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REVIEW

# Gut virome and diabetes: discovering links, exploring therapies

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**Abstract**
This review offers a comprehensive analysis of the intricate relationship between the gut virome and diabetes, elucidating the mechanisms by which the virome engages with both human cells and the intestinal bacteriome. By examining a decade of scientific literature, we provide a detailed account of the distinct viral variations observed in type 1 diabetes (T1D) and type 2 diabetes (T2D). Our synthesis reveals that the gut virome significantly influences the development of both diabetes types through its interactions, which indirectly modulate immune and inflammatory responses. In T1D, the focus is on eukaryotic viruses that stimulate the host's immune system, whereas T2D is characterized by a broader spectrum of altered phage diversities. Promisingly, in vitro and animal studies suggest fecal virome transplantation as a potential therapeutic strategy to alleviate symptoms of T2D and obesity. This study pioneers a holistic overview of the gut virome's role in T1D and T2D, its interplay with host immunity, and the innovative potential of fecal transplantation therapy in clinical diabetes management.

**Keywords** Gut · Virome · Diabetes 1 · Diabetes 2 · Host immunity

## Introduction

The human gut, a bustling ecosystem teeming with diverse microbes, has long been recognized for its critical role in health and disease. At the forefront of this microbiome is the gut virome, an ensemble of viruses that extend beyond the bacterial realm, influencing our immune responses, metabolic pathways, and overall well-being. The interplay between the gut virome and diabetes, a group of metabolic disorders affecting millions worldwide, is an area of research that has gained considerable traction. Recent studies have shed light on how the complex dynamics of viral populations within the gut might shape the trajectory of diabetes, offering new insights into disease mechanisms and therapeutic opportunities (Anderson 2023; Gavin et al. 2022).

This research endeavors to dissect the intricate relationship between the gut virome and diabetes, with a particular focus on type 1 and type 2 diabetes. We will traverse the landscape of current research to elucidate the potential mechanisms by which the gut virome could influence diabetes development and progression. By integrating findings from cutting-edge studies, we aim to provide a comprehensive overview of this burgeoning field, highlighting the transformative potential of the gut virome in diabetes research and clinical practice (Fan et al. 2023; Rasmussen et al. 2020). Our synthesis underscores the necessity for deeper exploration into the virome's role, paving the way for innovative diagnostic and therapeutic strategies that could revolutionize diabetes management.

## The human gut virome

The human virome, which comprises viruses that colonize the body by replicating in cells, also includes viruses that infect both prokaryotic and eukaryotic components of the microbiome (Koonin et al. 2021). The gut virome encompasses all viruses present in the human gastrointestinal tract, including numerous endogenous retroviruses, eukaryotic viruses, and the majority of bacteriophages that infect bacteria (Kumata et al. 2020). Recent advancements in shotgun metagenomic sequencing techniques have unveiled the rich

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diversity and populations of virus-like particles in the human body. These particles are approximately equal in number to bacterial and human cells with around $10^9$ virus-like particles per gram of feces (Liang and Bushman 2021), summing up to a total of $10^{13}$. Many viruses, however, remain undiscovered (Shkoporov and Hill 2019). Based on viral genome characterization, viruses in the human gut are categorized as either double-stranded or single-stranded DNA or RNA viruses (Fulci et al. 2021), as detailed in Table 1 below.

Single-stranded DNA viruses, such as Anelloviridae and Circoviridae, which are occasionally detected, may not be related to clinically relevant diseases (Mukhopadhya et al. 2019). However, double-stranded DNA viruses including Polyomaviridae, Adenoviridae, Papillomaviridae, and Herpesviridae, are associated with some infectious diseases (Almand et al. 2017), with the exception of Iridoviridae, Marseilleviridae, Mimiviridae, and Poxviridae. Furthermore, RNA viruses are more prevalent in the human gut, such as the double-stranded Reoviridae (Taboada et al. 2021) and single-stranded Picornaviridae, Virgaviridae. Some of these viruses, including certain single-stranded RNA viruses like Caliciviridae, Astroviridae, and Picornaviridae, are known to induce gastroenteritis. Additionally, other single-stranded RNA viruses, such as Retroviridae and Togaviridae, have been implicated in various diseases, although their association with gastroenteritis specifically requires further clarification (Lim et al. 2015).

Conversely, viral gut imbalance also encompasses a wide range of bacteriophage variations. Bacteriophages infect their hosts and may exploit the replication of their genome in bacterial cells or disrupt the processes of bacterial transcription or translation to facilitate virus particle replication (Babickova and Gardlik 2015). The highest diversity of bacteriophage groups is found within the order Caudovirales, which mainly includes the family Siphoviridae, Podoviridae, and uncultured marine phages, as well as the Microviridae family (Shkoporov et al. 2019). The most abundant bacteriophages in the human gut are those infecting Escherichia, followed by *Lactococcus* and *Streptococcus* (do Socorro Fôro Ramos et al. 2021). The imbalance between bacteriophages and bacteria can lead to various diseases in the host; thus, summarizing the relationship between the virome and diabetes can lay the groundwork for exploring new treatments, as well as prevention and management methods for diabetes.

## Virome and host immunity

The virome, comprising various viruses that coexist within the host, plays a pivotal role in shaping the host's immune system and maintaining intestinal homeostasis. Viruses in

**Table 1** Classification of gut viruses. This table categorizes viruses found in the human gut by genetic material (DNA or RNA), structure (single- or double-stranded), and prevalence (common, occasional, or less common). It also indicates associated diseases for each virus category

| Virus Category | Genetic Material | Structure | Prevalence in Human Gut | Associated Diseases | References |
|---|---|---|---|---|---|
| Double-stranded DNA viruses | DNA | Various | Common | Polyomaviridae, Adenoviridae, Papillomaviridae, Herpesviridae (except Iridoviridae, Marseilleviridae, Mimiviridae, Poxviridae) | Almand et al. 2017 |
| Single-stranded DNA viruses | DNA | Various | Occasionally detected | Anelloviridae, Circoviridae | Mukhopadhya et al. 2019 |
| Double-stranded RNA viruses | RNA | Various | Less common | Reoviridae | Taboada et al. 2021 |
| Single-stranded RNA viruses | RNA | Various | More prevalent | Picornaviridae, Virgaviridae, Caliciviridae, Astroviridae, Retroviridae, Togaviridae | Lim et al. 2015 |

the human gut survive by infecting host cells or bacteria to perform virus particle replication and maintain virulence, unlike bacteria, that can self-replicate independently (Seo and Kweon 2019). Additionally, bacteriophages can invade bacterial cells and sometimes host cells. If an imbalance occurs, it may indirectly induce inflammatory-related cell damage. Conversely, with the co-evolution of microbes and hosts, host cells may defend against gut viruses in various ways (Rostøl and Marraffini 2019). Research on the intricate interactions between the virome and host immunity, revealed a dynamic relationship that extends beyond the mere presence of viruses in the host (Li et al. 2021).

Eukaryotic virus infection-induced IFN-γ can also lead to antibacterial immune responses (Lee et al. 2018). The host uses pattern recognition receptors (PRRs) to recognize pathogenic viruses in the gut (Zhao et al. 2017). The host may combat gut viral infections, including ssRNA and dsRNA viruses, through Toll-like receptors (TLR) 3 and TLR7, followed by increased secretion of IFN-β (Yang et al. 2016). This indicates that enteric viruses can interact with the host's immune system to regulate inflammatory responses and maintain gut health by activating specific immune pathways. Some commensal viruses maintain intestinal immunity function via noncanonical RIG-I signaling (Liu et al. 2019), affecting the secretion of IL-15, as shown in Fig. 1. This study highlights the role of commensal viruses in regulating the host's mucosal immune surveillance and defense functions, particularly in the gut. Interestingly, human virus-specific memory T cells may highlight the potential of adoptively transferred T cell therapy for the treatment of chronic gut viral infections (Hanajiri et al. 2020). This has implications for immunotherapy, as it suggests that T cells targeting specific viruses can enhance the host's immune protection against a range of viral variants.

Concurrently, human virus-specific memory T cells may highlight the potential of adoptively transferred T cell therapy for the treatment of chronic gut viral infections (D'Arc et al. 2018). The changes in the gut virome are associated with the host's immune status and disease susceptibility, providing insights into the complexity of host-virus interactions. Specifically, changes in the gut virome may affect immune-mediated diseases. Variations in the intestinal virome that occur before the onset of autoimmunity in children predisposed to Type I diabetes suggest a potential role for the gut virome as an early indicator of autoimmune disease development. This insight could lead to the identification of biomarkers that may enable early diagnosis and intervention strategies. The enteric virome plays a crucial role in maintaining intestinal homeostasis and immunity by simultaneously activating the innate immune response,

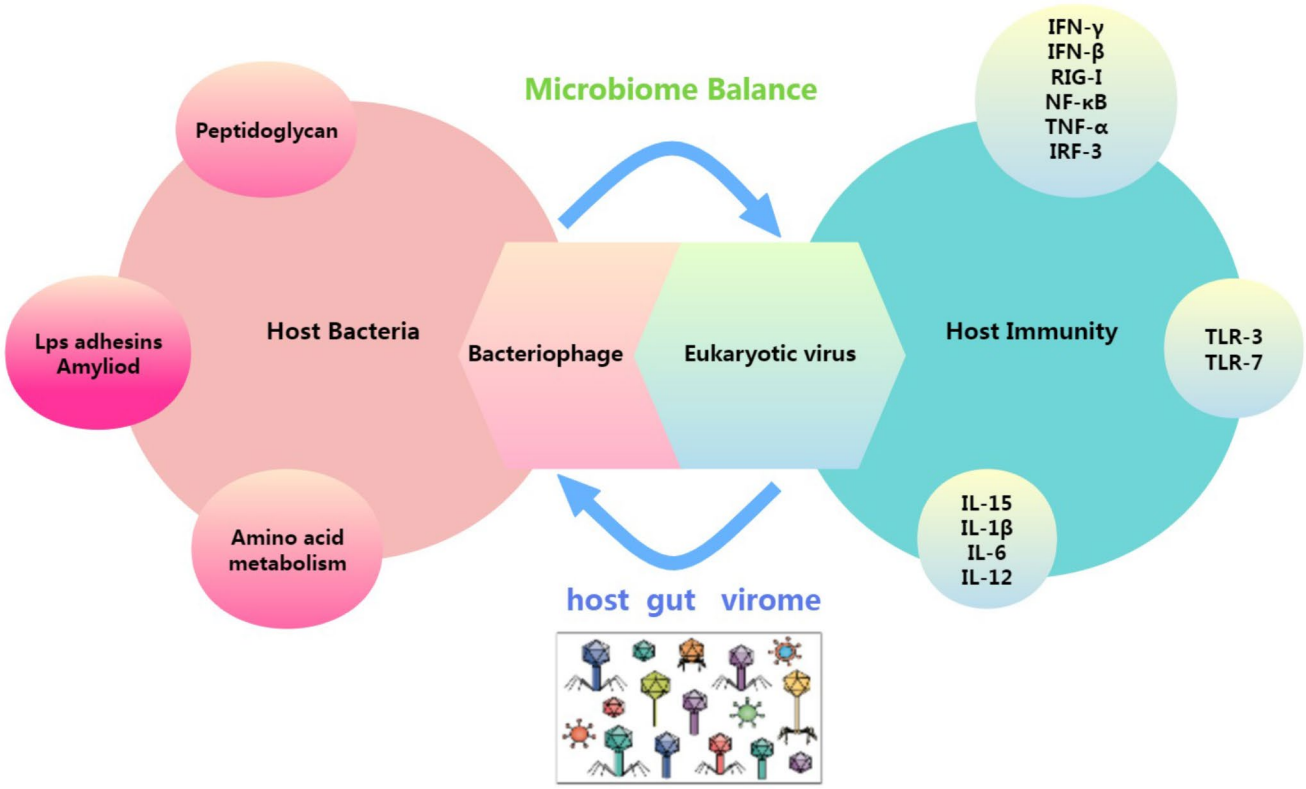


**Fig. 1** Schematic diagram of the mechanism of interaction between gut virome and the host. It shows how eukaryotic viruses and bacteriophages interact with host cells to modulate inflammatory responses and maintain intestinal homeostasis

which is essential for preserving a balanced microbial symbiosis (Metzger et al. 2018). Despite these pathways, the NF-κB–dependent proinflammatory cytokines production such as IL-1β, IL-6, IL-12, TNF-α,and IRF3,IRF7 constitute another essential sensor system (Lee and Baldridge 2019), particularly in recognizing viral RNA and initiating antiviral immune responses. In summary, a variety of viral components, including eukaryotic viruses and bacteriophages, contribute to the maintenance of intestinal equilibrium, the initiation of immune responses via Pattern Recognition Receptors (PRRs) and Toll-like Receptors (TLRs), as well as the modulation of proinflammatory cytokines, as depicted in Fig. 1. Hence, the virome's interaction with the host's immune system is a complex and multifaceted relationship. The gut virome can modulate immune responses, influence the host's susceptibility to infections, and contribute to the maintenance of intestinal homeostasis.

## Virome and bacteria

Bacteriophages, dominated by temperate phages in the human gut, are the most abundant viruses in the host virome (Neil and Cadwell 2018). Although there is a lower phage to bacteria ratio in the enteric virome than in some other environments, gut phages play vital roles in transforming the gut bacterial composition and transferring genes among bacterial host communities (Emencheta et al. 2023). Interactions between phages and bacterial hosts can affect the enteric immune system of the eukaryotic host (Matsuzawa-Ishimoto et al. 2020), due to the different lytic and lysogenic bacteriophage spatial distributions and life cycles, which induce the eubiosis of the gut microbiome (Happel et al. 2020). Bacteriophages are mainly located in intestinal mucosal surfaces and within the mucus, improving the interactions between mucin and Ig-like protein domains, a function mediated by the phage capsids for defense against bacterial pathogens (Almeida et al. 2019).

Phages invading bacteria can induce the release of proinflammatory factors, such as bacterial DNA, other components including peptidoglycan, LPS, and amyloid, inducing the host's protective response. Moreover, bacteriophage tails can bind bacterial LPS adhesins directly, which may dampen the host's immune response (Ongwae et al. 2022). Bacteriophage tail fibers can bind and sequester iron ions, influencing the virulence of pathogenic bacteria such as Salmonella typhimurium, Vibrio vulnificus, and Yersinia species (Nazik et al. 2017).

Bacteriophages can change the quantity and characteristics of bacteria in the human gut, regulating the ecological balance of microbial species and influencing the host's health, potentially inducing disease (Shuwen and Kefeng 2022). Phages can also effectively capture and split host bacteria by mediating horizontal gene transfer, changing the intestinal flora (Habusha et al. 2019), such as Staphylococcus aureus (Ruzin et al. 2001) and Salmonella strains (Johnson et al. 2017; Zhang et al. 2022). Virulence factors, such as toxin-coding genes, can be spread among the bacterial population, including *Vibrio cholerae*(Li et al. 2023)d *coli*(Koudelka et al. 2018), by phages.

Simultaneously, phages are involved in the regulation of bacterial metabolism. Research has shown that the concentration of Klebsiella phage is negatively correlated with the metabolism of cysteine, proline, and tryptophan (Yang et al. 2020). When *E. faecalis* is treated with the phage, the concentration of tyrosine fluctuates constantly (Hsu et al. 2019). Phages may affect the expression of metabolite-related genes in the host bacteria and the number of them, such as *Enterococcus*, influencing the level of lysozyme metabolite (Duan et al. 2019). However, besides the target bacteria, phages also affect the non-target bacteria community to maintain intestinal stability. For example, *E. coli* depletion through the phage T4 induces the growth inhibition of *B. fragilis* but promotes the growth of *B. vulgatus*(Hsu et al. 2019).

## Virome and T1D

Type 1 diabetes (T1D) is one of the most common chronic diseases in childhood (Mannering et al. 2019), characterized by insulin deficiency due to autoimmune destruction or functional loss of pancreatic β-cells (Piganelli et al. 2020) and the etiology of T1D is multifactorial, involving complex interactions between genetics, immune system dysregulation, and environmental factors.

The prevalence of T1D has been increasing globally, with a variable incidence rate that is influenced by geographical location, ethnicity, and genetic factors. Recent data indicate that the annual incidence of T1D in children under 15 years of age is approximately 2 per 100,000, though this rate can be significantly higher in certain populations (Lin et al. 2020). The rise in T1D prevalence underscores the importance of understanding its etiology and risk factors, including environmental and lifestyle factors that may contribute to the onset of the disease.

Gut microbiota dysbiosis, an imbalance in the gut microbial community, has been implicated in the pathogenesis of T1D. Studies have reported alterations in the gut microbiota composition of individuals with T1D, including reduced diversity and changes in the relative abundance of specific bacterial taxa (Gradisteanu Pircalabioru et al. 2021). These alterations are hypothesized to influence the development of T1D through various mechanisms, such as modulating the host's immune system, impacting the gut barrier function,

**Table 2** Virome changes in T1D and T2D from recent 6-Year studies. This table highlights differences in viral abundance and diversity between cases and controls, noting specific increases and decreases in particular viral families and species

| Study | Year | Case/control | Virome Variation | Increase | Decrease |
|---|---|---|---|---|---|
| T1D | | | | | |
| Herbert W. Virgin, etc. | 2017 | 11/11 | Lower abundance of Circoviridae-related sequences and low virome diversity in cases. | - | Myoviridae、Microviridae、Podoviridae |
| TEDDY Study Group, etc. | 2019 | 93/93 | Less Human mastadenovirus C. | - | *Enterovirus B* |
| Maria E. Craig, etc. | 2019 | 25/25 | Human bocavirus, and rotavirus A 、some noroviruses were more abundant in the infants of mothers with type 1 diabetes. | - | Human parechoviruses, coxsackievirus A6, Rhinovirus C, and torque teno Viruses. |
| Emma E. Hamilton-Williams, etc. | 2022 | 40/40 | Mastadenovirus, which has been associated with a reduced risk of T1D. | - | - |
| Maria E.Craig, etc. | 2019 | 45/48 | Higher abundance of enterovirus A species in the gut of children with islet autoimmunity. | - | - |
| **T2D** | | | | | |
| Chenli Liu, etc. | 2018 | 71/74 | A significant increase in the number of gut phages in the T2D group and, in particular, identified 7 pOTUs specific to T2D. | - | - |
| Chang Liu, etc. | 2020 | 17/29 | The abundance of *Enterobacteriaceae* phage in the gut was significantly increased. | Phages in Klebsiella bacteria and Shigella bacteria | |
| Siew C. Ng, etc. | 2021 | 128/101 | 17 differentially abundant viruses were identified between ObT2 and lean controls in Kunming. | Micromonas pusilla virus, Cellulophaga phage, Bacteroides phage, and Halovirus | 13 viral species, including Hokovirus, Klosneuvirus, and Catovirus, etc. |
| Yi Zhang, etc. | 2023 | 41/49 | 81 viral species were identified to be significantly altered in T2D subjects, including a decrease in some phages. | - | Flavobacterium phage and Cellulophaga Phage. |

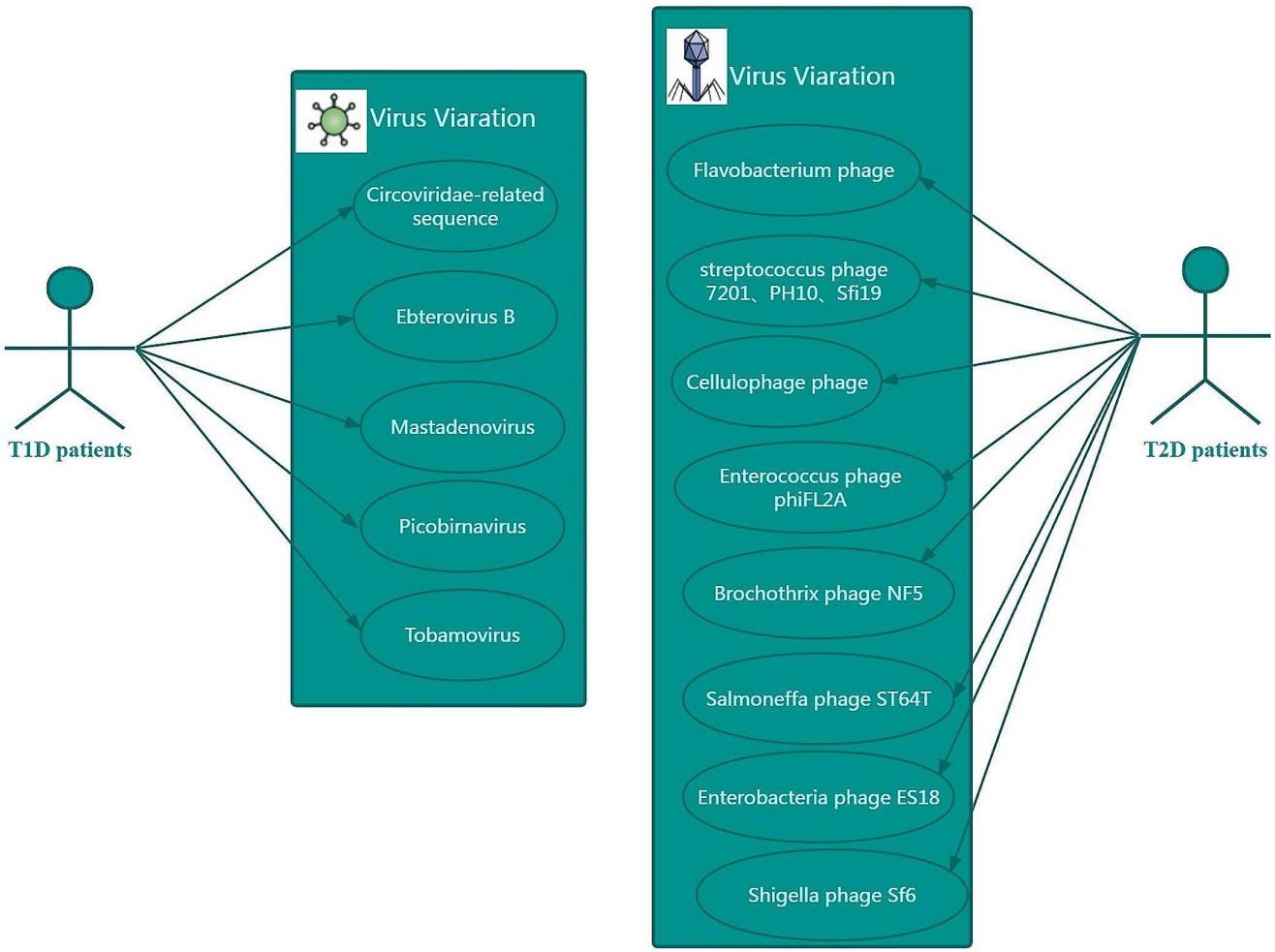


**Fig. 2** Main Viral Variations in T1D and T2D Hosts. This figure delineates the differential gut virome changes between T1D, marked by variations in eukaryotic viruses, and T2D, characterized by altered phage diversity

and altering metabolic pathways. The interplay between the gut virome and the host metabolism is a critical area of research, as it may provide insights into the complex interactions between viral elements and the host's metabolic health. Strong evidence supports that enteroviruses are closely related to T1D (Balke et al. 2018; Isaacs et al. 2021). Emerging research suggests that the gut virome could influence insulin sensitivity and glucose homeostasis, potentially contributing to the development of T1D (Vatanen et al., 2023). With the development of next-generation sequencing technology, research has shown that some viruses could trigger T1D (Anderson 2023). Enteroviruses and bacteriophages, across all these classifications, exhibit alterations at the onset of pediatric Type 1 Diabetes Mellitus (T1DM), although they are difficult to detect.

Manering et al. (Mannering et al. 2019) and Piganelli et al. (Piganelli et al. 2020) have contributed to the understanding of how β-cell stress and the subsequent presentation of neo-epitopes can trigger autoimmunity in T1D. The concept of neo-epitopes, which are cryptic self-proteins unveiled due to tissue damage or stress, has added a new dimension to the autoimmune process in T1D, where viral infections may play a role in inducing β-cell stress. Research has shown that children with T1D have less viral diversity and a lower abundance of Circoviridae-related sequences compared to healthy controls (Rodriguez-Calvo and von Herrath 2015). The temporal dynamics of Shannon diversity and changes in richness exhibit distinct patterns among the families Microviridae, Myoviridae, and Podoviridae (Zhao et al. 2017). However, prolonged Enterovirus B (EV-B) infections, rather than short-duration EV-B infections alone, may be related to the production of islet autoimmunity but not T1D in some young children (Vehik et al. 2019). These studies have identified an association between enterovirus infections and the onset of islet autoimmunity, suggesting that viral infections may contribute to the autoimmune destruction of pancreatic β-cells.

Other research has shown that the gut virome profile in infants whose mothers have type 1 diabetes exhibits a higher prevalence and greater number of viruses after more in-depth data acquisition (Kim et al. 2020). Mastadenovirus, which is associated with a reduced risk of T1D, changes the metaproteome, shifting the function of the gut microbiota (Gavin et al. 2022). These findings point to a possible role of the gut microbiome in the modulation of immune responses and the development of T1D. More importantly, research has shown that there are more picobirnaviruses and tobamoviruses observed in pregnant women with T1D, and 77 viruses exist differently between the two maternal groups, especially containing 88 types of enterovirus B (Kim et al. 2019). These data prove that significant differences exist between the gut virome of T1D patients and control groups (Fuhri Snethlage et al. 2021).

Viral infections may induce β-cell stress, leading to the presentation of neo-epitopes and the activation of autoimmunity. The influence of the gut microbiome on immune responses and its potential role in modulating T1D risk in genetically predisposed individuals are areas of active research. These findings open up new avenues for the prevention and treatment of T1D, potentially through modulating the gut virome and managing immune responses to viral infections. Nevertheless, more large-scale studies may be needed to draw more precise conclusions (Elhag et al. 2020) about the relationship between the inflammatory response and changes of the virome.

## Virome and T2D

Type 2 diabetes (T2D) is a common chronic metabolic disease worldwide, resulting from a combination of genetics, diet, and lifestyle (Harding et al. 2019; Santiago-Rodriguez and Hollister 2019). Several findings have suggested that disease-specific gut viromes are associated with T2D (Rasmussen et al. 2020); However, the relationship has not been fully illustrated, providing new clues for the diagnosis and treatment of the disease. Recent studies have highlighted the importance of the gut virome in the etiology and progression of T2D. In particular, the gut virome of T2D patients has been shown to undergo substantial alterations in T2D patients, which are characterized by a decrease in viral diversity and changes in specific virus species. These alterations can disrupt the intricate balance between viral and bacterial populations, leading to metabolic dysregulation and inflammation, key factors in the development of T2D and its complications, such as diabetic nephropathy (DN) (Fan et al. 2023). The studies have revealed that T2D subjects, especially those with DN, exhibited significantly lower viral richness and diversity compared to healthy controls. The researchers have identified 81 viral species that were significantly altered in T2D subjects, with a decrease in some phages, such as Flavobacterium phage and Cellulophaga phage. This reduction in viral diversity and specific changes in the virome composition can lead to a loss of viral functions, particularly those related to phage lysis of host bacteria, which are crucial for maintaining a healthy gut microbiota. Consequently, the disruption of viral-bacterial interactions observed in T2D and DN patients can have profound effects on the host's metabolism. The role of the gut virome in modulating the host's immune response and nutrient absorption is particularly relevant in the context of T2D, where inflammation and insulin resistance are central pathological features (Fan et al. 2023).

Moreover, the complex relationship between the gut virome and type 2 diabetes mellitus (T2DM) has been increasingly recognized in recent clinical studies, highlighting the potential of the gut virome as a key player in the pathophysiology of metabolic diseases. A clinical experiment conducted in Hong Kong provided compelling evidence of the gut virome's role in obesity and T2DM, which showed that obese subjects with T2DM had lower gut viral richness and diversity compared to lean controls (Yang et al. 2021) and 17 differentially abundant viruses were identified. This observation suggests that alterations in the gut virome may contribute to the metabolic disturbances characteristic of T2DM. These findings were complemented by another investigation, which observed a significant increase in gut phage numbers in the T2DM group compared to the control group, as reported by Ma etal. (Ma et al. 2018). An important study concluded that a consortium of eight phages, including Streptococcus phage PH10, Streptococcus phage 7201, Enterococcus phage phiFL2A, Brochothrix phage NF5, Streptococcus phage Sfi19, Salmonella phage ST64T, Enterobacteria phage ES18, and Shigella phage Sf6, could distinguish T2D patients from non-diabetic subjects with an AUC > 0.995 (Chen et al. 2020). This high level of discrimination suggests that these specific phages may serve as potential biomarkers for T2DM, offering a novel approach to disease diagnosis and potentially treatment.

In addition to these clinical findings, in vitro and animal model research has provided valuable insights into the therapeutic potential of modulating the gut virome. A groundbreaking study by Rasmussen et al. (Rasmussen et al. 2020), demonstrated that fecal virome transplantation could ameliorate symptoms of T2DM and obesity in a murine model. This intervention not only reduced the metabolic complications associated with these conditions but also underscored the feasibility of using virome-based therapies for the treatment of human metabolic diseases. Therefore, The identification of differentially abundant viruses, the correlation of specific phages with T2DM, and the successful use of fecal

virome transplantation in animal models collectively point towards the gut virome as a promising target for the diagnosis, monitoring, and treatment of T2DM and associated metabolic disorders.

## Conclusion

This study concluded that the virome interferes with the development of T1D and T2D in multiple ways by interacting with both human cells and the bacteriome, indirectly affecting immunity or inflammatory responses. The variations in the gut virome in T1D are focused on eukaryotic viruses, while greater phage diversity are altered in T2D patients, as depicted in Table 2; Fig. 2.

The in vivo mouse model has indicated the effectiveness of fecal virome transplantation therapy for T2D and obesity, which may be extended to humans in the time to come. However, to date, there is no established viral marker that can universally distinguish diabetes types across different regions, due to the limited number of diseased cases and the depth of data sequencing and statistical analysis. The mechanism of how viral diversity specifically influences the host immune response to diabetes is still unclear and requires more specific and detailed research in the future. Further research is needed to fully understand the mechanisms by which the gut virome interacts with the host's metabolic processes and to develop potential therapeutic strategies that target the gut virome to prevent or treat diabetes. As our knowledge of the gut virome expands, it is likely that new insights into the prevention and management of diabetes will emerge, offering hope for improved health outcomes for individuals living with this chronic condition.

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**Data availability** No datasets were generated or analysed during the current study.

## Declarations

**Competing interests** The authors declare no competing interests.

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