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MINIREVIEWS

Nitrate-nitrite-nitrosamines exposure and the risk of type 1 diabetes: A review of current data

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Abstract

The potential toxic effects of nitrate-nitrite-nitrosamine on pancreatic β cell have remained a controversial issue over the past two decades. In this study, we reviewed epidemiological studies investigated the associations between nitrate-nitrite-nitrosamines exposure, from both diet and drinking water to ascertain whether these compounds may contribute to development of type 1 diabetes. To identify relevant studies, a systematic search strategy of PubMed, Scopus, and Science Direct was conducted using queries including the key words "nitrate", "nitrite", "nitrosamine" with "type 1 diabetes" or "insulin dependent diabetes mellitus". All searches were limited to studies published in English. Ecologic surveys, case-control and cohort studies have indicated conflicting results in relation to nitrate-nitrite exposure from drinking water and the risk of type 1 diabetes. A null, sometimes even negative association has been mainly reported in regions with a mean nitrate levels < 25 mg/L in drinking water, while increased risk of type 1 diabetes was observed in those with a maximum nitrate levels > 40-80 mg/L. Limited data are available regarding the potential diabetogenic effect of nitrite from drinking water, although there is evidence indicating dietary nitrite could be a risk factor for development of type 1 diabetes, an effect however that seems to be significant in a higher range of acceptable limit for nitrate/nitrite. Current data regarding dietary exposure of nitrosamine and development of type 1 diabetes is also inconsistent. Considering to an increasing trend of type 1 diabetes mellitus (T1DM) along with an elevated nitrate-nitrite exposure, additional research is critical to clarify potential harmful effects of nitrate-nitrite-nitrosamine exposure on β-cell autoimmunity and the risk of T1DM.

Key words: Nitrate; Nitrite; Nitrosamine; Type 1 diabetes

Core tip: The potential toxic effects of nitrate-nitrite-nitrosamine on pancreatic β cell have remained a controversial issue over the past two decades. Ecologic surveys, case-control and cohort studies have indicated conflicting results in relation to nitrate-nitrite exposure from drinking water and the risk of type 1 diabetes. An increased risk of type 1 diabetes was observed in regions with a maximum nitrate levels > 40-80 mg/L. Dietary nitrite could be a risk for development of type 1 diabetes in a higher range of acceptable limit. Additional research is critical to clarify potential harmful effects of nitrate-nitrite-nitrosamine exposure on β-cell autoimmunity and the risk of type 1 diabetes mellitus.

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INTRODUCTION

An overview of type 1 diabetes

Type 1 diabetes mellitus (T1DM), one of the main autoimmune disorders caused by immune-mediated destruction of pancreatic β-cells, eventually develops to an absolute insulin deficiency, impaired glucose homeostasis, and physiological dependence on exogenous insulin[1]. An overall approximately 3% increased per year in the incidence of T1DM along with a different geographical incidence has been observed worldwide[2,3]. A higher incidence rate of T1DM has been reported in European countries, especially Finland and Sardinia, however recently the incidence of T1DM has risen rapidly in low-incident populations including parts of India, the Middle East, and Sub-Saharan Africa[4]. The incidence of T1DM had an increasing trend in both developed and developing countries during a recent decade[5-8]. According to current trends, it is predicted that new cases of T1DM in European children < 5 year will be doubled and prevalent cases < 15 years will be raised by 70%, between 2005 and 2020[7].

Risk factors of T1DM

T1DM has a multifactorial nature; besides genetic factors and family history which account for about 30%-50% onset of T1DM, several factors such as environmental contaminants, infection agents, drugs, and dietary factors have been known as important etiologically relevant to β-cell autoimmunity and T1DM development[9-11]. Dietary factors implicated in the pathogenesis of T1DM are cow milk proteins (casein, bovine serum albumin, β-lactoglobulin, and bovine insulin), gluten, zinc and vitamin D deficiency, as well as nitrate and nitrite; some ecologic, animal, and human studies have confirmed that *N*-nitroso compounds, nitrate and nitrite play a role in development of T1DM[12-14]. Diabetogenic agents from diet may induce their effects by several suggested pathways, including apoptosis of β-cell, increased oxidative stress, impaired insulin response and immune function, and some postprandial modifications[15].

Diabetogenic hypothesis of nitrate-nitrite exposure

Inorganic nitrate (NO_3) and nitrite (NO_2) are naturally occurring compounds in foods and are also used as food additives; major sources of exogenous nitrate exposure are vegetables and drinking water, whereas processed meat and animal food products are the main sources of nitrite[16]. Considering both acute and chronic potential toxicities, some limitations have been legislated for dietary intakes of nitrate and nitrite; the acceptable daily intakes (ADI) of nitrate and nitrite from food sources as designated by the Scientific Committee on Foods and the Joint Food and Agriculture Organization/World Health Organization (WHO) Expert Committee on Food Additives defined as 3.7 and 0.06 mg/kg body weight, respectively[17]. Moreover, due to substantial concentrations of nitrate-nitrite in drinking water, WHO restricted the acceptable concentrations of drinking water to < 50 mg/L and 3 mg/L for nitrate and nitrite, respectively[18,19].

Recent investigations have however highlighted the beneficial therapeutic effects of nitrate-nitrite against metabolic disorders such as type 2 diabetes[20-22], possible adverse complications such as thyroid disorders and T1DM[23,24] are still remaining due to indiscriminate increased use of fertilizers and nitrite-containing food additives and increased exposure of nitrate-nitrite from both diet and drinking water. It has been proposed that nitrate-nitrite may have toxic effects on pancreatic β-cells due to generation of peroxynitrite, reactive nitrogen intermediates, and nitrosamines[25].

Although data have shown elevated risk of β-cell autoimmunity and T1DM due to high intakes of nitrate-nitrite over the past two decades[26], this data has however not yet led to a consistent confirmed conclusion[27-30].

Aim of this study

This review will focus on the potential effect of nitrate-nitrite-nitrosamines exposure on development of T1DM. We reviewed epidemiological studies investigating the associations between nitrate-nitrite-nitrosamines exposure, from both diet and drinking water to ascertain whether higher nitrate-nitrite may contribute to the development of T1DM.

To identify relevant studies, a systematic search strategy of PubMed, Scopus, and Science Direct was conducted using queries including the key words "nitrate", "nitrite", "nitrosamine" with "T1DM" or "insulin dependent diabetes mellitus". All searches were limited to studies published in English.

EXPOSURE OF NITRATE-NITRITE FROM DRINKING WATER AND THE RISK OF T1DM

Possible relation between quality of drinking water and T1DM, particularly concentrations of nitrate or nitrite has been investigated in several studies. An overview of current data indicates that potential diabetogenic effects of nitrate-nitrite have mainly been investigated by estimation of nitrate-nitrite exposure from drinking water, a relationship also evaluated in the framework of ecological studies[28-32].

An ecological analysis of insulin dependent diabetes mellitus registry data on children aged < 18 year during 1978-1988 in relation to public water supplies and well water systems in Colorado between 1984 and 1988, showed a significant correlation between T1DM incidence and water nitrate level (r = 0.27, P = 0.03)[29]. This correlation was higher in countries where nitrate levels in the public water system were in the highest tertile (r = 0.29, P = 0.02), and the rate of T1DM was higher in the highest compared to the lowest tertile of nitrate exposure (PI = 15/100000 *vs* PI = 7/100000, in 0.77-8.2 mg/L *vs* 0-0.08 mg/L nitrate levels, model R^2 = 0.14); the authors pointed out that findings of the study should be interpreted considering to some limitations such as lack of data on individual's nitrate exposure and inappropriate timing of the exposure measurement[29].

In another ecological analysis, conducted on a population-based study in the framework of Yorkshire Regional Health Authority during 1978-1994, Parslow *et al*[28] reported that the incidence of T1DM was positively associated with mean nitrate levels in drinking water; an increasing trend in standardized incidence ratio (SIR) of T1DM was observed across increasing levels of nitrate in drinking water (SIR = 85, 95%CI: 78-93; SIR = 99, 95%CI: 91-107; SIR = 115, 95%CI: 107-124; in levels of 1.5-3.2, 3.2-14.5 and 14.9-40.0 mg/L, respectively, χ^2 = 26.8, P < 0.001)[28]. Moreover, a 30% higher incidence rate of diabetes was observed among doses in water supply zones with mean nitrate levels 14.9-40.0 mg/L, compared with those in zones with a mean nitrate levels < 3.2 mg/L (IRR = 1.27, 95%CI: 1.09-1.48). In this study, over 30% of drinking water samples contained > 25 mg/L nitrate levels.

Analysis of drinking water in Finland for nitrate, nitrite, nitrate-nitrogen and nitrite-nitrogen, among families with a child, diagnosed as type 1 diabetic compared to controls, showed that higher levels of nitrate in drinking water was related to increased risk of T1DM (OR = 1.32, 95%CI: 1.06-1.64; P = 0.013); nitrite concentrations had no significant association with the risk of T1DM (OR = 0.36, 95%CI: 0.06-2.03; P = 0.25)[33]. Mean nitrate and nitrite levels of drinking water in this population were 4.43 (0-80 mg/L) and 0.02 (0.02-0.16 mg/L), respectively; mean nitrate and nitrite levels in municipalities with high compared to low incidence of T1DM, was lower (1.27 mg/L *vs* 3.25 mg/L, 0.02 mg/L *vs* 0.03 mg/L, for nitrate and nitrite, respectively)[33].

In contrast, some studies report findings to reject diabetogenic hypothesis of the nitrate-nitrite exposure. The incidence of T1DM was not related to nitrate exposure, in an ecological study of children, aged < 15 year, in the Netherlands, conducted using the Dutch Pediatric Surveillance Unit (1993-1995) and nitrate drinking water data from the National Institute of Public Health and Environmental Protection (1991-1995)[31]; standardized incidence rate of T1DM was 1.45 for nitrate levels ranging > 25 mg/L (95%CI: 0.85-2.07). Lack of information on the individual's quantity of water consumption, length of exposure and data on potential risk factors of such as family history of T1DM, were important limitations of this study. Moreover, non-significant findings have been attributed to small number of cases in the > 25 mg/L category; in this study, only 1% of the children were exposed to nitrate levels between 25-41 mg/L[31].

In a Finnish nation-wide case-control study, exposure of nitrate and nitrite in children and their parents from drinking water were assessed in relation to risk of T1DM; no differences were observed in intakes of nitrate or nitrite from drinking water between cases and controls[26].

Analysis of data on nitrate concentration of both tap and bottled water in Italy during 1993-1994, showed no significant association between nitrate exposure and incidence of T1DM during 1989-1998, in the subjects, aged 0-14 y (r = -0.06) or in the group, aged 0-29 year (r = -0.17)[32]. There was no effect from sex in the same age-groups; in contrast with previous reports, a negative trend between nitrate levels and T1DM was also noted[32]; in this study, both tap and bottled water were within the acceptable maximal concentration of 50 mg/L legislated by the European Community and also under the recommended levels of 25 mg/L.

In a retrospective study of 153 Sardinian communes, among 0-14 year Italian children, a significantly inverse trend between childhood diabetes and mean nitrate exposure was observed; higher nitrate of drinking water was reported in districts with low compared to high incidence of T1DM (8.9-14.5 mg/L *vs* 4.3-7.8 mg/L)[34]. The risk of T1DM in subjects exposed to highest compared to the lowest nitrate levels in drinking water (6.5-28.9 mg/L *vs* ≤ 2.5 mg/L) decreased 40% (RR = 0.6, 95%CI: 0.4-1.0, P = 0.027).

An initial assessment of nitrate exposure from domestic water during 1993-1997, in relation to T1DM diagnosed in children aged 0-15 year in England between 1975-1996, suggested that nitrate may had a protective effects against development of T1DM[35]; standardized incidence ratio in the highest compared to the lowest tertile of nitrate levels (7.48-16.58 mg/L *vs* 1-3.65 mg/L) was lower (SIR = 90.2, 95%CI: 77-105 *vs* SIR = 111.8, 95%CI: 96-129; χ^2 = 3.89, P = 0.048), however, Poisson regression analysis failed to support this relationship; mean nitrate levels of drinking water was 6.02 mg/L (min = 0.48 and max = 31.9 mg/L).

Moltchanova *et al*[36] in a study of children aged < 15 in Finland between 1987-1996, showed an increasing

risk of T1DM along with increasing nitrate concentration of drinking water. The posterior mean unit effect of nitrate on diabetes risk was 0.003 (-0.009, 0.0138), *i.e.,* 1 mg/L increased nitrate concentration in the ground water resulted in 0.3% increased risk of T1DM; mean nitrate level of groundwater was 6.22 mg/L (0.20 and 6.64 in the 1st and 4th quartiles, respectively)[36].

In a retrospective study from Saudi Arab, type 1 diabetic patients, diagnosed between 1980 and 2009, no etiological effects for nitrate levels in drinking water of the study areas were observed; mean nitrate level in drinking water showed levels between 0.6 and 4 mg/L, during 30 years which were much lower than the toxic levels[37].

A nested case-control analysis on 95 islet auto-antibody-positive (Islet Ab$^+$) and 139 Islet Ab$^-$ children, conducted in the framework of German BABYDIAB study, indicated no association between nitrate content of drinking water and the risk of islet autoimmunity, whereas higher levels of nitrite ($\geqslant$ 0.009 mg/L *vs* < 0.009 mg/L) had a borderline protective effect (OR = 0.6, 95%CI: 0.4-1.0)[30]; mean nitrate levels of water were 9.5 mg/L (4.8-16.6) and 9.2 mg/L (3.8-21.2) in Islet Ab$^+$ and Islet Ab$^-$ children, respectively; upper nitrite level of drinking water was marginally higher in Islet Ab$^-$ compared to Islet Ab$^+$ children (0.01 mg/L *vs* 0.009 mg/L, P = 0.06). The odds of the progression of islet autoimmunity to T1DM in higher levels of nitrate and nitrite in drinking water ($\geqslant$ 9.58 and $\geqslant$ 0.009 mg/L) was 0.9 (95%CI: 0.4-2.0) and 1.5 (95%CI: 0.6-3.5), respectively[30]. Another important finding was an inverse relation between nitrate concentrations and pH levels of drinking water (r = -0.28, P = 0.001), along with a positive relation between pH of water and progression of T1DM (OR = 2.5, 95%CI: 1.1-5.7)[30]; it may be indirectly provide evidence for hazardous effects of nitrate on T1DM. This study was the first try to investigate the association of nitrate-nitrite exposure during the first year of life in children and the risk of islet autoimmunity; due to importance of this period in developing of islet autoimmunity, this study provided an opportunity to evaluate a potential causal relationship between nitrate-nitrite of drinking water and T1DM progression. Matching for date of birth, duration of follow-up, human leukocyte antigen (HLA), gender and geographical region and also adjustment of main potential risk factors of T1DM including genetic factors (HLA DR 3/4, 4/4) and maternal T1DM were other strengths of the study.

Tables 1 and 2 provide a summary of results from ecological, case-control and cohort studies of mean nitrate-nitrite levels from drinking water in relation to incidence of T1DM.

DIETARY EXPOSURE OF NITRATE-NITRITE AND THE RISK OF T1DM

The risk of T1DM in response to nitrate-nitrite exposure from diet has been evaluated in a limited number of studies. In a prospective case-control study of Swedish children, aged 0-14 years, matched for age, sex, and country of residence, a significant increasing trend of T1DM was noted for higher intakes of foods containing nitrate and nitrite[27]. In this study, fresh green vegetables, boiled vegetables, root vegetables, cheese, sausage and bacon have been defined as high nitrate-nitrite containing foods; mean frequency of nitrate-nitrite rich foods was higher in diabetics compared to controls; highest compared to the lowest (> 75th centile *vs* < 25th centile) frequency of consumption of nitrate-nitrite rich foods was related to an elevated risk of T1DM (OR = 2.41, 95%CI: 1.64-3.54, P = 0.001)[27]. After adjustment of some potential confounding variables including age, sex, maternal age, maternal education, and family history insulin dependent diabetes, the chance of having T1DM was 0.89 and 2.68 in individuals with medium and high nitrate-nitrite exposure from diet[27]. In further analysis, stratified for vitamin C rich foods, risk estimate for medium and highest nitrate-nitrite intakes along with low vitamin C intakes was 0.94 and 2.44 (P < 0.001), respectively; in contrast, higher intakes of nitrate-nitrite were not associated with T1DM in the presence of higher intakes of vitamin C. An indirect estimation of nitrate-nitrite based on food frequency intakes, was an important limitation of this study; lack of data on nitrate-nitrite exposure from drinking water was also another source of bias in estimation of nitrate and nitrite exposure.

In a Finnish nation-wide case-control study, intakes of nitrate and nitrite of children and their parents from food and drinking water were assessed in relation to risk of T1DM[26]. Compared to controls, dietary intakes of nitrite were higher in diabetic children and their mothers (0.9 mg/d *vs* 0.8 mg/d). Higher intakes of nitrate were also observed in cases mother's compared to controls (P < 0.05). The risk of T1DM increased across increasing intakes of dietary nitrite among children (OR = 1.16, 95%CI: 0.82-1.65; OR = 1.49, 95%CI: 1.06-2.10; OR = 2.32, 95%CI: 1.67-3.24 in the second, third, and fourth quartiles, respectively), and their mothers (OR = 1.15, 95%CI: 0.76-1.74; OR = 1.29, 95%CI: 0.87-1.91; OR = 1.98, 95%CI: 1.35-2.90, in the second, third, and fourth quartiles, respectively), a relationship independent of age, mother's education, place of residence or smoking status of mothers[26].

A case-control study on dietary intakes of nitrate and nitrite during the year prior to diagnosis of diabetes, after adjustment of age, sex, and total energy intake, showed a non-significant positive dose-response relationship between risk of T1DM and nitrate intakes from foods (OR = 1; OR = 1.01, 95%CI: 0.0.28-3.61; OR = 1.19, 95%CI: 0.31-4.52, OR = 2.25, 95%CI: 0.45-11.14 in the first to fourth quartiles; P = 0.29); dietary intakes of nitrate were < 5.66, 5.66-7.27, 7.27-9.01, and $\geqslant$ 9.01 mg/d in the first to fourth quartiles, respectively. The risk of T1DM increased 30% (OR = 1.30, 95%CI: 0.30-5.59) in the highest, compared to the lowest quartiles of nitrite intakes ($\geqslant$ 4.82 mg/d *vs* < 1.83 mg/d)[38]. Neither were total intakes of nitrate + nitrite (from both diet and

Table 1 Summary of results from ecological, case-control and cohort studies of mean nitrate levels from drinking water in relation to incidence of type 1 diabetes

Ref.	Country	Exposure levels (mg/L)	Findings
Muntoni *et al*[34]	Italy	≤ 2.5	OR = 1.0
		2.5-4.0	OR = 0.6 (95%CI: 0.4-1.0)
		4.0-6.5	OR = 0.5 (95%CI: 0.3-0.7)
		6.5-28.9	OR = 0.6 (95%CI: 0.4-1.0)
			P = 0.027
Parslow *et al*[28]	United Kingdom	1.5-3.2	OR = 1.0
		3.2-14.9	OR = 1.11 (95%CI: 0.98-1.26)
		14.9-40.0	OR = 1.27 (95%CI: 1.09-1.48)
Winkler *et al*[30]	Germany	< 9.58	OR = 1.0
		≥ 9.58	OR = 0.9 (95%CI: 0.6-1.3)
Zhao *et al*[35]	England	1-3.6	SIR = 1.11 (95%CI: 0.96-1.29)
		3.6-7.8	SIR = 0.99 (95%CI: 0.85-1.15)
		7.8-16.6	SIR = 0.90 (95%CI: 0.77-1.05)
			χ^2 = 3.8, P = 0.048
van Maanen *et al*[31]	The Netherland	< 10	SIR = 0.99 (95%CI: 0.93-1.06)
		10-25	SIR = 0.99 (95%CI: 0.84-1.14)
		≥ 25	SIR = 1.45 (95%CI: 0.85-2.07)
		0.2-2.1	SIR = 1.02 (95%CI: 0.92-1.13)
		2.1-6.4	SIR = 0.95 (95%CI: 0.85-1.06)
		6.4-41.2	SIR = 1.02 (95%CI: 0.92-1.12)
Casu *et al*[32]	Italy	Approximately 10	Simple correlation = -0.17, P = NS
Samuelsson *et al*[33]	Sweden	0-80	OR = 1.32 (95%CI: 1.06-1.64), P = 0.013
Moltchanova *et al*[36]	Finland	0.2-6.64	Posterior mean unit effect = 0.0026 (95%CI: -0.0093-0.0138)
Kostraba *et al*[29]	United States	0-8.2	Correlation = 0.23, P = 0.07

OR: Odds ratio; SIR: Standardized incidence ratio; NS: No significance.

Table 2 Summary of results from ecological, case-control and cohort studies of mean nitrite levels from drinking water in relation to incidence of type 1 diabetes

Ref.	Country	Exposure levels (mg/L)	Findings
Winkler *et al*[30]	Germany	< 0.009	OR for β-cell autoimmunity = 1.0
		≥ 0.009	OR for β-cell autoimmunity = 0.6 (95%CI: 0.4-1.0), P = 0.07
		< 0.009	OR for type 1 diabetes = 1.0
		≥ 0.009	OR for type 1 diabetes = 1.5 (95%CI: 0.6-3.5), P = 0.074
Samuelsson *et al*[33]	Sweden	0.02-0.16	OR = 0.36 (95%CI: 0.06-2.03), P = 0.25

OR: Odds ratio.

drinking water) related to risk of T1DM. It should be noted that the highest intakes of dietary nitrate in this population were much lower than the ADI limit value (9 mg/d *vs* 259 mg/d for an adult subject) whereas dietary nitrite intakes in the highest quartile were higher than the recommended values (4.82 mg/d *vs* 4.2 mg/d for adults). An accurate estimation of nitrate intakes from diet and assessment of the individual's drinking water intakes may be considered as important strengths of this study.

NITROSAMINE EXPOSURE AND THE RISK OF T1DM

N-nitrosodiethylamine and nitrosodimethylamine are two main nitrosamine compounds that contaminate food and water sources; the major known sources of dietary volatile nitrosamines are nitrite-cured meats, especially sausage and fried bacon[39,40]. Nitrosamines mediate their adverse effects due to induction of DNA damage, oxidative stress, lipid peroxidation, and activation of inflammatory signalling pathways, which lead to increased cellular degeneration and death[41].

For the first time in 1981, in a study of children aged 0-14 year in Island, Helgason *et al*[42] provided some primary evidence for the potential role of dietary intakes of nitrosamines in the development of T1DM. Subsequent studies have reported conflicting results. Findings of a case-control study of Australian, children aged 0-15 year, rejected this hypothesis and showed that those children who consumed higher amounts of foods containing nitrosamines did not have an increased risk of diabetes; the odds (95%CI) of T1DM were 0.71 (0.44-1.14) and 1.07 (0.66-1.74), in the middle and highest tertile compared to the lowest tertile of nitrosamine-containing foods, respectively[14].

A prospective case-control study of Swedish children, aged 0-14 year, dietary frequency of nitrosamines rich foods including smoked fish, bacon and sausage, increased risk of T1DM in a dose-response manner[27]. Dietary exposure of nitrosamines was also positively

related to increased risk of T1DM (OR = 1.73, 95%CI: 1.23-2.44 and OR = 2.56, 95%CI: 1.83-3.59 in the medium and high categories, respectively)[27]. Further analysis stratified for different levels of dietary protein intakes, showed that higher nitrosamine intake was risk factor for diabetes, only in the presence of higher levels of protein (OR = 2.08, 95%CI: 0.94-4.60; OR = 2.12, 95%CI: 1.11-4.04, $P = 0.03$)[27].

Another case-control study of Canadian children indicated no significant association between nitrosamines intakes and risk of T1DM (OR = 0.57, 95%CI: 0.21-1.57; OR = 0.66, 95%CI: 0.18-2.45; OR = 0.62, 95%CI: 0.19-2.00; in the second, third and fourth quartiles, $P = 0.51$); daily intakes of nitrosamines were estimated < 0.01, 0.01-0.03, 0.03-0.04, and ⩾ 0.4 mg/d across the quartile categories[38].

CONCLUSION

Ecologic surveys, case-control and cohort studies have indicated conflicting results in relation to nitrate-nitrite exposure from drinking water and the risk of T1DM. A null, sometimes even a negative association has been mainly reported in populations with a mean nitrate levels < 25 mg/L in drinking water, whereas increased risk of T1DM was reported in regions with maximum nitrate levels > 40-80 mg/L. Limited data are available regarding potential diabetogenic effects of nitrite from drinking water, a hypothesis not yet confirmed. Inconsistent findings of the studies may be attributed to a wide variation in nitrate-nitrite exposure, different cut off points used for definition of nitrate-nitrite exposure, differences in the duration of exposure and variation in potential confounding variables, adjusted in the statistical models. Lack of significant association between dietary nitrate intakes with the risk of T1DM, observed in previous studies, may be attributed to mean nitrate intakes lower than ADI. There is evidence which indicates dietary exposure of nitrite may be risk factor for development of T1DM, an effect however seems to be significant in a higher range of acceptable limits. Current data regarding dietary exposure of nitrosamine and development of T1DM is also inconsistent. To conclude findings of previous studies on nitrate-nitrite exposure and risk of T1DM, it should be noted that most studies reviewed had an ecological nature; they provided only an indirect crude estimation of exposure and described only the association between the incidence of T1DM and average level of exposure in a set of data. Considering the fact that nitrate exposure should be assessed based on individual's intake, overall estimation according to nitrate levels of water supplies, lack of data on amount of drinking water and dietary intakes of nitrate-containing foods, were main limitations of previous studies which could lead to potential misclassification of exposure; findings therefore should be considered conservatively. Relevant timing of exposure is also an important issue in assessment of the possibly diabetogenic effect of nitrate, somewhat neglected in the previous studies.

In future studies, a more accurate estimation of nitrate-nitrite exposure at an individual level is recommended to examine the potential effects on β-cell destruction and development of T1DM. Taking into account islet autoimmunity status and assessment of islet autoantibody levels such as insulin autoantibodies, glutamic acid decarboxylase, and IA-2, should also be considered in future investigations of the association between nitrate exposure and the risk of T1DM development, determine the role of nitrate-nitrite at different stages of the disease as initiators, promoters or trigger of the T1DM.

It should be noted the studies investigated possible association of nitrate-nitrite exposure and the risk of T1DM, are mainly limited to European countries, especially high-incidence rate populations including Sweden, Finland, England, Germany and Italy. It is also noteworthy that epidemiological investigations on diabetogenic effects of nitrate-nitrite exposure was of interest during two past decades, and scientific communities have been silent on this issue in recent years; low nitrate-nitrite exposure levels in the mentioned countries may be a reason for this trend.

Considering to an increasing trend of T1DM along with an elevated nitrate-nitrite exposure due to increased use of fertilizers and nitrite-containing food additives, additional research is critical to clarify potential harmful effects of nitrate-nitrite-nitrosamine exposure on β-cell autoimmunity and the risk of T1DM. Given that the incidence of T1DM is alarming among previously secured populations including Middle East, Asian and African countries, and nitrate-contaminated drinking water is currently a public health problem among these populations[43,44], clarifying of the issue should be considered as a public health priority in developing countries.

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