Is there any association between gut microbiota and type 1 diabetes? A systematic review

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Abstract

Introduction: Type 1 diabetes (T1D) is the second most common autoimmune disease among children. There is evidence suggesting that dysbiosis of some gut colonizing bacteria are associated with the pathogenesis of T1D. However, these studies are still controversial and a systematic review was conducted to evaluate the association between gut microbiota and T1D.

Methods: A systematic search was carried out in Medline (Via Pubmed) and Embase from January 2000 to January 2019 for all original cross-sectional, cohort, case–control or nested case–control studies investigating the association between gut microbiota and T1D.

Results: Of 568 articles identified, 26 studies met the inclusion criteria. The total population study of these articles consists of 2600 children (under 18 years old) and 189 adults. Among the included studies, 24 articles confirmed the association between gut microbiota dysbiosis and T1D. The most common bacterial alterations in T1D patients included Bacteroides spp., Streptococcus spp., Clostridium spp., Bifidobacterium spp., Prevotella spp., Staphylococcus spp., Blautia spp., Faecalibacterium spp., Roseburia spp., and Lactobacillus spp.

Conclusion: Our study showed a significant association between alterations in intestinal microbial composition and T1D; however, in some articles, it is not clear which one happens first. Investigation of altered gut microbiota can help in the early detection of T1D before seropositivity. Targeted microbiome modulation can be a novel potential therapeutic strategy.

Keywords: Type 1 diabetes, Microbiota, Dysbiosis

Introduction

Type 1 diabetes (T1D) is the second most common autoimmune disease among children. It is accompanied by many complications and has life-long morbidity [1]. The incidence of T1D is increasing universally and accounts for 5–10% of all diabetic morbidity [2]. T1D is a chronic autoimmune inflammatory process that affects insulin-producing beta cells of the pancreas, results in less insulin production [3]. Destruction of 90% of beta cells is a critical point that clinical manifestations emerge [4]. Because of the early onset of disease and chronicity, T1D is of great importance. Previous animal and human studies have shown the role of genetic factors like human leukocyte antigen (HLA) DQ and DRB in the pathogenesis of disease but recent studies propose the significant role of environmental factors such as gut colonizing bacteria [5]. Gut microbiota has an important role in the regulation of metabolism, systemic and local immunity [6]. From birth to age 3, gut
microbiota undergoes a lot of changes and the microbiota composition of a 3-year-old child is similar to that of an adult [7]. The most important factors affecting gut microbiota include the type of delivery [8], breastfeeding [9] or bottle feeding, maternal microbiota composition, mother’s diet during pregnancy and the western diet [5, 10–13], contact with peers, environment, and use of antibiotics [14–17]. Gut dysbiosis, an imbalance of the microbial communities, can be associated with metabolic disorders, obesity, insulin resistance, Type 2 diabetes (T2D), inflammatory bowel disease, celiac disease and immunity dysfunction [18–20]. Lately, there is evidence suggesting the correlation between dysbiosis and pathogenesis of T1D [21]. However, these studies are still controversial and need further investigation; Thus, we carried out a systematic review about the association between gut microbiota and T1D according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [22].

Materials and methods

Search strategy

A systematic search was carried out in Medline (Via Pubmed) and Embase from January 2000 to January 2019. Medical Subject Headings (MeSH) were “gastrointestinal microbes”, “dysbiosis”, “gut microbiota”, “gut bacteria”, “gut microbes” combined with “type 1 diabetes mellitus”. Lists of references of selected articles and relevant review articles were hand-searched to identify further studies. Only studies written in English were selected.

Study selection

Two reviewers independently performed the review of titles and abstracts and chose those fitting selection criteria for full-text evaluation. Discrepancies were discussed with a third reviewer. All original cross-sectional, cohort, case–control or nested case–control studies investigating the association between gut microbiota and T1D patients were considered. The following articles were excluded: animal studies, case reports, reviews, and editorials.

Data extraction

The following variables were extracted: first author; year of publication; study duration, type of study, country/ies where the study was conducted; the number of cases with T1D; age; gender; microbiota analysis technique; modifications of intestinal microbiota and modifications of biochemical and immunological factors. Data were independently collected by two authors.

Results

The selection process of articles is shown in Fig. 1. Twenty-six articles were included and classified into 16 case–control studies [18, 21, 23–36], 6 cohort studies [37–42], 2 cross-sectional studies [5, 43] and 2 nested case–control studies [44, 45]. Four of these studies were conducted in the USA, three in Italy, three in Finland, two in China, two in Spain and others in Netherland, Germany, Turkey, UK, Portugal, Poland, Russia, Mexico, Brazil, Australia, Czech Federation, and France. The population of these articles consists of 2600 children (under 18 years old) and 189 adults. The most applied techniques for detection and assessment of gut microbiota in stool samples where PCR, real-time quantitative PCR, 16s rRNA sequencing, microarray analysis, proteomics and quantitative cultures of stool samples (Table 1).

Gut microbiota and type 1 diabetes

Twenty-four out of twenty-six articles confirmed the association of T1D and gut microbiota dysbiosis. In one study alterations could not be attributable to T1D [23] and one of the articles is only a preliminary study and doesn’t have any obvious conclusion yet [21] (Table 2). The most common bacterial alterations in T1D patients group versus healthy individuals included Bacteroides spp., Streptococcus spp., Clostridium spp., Bifidobacterium spp., Prevotella spp., Staphylococcus spp., Blautia spp., Faecalibacterium spp., Roseburia spp., and Lactobacillus spp. Details indicating the altered bacteria are shown in Table 3.

The relationship between intestinal microbiota and HbA1C, inflammatory mediators and serum zonulin level

Some articles reported evidence of an association between HbA1C level and bacterial groups such as Blautia spp. count and Firmicutes:Bacteroidetes ratio (F:B ratio) [18, 33]. Murri et al. [26] in 2013 by designing a case–control study noticed the HbA1C level affected Clostridium spp. positively and F:B ratio negatively in both uni and multivariate statistical analysis. Univariate statistical analysis also showed that Bifidobacterium spp. and Lactobacillus spp. may affect HbA1C levels [26]. On the contrary, Alkanani et al. [5] reported that bacterial alterations in the case group were not associated with the HbA1C level.

There is an elevated level of TNF-α expression in lamina propria of intestinal biopsy in T1D patients in comparison with healthy individuals [27]. Higuchi et al. [34] reported a negative correlation between TNF plasma level and Proteobacteria and Clostridiaceae abundance. In another study, increment of Bacteroides spp. and...
decrement of *Roseburia* spp. was correlated with TNF-α level [33].

Interleukin-6 has an important correlation with Ruminococcaceae abundance as reported by the Higuchi et al. study [34]. Increase of *Bacteroides* spp. and decrease of *Roseburia* spp. abundance is correlated with serum IL-6 level [33].

According to Leiva-Gea et al. [33] an increase in *Bacteroides* spp. and *Veillonella* spp. and decrease in *Bifidobacterium* spp., *Roseburia* spp. and *Faecalibacterium* spp. was associated with serum IL-1β; in addition, an increase of *Streptococcus* spp. and decrease of *Bifidobacterium* spp. was reported related to serum IL-10 and IL-13 levels.

Serum zonulin level has a significant role in the pathogenesis of T1D. Leiva-Gea et al. [33] showed that an increase in *Bacteroides* spp. and *Veillonella* spp. and decrease in *Faecalibacterium* spp. and *Roseburia* spp. was correlated with an increased serum zonulin level.
Discussion

We reviewed 26 articles, twenty-four of them approved a straight correlation between microbiota and diabetes; however, most of them didn’t clarify if microbiota induces T1D or T1D changes gut microbiome. The articles were screened according to the type of gut microbiota and correlation with T1D as explained below: one article mentioned that microbiome alteration occurs after diabetes [26], two articles studied microbiota as a therapeutic agent on T1D [35, 41], seven articles just showed the differences in gut microbiota of healthy and diabetic people and didn’t discuss the type of relation [21, 24, 29, 32, 34, 36, 40], finally fourteen articles suggested the exact mechanism that leads to autoimmunity by the change in gut microbiome [5, 18, 25, 27, 28, 31, 33, 37, 39, 42–46] (one article was just in the abstract form and we couldn’t read the details [30]).

Different mechanisms have been suggested about the role of gut microbiota in the pathogenesis of T1D. These mechanisms are mainly derived from the 14 articles mentioned above. In more details, the following points can be noticed:

Table 1 Characteristics of included studies

| Authors             | Year | Country       | Type of study | Study population (control and case) | Age (mean) | Microbiota analysis technique |
|---------------------|------|---------------|---------------|------------------------------------|------------|-----------------------------|
| Rozanova et al. [41]| 2002 | Russia        | Cohort        | 38 T1D                             | 3 years    | Not mentioned               |
| Brown et al. [23]   | 2011 | Finland       | Case–control  | 8 T1D                              | Children   | DNA sequencing              |
| Giongo et al. [31]  | 2011 | USA           | Case–control  | Control: 4, case: 4                | 5 months   | 16s rRNA sequencing         |
| Muri et al. [26]    | 2013 | Spain         | Case–control  | Control: 16, case: 16              | 7 years    | Real time quantitative PCR   |
| Richardson et al. [37]| 2014 | Finland      | Cohort        | Control: 47, case: 29              | 2 years    | 16s rRNA sequencing         |
| de Goffau et al. [24]| 2014 | Netherlands   | Case–control  | Control: 27, case: 28              | 3 years    | Microarray analysis         |
| Endesfelder et al. [38]| 2014 | Germany       | Cohort        | Control: 22, case: 22              | 19.5 months| 16s rRNA sequencing         |
| Mejia et al. [30]   | 2014 | Mexico        | Case–control  | Control: 8, case: 21               | 12.5 years | 16s rRNA pyrosequencing      |
| Soyuçen et al. [28] | 2014 | Turkey        | Case–control  | Control: 35, case: 35              | 10 years   | Quantitative cultures on selective and non-selective media |
| Kostic et al. [39]  | 2015 | Finland       | Cohort        | Control: 22, case: 11b             | Infants    | 16s rRNA sequencing         |
| Alkanani et al. [5] | 2015 | USA           | Cross-sectional | Control: 23, case: 88            | 11 years   | 16s rRNA sequencing         |
| Cui et al. [18]     | 2016 | China         | Case–control  | Control: 15, case: 15              | 11 years   | 16s rRNA sequencing         |
| Maffeis et al. [25] | 2016 | Italy         | Case–control  | Control: 10, case: 10              | 11 years   | Semi-quantitative PCR        |
| Stewart et al. [29] | 2017 | UK            | Case–control  | Control: 10, case: 10              | 27 years   | 16s rRNA sequencing         |
| Pinto et al. [40]   | 2017 | Portugal      | Cohort        | Control: 3, case: 3                | 9 years    | Real time quantitative PCR   |
| Pellegrini et al. [27]| 2017 | Italy         | Case–control  | Control: 35’, case: 19             | 36 years   | Real time quantitative PCR   |
| Traversi et al. [21]| 2017 | Italy         | Case–control  | Control: 13, case: 13              | 8 years    | Real time quantitative PCR   |
| Gao et al. [42]     | 2018 | France        | Cohort        | 33 genetically predisposed to T1D  | 1.5 years  | 16s rRNA sequencing         |
| Vatanen et al. [44] | 2018 | USA           | Nested case–control | Control: 415, case: 368d         | 3 month    | 16s rRNA sequencing         |
| Stewart et al. [45] | 2018 | USA           | Nested case–control | 903 children                 | 24.5 month | 16s rRNA sequencing         |
| Huang et al. [32]   | 2018 | China         | Case–control  | Control: 10, case: 12              | 23.5       | 16s rRNA sequencing         |
| Gavin et al. [43]   | 2018 | Australia     | Cross-sectional | Control: 22, case: 69e            | 10.8       | Proteomics and 16s rRNA sequencing |
| Leiva-Gea et al. [33]| 2018 | Spain         | Case–control  | Control: 13, case: 15 T1D          | 12.6       | 16s rRNA pyrosequencing      |
| Higuchi et al. [34] | 2018 | Brazil        | Case–control  | Control: 28, case: 20              | 23.1       | 16s rRNA sequencing         |
| Salamon et al. [35] | 2018 | Poland        | Case–control  | Control: 23, case: 22              | 42.5       | 16s rRNA sequencing         |
| Cinek et al. [36]   | 2018 | Czech federation | Case–control    | Control: 103, case: 73f          | 11.8       | 16s rRNA sequencing         |

* 35 new-onset patients; 21 seropositive; 32 seronegative FDRs (first degree relatives)

* Seroconverters

* 16 healthy control; 19 gut inflammatory disease as the second control

* 267 seroconverters and 101 diagnosed with T1D

* 23 recent onset type 1 diabetes; 17 islet autoantibody–positive subjects; 29 low-risk autoantibody-negative subjects

* Azerbaijan: 19, Jordan: 20, Nigeria: 14, Sudan: 20
1. In patients with T1D, some bacteria increase mucin degradation, results in reduced integrity and increased permeability of intestinal mucosa that leads to bacterial penetration [47]. The penetration of bacteria into intestinal mucosa leads to stimulation of the immune system and production of antibodies [47]. Cross-reaction of these antibodies and surface antigens of pancreatic beta cells, as well as T cell cross-reactivity results in the destruction of beta cells and formation of T1D [47].

2. Butyrate is one of the most important byproducts of microbiota metabolisms and plays an important role in colonic T-reg induction, down-regulation of pro-inflammatory macrophages and integrity enhancement of gut barriers through increasing mucin production [48, 49].

3. Zonulin is a protein that can be assumed as an important indicator of mucosal integrity and gut permeability [33]. This protein modulates intercellular junctions and macromolecular passage through them [33]. Some bacterial groups can alter mucosal integrity by affecting zonulin; increase in Bacteroides spp. and Veillonella spp. or decrease in Faecalibacterium spp. and Roseburia spp. correlates with increased serum zonulin levels in T1D patients [33]. However, according to Leiva-Gea et al. [33] the impaired gut permeability in T1D patients can be more attributed to the binding of Veillonella to colonic crypt cells rather than change in zonulin levels. Lactate produced by Veillonella is pushed to the luminal surface and weakens tight junctions [33].

4. Gut microbiota ingests and ferment fibers and produce short-chain fatty acids (SCFA) [50–52]. SCFAs enter the blood circulation and modulate T-reg differentiation; thus autoimmunity is prevented [5, 53–55].

With keeping these mechanisms in mind, now we are going to discuss the known attributable mechanism of some highlighted bacteria in more details:
### Table 3  Intestinal microbiota modifications

| Authors               | Intestinal microbiota modifications                                                                                                                                 |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Rozanova et al. [41]  | **Increased** Lactose-negative Enterobacteriaceae, *Klebsiella* spp., *Enterococcus* spp., *Candida* spp., *Clostridium* spp., *Staphylococcus epidermidis*         |
|                       | **Decreased** *Bifidobacterium* spp., *Lactobacillus* spp., *Escherichia coli*                                                                                       |
| Brown et al. [23]     | **Increased** *Bacteroides* spp., *Veillonella* spp., *Alistipes* spp.                                                                                               |
|                       | **Decreased** *Prevotella* spp., *Akkermansia* spp.                                                                                                                   |
| Giongo et al. [31]    | **Increased** Bacteroidetes                                                                                                                                              |
|                       | **Decreased** Firmicutes                                                                                                                                                 |
| Murri et al. [26]     | **Increased** *Clostridium* spp., *Bacteroides* spp. and *Veillonella* spp.                                                                                           |
|                       | **Decreased** *Lactobacillus* spp., *Bifidobacterium* spp., *Blautia coccoides*, *Eubacterium rectale*, *Prevotella* spp., lactic acid-producing bacteria, butyrate-producing bacteria and mucin-degrading bacteria |
| Richardson et al. [37]| **Increased** *Bacteroides dorei*, *Bacteroides vulgatus*                                                                                                               |
|                       | **Decreased** –                                                                                                                                                         |
| de Goffau et al. [24] | **Increased** *Streptococcus mitis*, Bacteroidetes                                                                                                                     |
|                       | **Decreased** –                                                                                                                                                         |
| de Goffau et al. [24] | **Increased** Non butyrate producing species of *Clostridium* cluster 14a, *Clostridium stercolarium*                                                                |
|                       | **Decreased** –                                                                                                                                                         |
| Endesfelder et al. [38]| **Increased** *Enterococcus* spp., *Sarcina* spp., *Prevotella* spp., *Corynebacterium* spp.                                                                    |
|                       | **Decreased** –                                                                                                                                                         |
| Endesfelder et al. [38]| **Increased** *Barnesiella* spp., *Candidatus Nardonella*                                                                                                               |
|                       | **Decreased** *Staphylococcus* spp., *Nocardioides* spp.                                                                                                                 |
| Mejia et al. [30]     | **Increased** *Bacteroides* spp.                                                                                                                                           |
|                       | **Decreased** *Prevotella* spp.                                                                                                                                            |
| Soyucen et al. [28]   | **Increased** Enterobacteriaceae, *Candida albicans*                                                                                                                     |
|                       | **Decreased** *Bifidobacterium* spp.                                                                                                                                       |
| Kostic et al. [39]    | **Increased** –                                                                                                                                                         |
|                       | **Decreased** *Coprococcus eutactus*, *Dialister invisus*                                                                                                                 |
| Alkanani et al. [5]   | **Increased** *Lactobacillus* spp., *Staphylococcus* spp.                                                                                                                 |
|                       | **Decreased** *Prevotellaceae*                                                                                                                                              |
| Maffeis et al. [25]   | **Increased** *Blautia* spp., *Haemophilus* spp., *Lachnospira* spp., *Intestinimonas* spp., *Dialister* spp., *Micrococcales* spp.                                         |
|                       | **Decreased** *Pasteurella* spp., *Caulobacterales* spp.                                                                                                                  |
| Cui et al. [18]       | **Increased** *Blautia* spp., *Haemophilus* spp., *Lachnospira* spp., *Intestinimonas* spp., *Dialister* spp., *Micrococcales* spp.                                         |
|                       | **Decreased** *Pasteurella* spp., *Caulobacterales* spp.                                                                                                                  |
| Stewart et al. [29]   | **Increased** *Actinomyces* spp.                                                                                                                                 |
|                       | **Decreased** –                                                                                                                                                         |
Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria were of great importance in our reviewed articles. Genera Bacteroides and Prevotella are two important subgroups in Phylum Bacteroides that were increased in most of the T1D patient’s samples and can affect gut microbial composition by several mechanisms. Succinate and acetate are the main byproducts of anaerobic metabolism in this phylum that compromise epithelial tight junctions, decrease gut mucosal integrity, block T-reg differentiation and activates inflammatory pathways [25, 32, 33]. These bacteria also produce Glutamic acid decarboxylase (GAD) which can stimulate GAD autoimmunity by molecular mimicry [24, 32].

### Table 3 (continued)

| Authors | Intestinal microbiota modifications |
|---------|-----------------------------------|
| Pinto et al. [40] |  
Increased: *Eubacterium rectale*, *Faecalibacterium prausnitzii*, *Bacteroides dorei*, *Bacteroides uniformis*  
Decreased: *Collinsella aerofaciens*, *Coprococcus Comes*, *Clostridium spp.*, *Bifidobacterium adolescentis*, *Bifidobacterium longum infantis*, *Ruminococcus spp.*, *Collinsella spp.* |
| Pellegrini et al. [27] |  
Increased: Firmicutes  
Decreased: *Clostridium* spp., *Bacteroidetes*, *Proteobacteria* |
| Traversi et al. [21] |  
Increased: *Bacteroides claus*, *Alistipes obesi*, *Bifidobacterium longus*, *Methanobrevibacter Smithii*  
Decreased: *Bacteroides coprophilus*, *Bacteroides dorei*, *Fusobacterium saccharivorans*, *Bacteroides vulgatus*, *Bacteroides oleicplenus*, *Firmicutes* |
| Gao et al. [42] |  
This study emphasizes on interactions between gut microbiota rather than quantitative changes |
| Vatanen et al. [44] |  
Increased: *Bifidobacterium pseudocatenulatum*, *Roseburia hominis*, *Alistipes shahii*  
Decreased: *Streptococcus thermophilus*, *Lactococcus lactis* |
| Stewart et al. [45] |  
Increased: *Ruminococcus* spp., *Lactococcus* spp., *Streptococcus* spp., *Akkermansia* spp.  
Decreased: *Ruminococcus* spp., *Barnesiella* spp., *Clostridium* spp., *Dorea* spp., *Faecalibacterium Prausnitzii* |
| Huang et al. [32] |  
Increased: Bacteroidetes/Firmicutes ratio, *Porphyromonadaceae*  
Decreased: *Ruminococcus* spp., *Veillonella* spp., *Phascolarctobacterium* spp., *Fusobacterium* spp., *Paenibacillaceae* |
| Gavin et al. [43] |  
Increased: *Bacteroides* spp., *Prevotella* spp.  
Decreased: *Alistipes* spp., *Ruminococcus* spp., *Barnesiella* spp., *Clostridium* spp., *Dorea* spp., *Faecalibacterium Prausnitzii* |
| Leiva-Gea et al. [33] |  
Increased: *Bacteroides* spp., *Rikenellaceae*, *Ruminococcus* spp., *Veillonella* spp., *Enterobacteriaceae*, *Blautia* spp., *Streptococcus* spp., *Prevotellaceae*, *Sutterella* spp.  
Decreased: *Bifidobacterium* spp., *Roseburia* spp., *Faecalibacterium* spp., *Lachnospira* spp., *Anaerostipes* spp., *Actinobacteria*, *Proteobacteria*, Firmicutes |
| Higuchi et al. [34] |  
Increased: *Bacteroides* spp., *Alistipes* spp., *Prevotella* spp.  
Decreased: – |
| Salamon et al. [35] |  
Increased: *Akkermansia* spp., *Ruminococcus* spp., *Bacteroides* spp., *Blautia* spp.  
Decreased: *Lachnospira* spp., *Faecalibacterium* spp., *Bifidobacterium* spp., *Coprococcus* spp., *Collinsella* spp., *Dorea* spp. |
| Cinek et al. [36] |  
Increased: *Escherichia coli*  
Decreased: *Eubacterium* spp., *Roseburia* spp., *Haemophilus* spp., *Clostridium clusters IV and XIVa* |

*a In cases with < 2.9 years  
*b In cases with > 2.9 years  
*c Eigenvector centrality (EC) at age 0.5 years  
*d EC at age 2 years*
Phylum Actinobacteria including genus Bifidobacterium is butyrate-producing taxa that have anti-inflammatory effects and augments gut barrier by cytokine modulation [33]. This bacteria also induces T-reg development that results in immune response suppression by regulation of IL-10 production [18].

The third important phylum, Firmicutes, consists of eight notable subgroups: Veillonella, Roseburia, Ruminococcus, Lactobacillus, Blautia, Streptococcus, Faecalibacterium, and Staphylococcus.

Association of T1D and Veillonella is controversy. Kostic et al. [39] reported a decrease in Veillonella in T1D patients and proposed the following mechanism: reduced level of lithocholic acid results in stimulation of gut inflammation by an increased level of reactive oxygen species, reactive nitrogen species and nuclear factor-kB (NF-kB) activity in epithelial cells. Sphingomyelin increment also inhibits NK-T cell function that prevents inflammation [39].

Ruminococcaceae are butyrate-producing taxa that were reported declined in some studies and increased in others. The mechanism of reduced Ruminococcaceae in T1D patients is the same as Veillonella reduction mechanism [33, 39].

Faecalibacterium and Roseburia have anti-inflammatory effects, their presence may augment gut barrier function by modulating cytokine production and butyrate synthesis [24, 33, 36]. These genera have decreased in almost all patient samples.

Genus Blautia is also butyrate-producing taxa that have declined in most of the reviewed articles and plays an important role in blood glucose regulation, lipid metabolism and regulation of T-cell differentiation [18, 33]. There is also evidence of its increment in literature.

Genus Lactobacillus eliminates peroxidase radicals by superoxide dismutase and peroxidase enzymes thus provide a suitable condition for Bifidobacterium reproduction [28]. Lactobacillus down-modulate inflammation and previous studies have demonstrated that dendritic cells co-cultured with species of lactobacilli induce polarization of T-reg cells [5, 56, 57].

Staphylococcaceae may stimulate the growth of Bifidobacterium, Clostridium and Bacteroides which results in augmentation of neonate’s gut maturation [5, 58]. Streptococcaceae produce GAD so they have the same effects as Bacteroides [24, 59].

Limitations
Limitations of our study that complicates interpretation of results can be listed as below: various geographical areas studied have an effect on diet of patients and controls; diversity of microbiota analysis techniques; colonizing microbiome and genetic susceptibility to T1D, some studies considered HLA as a genetic predisposing factor in the selection process of case and control individuals whereas others have ignored this point; different study design (e.g. some studies noticed seropositive group and seronegative FDRs in addition to T1D patients and healthy individuals while others just compared T1D patients with healthy individuals) [5, 25, 39, 44, 45]; various statistical analysis methods and different levels of p-value significance were reported in reviewed articles, however, in this study we used only statistical significant findings from the articles included.

Suggestions
According to our study, we suggest new therapeutic and diagnostic strategies that need further clinical trials for assessing their effectiveness:

1. Use of probiotics, prebiotics and fecal microbial transplantation to modulate gut microbiome; e.g. a probiotic mixture of certain bacteria (mentioned in “Results”) can reduce HbA1c level so it can be considered as a complementary strategy for T1D management.

2. In order to detect early evidence of dysbiosis and prevention of T1D progression, serial stool exams in genetically susceptible children can be done by using a specific kit that semi-quantitatively compares microbiota composition of healthy control and suspected individual. In designing the kit, Firmicutes: Bacteroidetes ratio should be considered because it has been reported decreased in all the reviewed studies.

Conclusions
Our study showed a significant association between alterations in intestinal microbial composition and T1D; however, in some articles, it is not clear which one happens first. Investigation of altered gut microbiota can help in the early detection of T1D before seropositivity against classical autoantigens. Targeted microbiome modulation can be a novel potential therapeutic strategy.

Acknowledgements
This study is related to the project No. 1397/68977 From Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran. We also appreciate “Student Research Committee” and “Research and Technology Chancellor” in Shahid Beheshti University of Medical Sciences for their financial support of this study.

Authors’ contributions
All authors had made considerable contributions to the present study. All authors read and approved the final manuscript.
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