yang et al. [16] conducted a systematic review and meta-analysis of 25 observational studies, incorporating different sample sources, such as pancreas, PBMCs, serum, and detection methods, such as RT-PCR, immunohistochemistry, and serology. They reported an odds ratio of nearly 6 for the association between enterovirus infection and clinical T1D, with stronger effects observed in pancreatic tissue and in children. Complementarily, Wang et al. [17] analyzed 38 case–control studies and confirmed this relationship across different geographic regions, including Europe, Asia, Africa, and Latin America, indicating that the link between EV infection and T1D is not confined to specific populations or methodologies. Taken together, these findings indicate that enterovirus infection is associated with an increased risk of T1D initiation.

Based on the epidemiological evidence, it is important to consider how viruses may contribute to the development of type 1 diabetes. Alves Abrantes et al. [18] reported that multiple viruses have been proposed as potential environmental triggers of T1D, and enteroviruses have received the strongest support. These agents are hypothesized to influence β-cell autoimmunity through diverse immunological pathways, including molecular mimicry, bystander activation, and persistent low-grade infections.

Among them, enteroviruses have been the most extensively studied. Lloyd et al. [19] highlighted several non-exclusive mechanisms by which they could promote islet autoimmunity: (1) enhanced β-cell susceptibility due to increased expression of the Coxsackievirus–adenovirus receptor; (2) induction of endoplasmic reticulum stress and miRNA dysregulation, impairing β-cell homeostasis; (3) molecular mimicry and presentation of defective ribosomal products, fueling cross-reactive T-cell responses; (4) cytokine-mediated bystander damage amplifying local inflammation. These mechanisms provide a plausible framework for linking viral infections to β-cell loss and T1D onset.

Building on these mechanisms, recent findings indicate that miRNA dysregulation itself can serve as an epigenetic mechanism to explain the β-cell destruction. Yu et al. [20] demonstrated that extracellular vesicles released from immune cells carry specific miRNAs, such as miR-142-3p and miR-155, that are taken up by pancreatic β cells, where they suppress antiapoptotic genes and activate pro-inflammatory signaling cascades. These changes lead to mitochondrial dysfunction and apoptotic β-cell loss, indicating an epigenetic way to explain how viral-induced immune activation can cause the spread of impaired β-cell through miRNA transfer. This evidence supports the view that EV infection may influence T1D pathogenesis not only through immune-mediated injury but also via stable epigenetic influence on β-cell gene expression.

Direct histopathological evidence further strengthens this model. Rodriguez-Calvo et al. [21] reported the detection of enteroviral VP1 protein in pancreatic islets of T1D organ donors, frequently accompanied by HLA class I hyperexpression, which supports the concept of a persistent viral

presence shaping local immune activation. Complementary studies have also demonstrated the presence of enteroviral RNA in the pancreas and lymphoid tissues. In the DiViD study of newly diagnosed patients, Oikarinen et al. [22] identified EV RNA in pancreatic biopsies. Laiho et al. [23] extended these findings to organ donors, showing that EV RNA was more frequently detected in individuals with early autoimmunity or insulin-positive islets compared to those with long-standing type 1 diabetes (T1D). Together, these studies provide consistent biological evidence from both living patients and cadaveric donors, supporting the hypothesis that low-grade persistent EV infections may act at early stages of T1D pathogenesis.

Compared to focusing only on immune abnormalities and β-cell injury induced by extracellular vesicles, exploring the epigenetic responses triggered by EV infections and identifying corresponding molecular biomarkers may provide a more comprehensive understanding of β-cell regulatory mechanisms in T1D. Such investigations could also contribute to understanding how environmental exposures translate into epigenetic alterations during autoimmune processes.

3. Epigenetic Mechanisms Bridging Environment and Autoimmunity

3.1 Mechanistic Pathways

Beyond triggering immune activation, environmental factors may also contribute to the development of T1D by influencing epigenetic regulation. Building on the concept of gene–environment interaction, environmental triggers interface with genetic susceptibility through epigenetic programs that shape immune tolerance and β-cell function. Nutritional factors such as vitamin D and B-vitamins can modify DNA methylation, histone marks, and microRNA expression, thereby affecting immune regulation and inflammatory balance [24]. Likewise, viral infections have been shown to induce persistent epigenetic alterations in immune and pancreatic pathways, linking acute infection to long-term autoimmune susceptibility [25]. Collectively, these researches suggest that epigenetic mechanisms act as the link between environmental exposures and autoimmune dysregulation, providing new insights and mechanistic directions for future T1D research.

DNA methylation, histone modifications, and non-coding RNA are currently the most important and mainstream research directions in epigenetics. DNA methylation is among the most widely studied epigenetic alterations in T1D. Xie et al. [26] highlighted abnormal methylation at immune- and β-cell-related genes such as HLA, INS, and IL2RA, which may disrupt immune tolerance and increase β-cell vulnerability. Akil et al. [27] further noted that metabolic cofactors and nutritional inputs can influence these methylation patterns, leading to immune dysregulation and providing potential therapeutic targets for restoring a normal methylation balance. Histone modifications also play a significant role in shaping gene accessibility and transcriptional activity. Xie et al. [26] reported that aberrant acetylation and methylation of histones can alter chromatin structure, thereby modulating immune activation and β-cell stress responses. Akil et al. [27] expanded this view by highlighting the contribution of histone deacetylase (HDAC) dysregulation in immune imbalance and β-cell apoptosis, and proposed HDAC inhibitors as potential therapeutic candidates. Non-coding RNAs constitute another layer of epigenetic regulation. Xie et al. [26] described how altered miRNAs, such as miR-21, miR-34a, and miR-146a, can modulate immune signaling and β-cell function, promoting either pro-inflammatory or protective responses. Akil et al. [27] further proposed that inflammation-induced disruptions of the miRNA–mRNA network may amplify β-cell apoptosis, while long non-coding RNAs could fine-tune survival and stress pathways, highlighting their potential as biomarkers.

3.2 Empirical Evidence

Much empirical evidence supports this view. Čugalj Kern et al. [28] conducted an epigenome-wide DNA methylation analysis in peripheral blood samples from children and adolescents with recently diagnosed T1D, stratified by long-term glycemic control (HbA1c < 7% vs. > 8%). Using Illumina EPIC arrays, they identified more than 8,000 differentially methylated CpG sites annotated

to over 1,800 genes, many of which were involved in inflammatory signaling, immune regulation, and β-cell function. These findings indicate that even in the early stages of disease, and in the absence of chronic complications, dysregulated glycemic control is accompanied by widespread DNA methylation alterations that affect immune and metabolic pathways. Similarly, Paul et al. [29] analyzed sorted T cells, B cells, and monocytes from patients with T1D and matched controls and found that methylation variability was significantly higher across these immune effector cell types in T1D. Twin studies further support these associations. Stefan et al. [30] examined monozygotic twin pairs discordant for T1D and detected reproducible methylation differences across immune-related loci, demonstrating that epigenetic divergence can occur despite identical genetic backgrounds. Collectively, these findings suggest a relationship between epigenetic regulation and the development of type 1 diabetes.

More importantly, longitudinal evidence provides stronger indications of causality. Johnson et al. [31] followed 87 children who later developed T1D and 87 matched controls in the prospective DAISY cohort, analyzing serial blood samples from birth through pre-seroconversion stages using 450 K and EPIC methylation arrays. They identified differential trajectories of methylation change across multiple genomic regions, including HLA-DQ, INS, and IL2RA, long before the onset of autoantibodies or clinical symptoms. Some alterations were already detectable at birth, implying early-life epigenetic programming of immune risk. These data suggest that progressive methylation shifts compromise immune tolerance and increase β-cell vulnerability, providing sufficient evidence for a causal association. However, most analyses focus on single-layer methylation data and peripheral blood samples. To capture the complex interactions between epigenetic regulation, transcriptional activity, and metabolic pathways, future work could employ integrated multi-omics strategies that reveal the causal mechanisms underlying disease progression.

3.3 Muti-Omics Integration

To explore causal relationships and uncover the mechanisms related to epigenetic and metabolic regulation, integrated multi-omics approaches are increasingly recognized as essential. DNA methylation, histone modification, and non-coding RNA alterations represent central epigenetic mechanisms that drive immune imbalance and β-cell apoptosis in T1D. However, these processes rarely act in isolation. Single-layer analyses cannot distinguish primary regulatory events from downstream consequences, nor can they reveal how environmental inputs are translated into complex molecular outcomes. Integrating genomic, epigenomic, transcriptomic, and metabolomic datasets can delineate a causal cascade, progressing through epigenetic modification and transcriptional dysregulation, and culminating in metabolic dysfunction. Such integration is crucial for identifying the key regulatory pathways that link immune dysregulation to β-cell failure and for exploring potential therapeutic entry points within these complex networks. [6]

Based on this concept, Codazzi et al. [32] conducted a large-scale empirical effort to integrate multi-omics data in childhood T1D. They analyzed 146 newly diagnosed children with T1D using an integrated approach that combined whole-blood transcriptomic profiles, circulating immune factors, and serum metabolic hormones through an unsupervised Multi-Omics Factor Analysis. Twelve latent factors were identified, capturing shared variation across omics layers. However, none successfully distinguished clinical subtypes or correlated with parameters, such as age, HLA genotype or C-peptide levels. They concluded that multi-omics approaches remain constrained by late sampling and the use of non-specific tissue. Because blood profiles at diagnosis reflect a downstream immune state instead of early events, future studies should focus on longitudinal sampling and tissue-specific analyses to uncover causal relationship. These methodological limitations underscore the need for earlier and tissue-specific data in the multi-omics design to make epigenetic findings more relevant for clinical research.

The application potential of the integrative strategies has been further argued by Fyvie et al. [33]. They discussed the use of omics-based biomarkers as a promising way to monitor disease progression and treatment response in T1D. Examples include circulating microRNAs, β-cell-derived cell-free

DNA, and protein marker panels that can reflect β-cell stress and immune activity in real time. However, they also noted that current methods still face major technical challenges, such as low detection sensitivity, inconsistent results, and a lack of standardized validation. Future research integrating epigenomic, transcriptomic, proteomic, and metabolomic data may practice by generating multiplex biomarker panels capable of early diagnosis, patient stratification, and personalized intervention. In summary, multi-omics integration is both a technical advance and an important step toward connecting molecular research with practical strategies for early prevention and targeted treatment in T1D.

4. Research Outlook

Although research has explored the environmental and epigenetic determinants of Type 1 Diabetes, unresolved issue still persists in understanding causal relationships and in integrating environmental and epigenetic perspectives. From an environmental perspective, most evidence remains associative but not causal. The majority of studies rely on observational or cross-sectional designs that can demonstrate correlation, while temporal sequence or mechanistic linkage is rare. This limitation is evident in the two most representative environmental factors: vitamin D and enterovirus infection. The former shows a high prevalence of deficiency and broad epidemiological coverage but lacks consistent causal confirmation, whereas the latter displays a much stronger and more reproducible association with T1D, yet still exists molecular mechanisms incompletely resolved. These two examples represent most of the studied links between environmental exposures and T1D. They highlight the current state of the field, which is characterized by an abundance of associative evidence but still lacks direct causal validation. In this sense, vitamin D and enterovirus together illustrate that current environmental research on T1D requires more longitudinal and experimental studies to establish clear causal relationships.

From the epigenetic perspective, the principal limitation is the lack of connection between environmental exposures, molecular regulation, and immune or β-cell outcomes. As emphasized by Xie et al. [26], although environmental cues can reshape gene expression through epigenetic mechanisms, the basic molecular pathways remain poorly understood. Minniakhmetov et al. [6] similarly indicate that epigenetic studies in T1D remain fragmented, with most investigations focusing on either genetic or epigenetic aspects independently, rather than combining these layers into a unified framework.

Overcoming these limitations will require clearer methods and more practical research designs. To strengthen causal evidence, future work should focus more on longitudinal cohort studies. Such studies can record when environmental exposures occur, how they affect epigenetic changes, and when autoimmune reactions begin. This approach would enable the identification of triggers from consequences and the detection of early molecular changes that occur before β-cell autoimmunity develops. At the same time, multi-omics approaches are useful for linking different biological layers and explaining how environmental factors lead to immune changes. As Minniakhmetov et al. [6] pointed out, combining genomic, epigenomic, transcriptomic, and metabolomic data can reveal the mechanisms of interaction between environmental exposures and genetic risk, thereby reshaping immune and metabolic pathways. Using these integrative methods in well-defined cohorts will help identify shared molecular pathways that explain the difference of disease developments among individuals. Moreover, turning molecular findings into functional understanding is also essential. Promising epigenetic targets should be tested in both cell and animal models, and techniques such as targeted epigenetic editing or pharmacologic intervention can be used to confirm their causal relation. Focusing on longitudinal studies, multi-omics integration, and functional validation together provides a clear direction for turning associative results into real mechanistic and clinically useful insights in T1D research.

Future progress in this field depends on turning molecular discoveries into practical biomarkers and treatments. Finding reliable early-stage biomarkers is especially important for predicting risk,

tracking disease progression, and evaluating the basic mechanism of therapies. As indicated by Fyvie and Gillespie [33], biomarker panels that combine genomic, epigenomic, transcriptomic, and metabolic data could detect molecular changes that occur before symptoms appear, thereby enabling earlier and more precise disease staging. Equally important is the transition from association studies toward causal and mechanistic research. Combining longitudinal designs with multi-omics analysis can not only clarify how environmental exposures and epigenetic regulation contribute to autoimmunity but also reveal modifiable nodes for intervention. Understanding these mechanisms will also support the development of new drugs and diagnostic innovations, for instance, by finding molecular targets that could prevent β-cell destruction or slow disease progression.

Furthermore, achieving these goals will require broad collaboration and the development of ethically responsible research infrastructures. Large, multi-center studies with standardized methods, open data sharing, and strong ethical review are essential to ensure reproducibility and safety. Collectively, these efforts can accelerate the shift from descriptive association studies toward building a mechanistic foundation for prevention and therapy.

5. Conclusion

Type 1 diabetes arises from a multifactorial interplay of genetic predisposition, environmental exposures, and epigenetic regulation. This review highlights how vitamin D deficiency and enterovirus infection, two prototypical environmental triggers, shape immune tolerance and β-cell vulnerability through immunological and molecular pathways. Although vitamin D is more closely associated epidemiologically and enteroviruses show stronger causal evidence, both ultimately point toward the same principle that environmental stimuli can reprogram immune and metabolic networks beyond the genome itself.

Epigenetic research has revealed that DNA methylation, histone modification, and non-coding RNA dysregulation form the molecular bridge, connecting these exposures with autoimmune pathogenesis. Longitudinal and twin studies further indicate that such epigenetic signatures may precede clinical onset, suggesting their potential as predictive biomarkers. Nevertheless, most current studies remain fragmentary, often limited to single-layer analyses. Integrative multi-omics approaches that link genome, epigenome, transcriptome, and metabolome will be essential to delineate causal cascades and identify actionable molecular nodes.

In summary, understanding the mechanisms by which environmental and epigenetic factors shape immune tolerance and β-cell resilience represents a significant step toward uncovering the mechanisms of T1D. Integrating longitudinal and multi-omics studies will not only advance mechanistic insight but also support the development of predictive biomarkers and targeted preventive strategies for this autoimmune disease.

References

[1] Noble, Janelle A. “Fifty Years of HLA-Associated Type 1 Diabetes Risk: History, Current Knowledge, and Future Directions.” Frontiers in Immunology 15 (2024): 1457213. https://doi.org/ 10. 3389/ fimmu. 2024. 1457213.

[2] Noble, Janelle A., and Ana M. Valdes. “Genetics of the HLA Region in the Prediction of Type 1 Diabetes.” Current Diabetes Reports 11, no. 6 (2011): 533–42. https://doi.org/10.1007/s11892-011-0223-x.

[3] Jerram, Samuel T., and Richard David Leslie. “The Genetic Architecture of Type 1 Diabetes.” Genes 8, no. 8 (2017): 209. https://doi.org/10.3390/genes8080209.

[4] Triolo, Taylor M., Alexandra Fouts, Laura Pyle, Liping Yu, Peter A. Gottlieb, and Andrea K. Steck. “Identical and Nonidentical Twins: Risk and Factors Involved in Development of Islet Autoimmunity and Type 1 Diabetes.” Diabetes Care 42, no. 2 (2019): 192–99. https://doi.org/10.2337/dc18-0288.

[5] Rewers, Marian, Daniel Agardh, Suzanne Bennett Johnson, et al. “Unfolding the Mystery of Autoimmunity: The Environmental Determinants of Diabetes in the Young (TEDDY) Study.” Diabetes Care 48, no. 7 (2025): 1125–35. https://doi.org/10.2337/dc24-2886.

[6] Minniakhmetov, Ildar, Bulat Yalaev, Rita Khusainova, et al. “Genetic and Epigenetic Aspects of Type 1 Diabetes Mellitus: Modern View on the Problem.” Biomedicines 12, no. 2 (2024): 399. https:// doi. org/ 10.3390/biomedicines12020399.

[7] Yang, Xin, Min Chai, and Meng Lin. “Proportion of Vitamin D Deficiency in Children/Adolescents with Type 1 Diabetes: A Systematic Review and Meta-Analysis.” BMC Pediatrics 24, no. 1 (2024): 192. https://doi.org/10.1186/s12887-024-04683-5.

[8] Daskalopoulou, Maria, Magdalini Pylli, and Konstantinos Giannakou. “Vitamin D Deficiency as a Possible Cause of Type 1 Diabetes in Children and Adolescents up to 15 Years Old: A Systematic Review.” The Review of Diabetic Studies: RDS 18, no. 2 (2022): 58–67. https://doi.org/10.1900/RDS.2022.18.58.

[9] Nascimento, Bárbara Folino, Carolina F. F. Moreira, Eliana R. da Fonseca, et al. “Effects of Vitamin D Supplementation on Glycemic Control of Children and Adolescents with Type 1 Diabetes Mellitus: A Systematic Review.” Journal of Pediatric Endocrinology & Metabolism: JPEM 35, no. 8 (2022): 973–88. https://doi.org/10.1515/jpem-2022-0044.

[10] Manousaki, Despoina, Adil Harroud, Ruth E. Mitchell, et al. “Vitamin D Levels and Risk of Type 1 Diabetes: A Mendelian Randomization Study.” PLoS Medicine 18, no. 2 (2021): e1003536. https:// doi. org/ 10.1371/journal.pmed.1003536.

[11] Durá-Travé, Teodoro, and Fidel Gallinas-Victoriano. “Type 1 Diabetes Mellitus and Vitamin D.” International Journal of Molecular Sciences 26, no. 10 (2025): 4593. https://doi.org/ 10.3390/ ijms 26104593.

[12] He, Lian-Ping, Yu-Xin Song, Ting Zhu, Wei Gu, and Chang-Wei Liu. “Progress in the Relationship between Vitamin D Deficiency and the Incidence of Type 1 Diabetes Mellitus in Children.” Journal of Diabetes Research 2022 (2022): 5953562. https://doi.org/10.1155/2022/5953562.

[13] Mazur, Artur, Paulina Frączek, and Jacek Tabarkiewicz. “Vitamin D as a Nutri-Epigenetic Factor in Autoimmunity—A Review of Current Research and Reports on Vitamin D Deficiency in Autoimmune Diseases.” Nutrients 14, no. 20 (2022): 4286. https://doi.org/10.3390/nu14204286.

[14] Cristelo, Cecília, Alexandra Machado, Bruno Sarmento, and Francisco Miguel Gama. “The Roles of Vitamin D and Cathelicidin in Type 1 Diabetes Susceptibility.” Endocrine Connections 10, no. 1 (2021): R1–12. https://doi.org/10.1530/EC-20-0484.

[15] Hyöty, Heikki, Jutta E. Laiho, and Suvi M. Virtanen. “Environmental Factors in Type 1 Diabetes.” Cold Spring Harbor Perspectives in Medicine, November 25, 2024, a041590. https://doi.org/ 10.1101/ cshperspect. a041590.

[16] Yang, Sen, BiYing Zhao, Zhen Zhang, XiaoLin Dai, YiLi Zhang, and LanWei Cui. “Association between Enterovirus Infection and Clinical Type 1 Diabetes Mellitus: Systematic Review and Meta-Analysis of Observational Studies.” Epidemiology and Infection 150 (December 2021): e23. https://doi. org/10. 1017/ S0950268821002442.

[17] Wang, Kan, Fei Ye, Yong Chen, et al. “Association Between Enterovirus Infection and Type 1 Diabetes Risk: A Meta-Analysis of 38 Case-Control Studies.” Frontiers in Endocrinology 12 (2021): 706964. https:// doi.org/10.3389/fendo.2021.706964.

[18] Alves Abrantes, Jayra Juliana Paiva, Jenner Chrystian Veríssimo de Azevedo, Fernando Liberalino Fernandes, et al. “Viruses as a Potential Environmental Trigger of Type 1 Diabetes Mellitus (Review).” Biomedical Reports 20, no. 5 (2024): 81. https://doi.org/10.3892/br.2024.1770.

[19] Lloyd, Richard E., Manasi Tamhankar, and Åke Lernmark. “Enteroviruses and Type 1 Diabetes: Multiple Mechanisms and Factors?” Annual Review of Medicine 73 (January 2022): 483–99. https://doi.org/ 10. 1146/annurev-med-042320-015952.

[20] Yu, Yueyang, Mengyin Li, Yuxuan Zhao, et al. “Immune Cell-Derived Extracellular Vesicular microRNAs Induce Pancreatic Beta Cell Apoptosis.” Heliyon 8, no. 12 (2022): e11995. https://doi.org/ 10.1016/ j. heliyon. 2022. e11995.

[21] Rodriguez-Calvo, Teresa, Jutta E. Laiho, Maarit Oikarinen, et al. “Enterovirus VP1 Protein and HLA Class I Hyperexpression in Pancreatic Islet Cells of Organ Donors with Type 1 Diabetes.” Diabetologia 68, no. 6 (2025): 1197–210. https://doi.org/10.1007/s00125-025-06384-9.

[22] Oikarinen, Sami, Lars Krogvold, Bjørn Edwin, et al. “Characterisation of Enterovirus RNA Detected in the Pancreas and Other Specimens of Live Patients with Newly Diagnosed Type 1 Diabetes in the DiViD Study.” Diabetologia 64, no. 11 (2021): 2491–501. https://doi.org/10.1007/s00125-021-05525-0.

[23] Laiho, Jutta E., Sami Oikarinen, Sofia Morfopoulou, et al. “Detection of Enterovirus RNA in Pancreas and Lymphoid Tissues of Organ Donors with Type 1 Diabetes.” Diabetologia 68, no. 6 (2025): 1211–25. https://doi.org/10.1007/s00125-025-06359-w.

[24] Kohil, Amira, Maha Al-Asmakh, Mashael Al-Shafai, and Annalisa Terranegra. “The Interplay Between Diet and the Epigenome in the Pathogenesis of Type-1 Diabetes.” Frontiers in Nutrition 7 (2020): 612115. https://doi.org/10.3389/fnut.2020.612115.

[25] Mittal, Rahul, Nathanael Camick, Joana R. N. Lemos, and Khemraj Hirani. “Gene-Environment Interaction in the Pathophysiology of Type 1 Diabetes.” Frontiers in Endocrinology 15 (January 2024): 1335435. https://doi.org/10.3389/fendo.2024.1335435.

[26] Xie, Zhiguo, Christopher Chang, Gan Huang, and Zhiguang Zhou. “The Role of Epigenetics in Type 1 Diabetes.” Advances in Experimental Medicine and Biology 1253 (2020): 223–57. https://doi.org/10. 1007/ 978-981-15-3449-2_9.

[27] Akil, Ammira-Sarah Al-Shabeeb, Laila F. Jerman, Esraa Yassin, Sujitha S. Padmajeya, Alya Al-Kurbi, and Khalid A. Fakhro. “Reading between the (Genetic) Lines: How Epigenetics Is Unlocking Novel Therapies for Type 1 Diabetes.” Cells 9, no. 11 (2020): 2403. https://doi.org/10.3390/cells9112403.

[28] Čugalj Kern, Barbara, Jernej Kovač, Robert Šket, et al. “Exploring Early DNA Methylation Alterations in Type 1 Diabetes: Implications of Glycemic Control.” Frontiers in Endocrinology 15 (2024): 1416433. https://doi.org/10.3389/fendo.2024.1416433.

[29] Paul, Dirk S., Andrew E. Teschendorff, Mary A. N. Dang, et al. “Increased DNA Methylation Variability in Type 1 Diabetes across Three Immune Effector Cell Types.” Nature Communications 7 (November 2016): 13555. https://doi.org/10.1038/ncomms13555.

[30] Stefan, Mihaela, Weijia Zhang, Erlinda Concepcion, Zhengzi Yi, and Yaron Tomer. “DNA Methylation Profiles in Type 1 Diabetes Twins Point to Strong Epigenetic Effects on Etiology.” Journal of Autoimmunity 50 (May 2014): 33–37. https://doi.org/10.1016/j.jaut.2013.10.001.

[31] Johnson, Randi K., Lauren A. Vanderlinden, Fran Dong, et al. “Longitudinal DNA Methylation Differences Precede Type 1 Diabetes.” Scientific Reports 10, no. 1 (2020): 3721. https://doi.org/10. 1038/ s41598-020-60758-0.

[32] Codazzi, Valentina, Nicola Baldoni, Giulia M. Scotti, et al. “A Multi-Omics Integration Approach Relying on Circulating Factors Does Not Discern Subtypes of Childhood Type 1 Diabetes.” Communications Medicine 5, no. 1 (2025): 201. https://doi.org/10.1038/s43856-025-00922-7.

[33] Fyvie, Maxwell J., and Kathleen M. Gillespie. “The Importance of Biomarker Development for Monitoring Type 1 Diabetes Progression Rate and Therapeutic Responsiveness.” Frontiers in Immunology 14 (2023): 1158278. https://doi.org/10.3389/fimmu.2023.1158278.