ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2019 December 15; 10(12): 546-580

Published by Baishideng Publishing Group Inc

World Journal of Diabetes

Contents

Monthly Volume 10 Number 12 December 15, 2019

ORIGINAL ARTICLE

Basic Study

SYSTEMATIC REVIEWS

Contents

World Journal of Diabetes

Volume 10 Number 12 December 15, 2019

ABOUT COVER

Editorial Board Member of *World Journal of Diabetes*, Rachel Hudacko, MD, Assistant Professor, Department of Pathology and Laboratory Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NY 08903, United States

AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Mei-Yi Liu*

Proofing Production Department Director: *Xiang Li*

NAME OF JOURNAL
World Journal of Diabetes

ISSN
ISSN 1948-9358 (online)

LAUNCH DATE
June 15, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Timothy Koch

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-9358/editorialboard.htm

EDITORIAL OFFICE
Ruo-Yu Ma, Director

PUBLICATION DATE
December 15, 2019

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Diabetes

Submit a Manuscript: https://www.f6publishing.com

World J Diabetes 2019 December 15; 10(12): 546-559

DOI: 10.4239/wjd.v10.i12.546

ISSN 1948-9358 (online)

ORIGINAL ARTICLE

Basic Study

Influence of 10-(6-plastoquinonyl) decyltriphenylphosphonium on free-radical homeostasis in the heart and blood serum of rats with streptozotocin-induced hyperglycemia

Aleksander A Agarkov, Tatyana N Popova, Yana G Boltysheva

ORCID number: Aleksandr A Agarkov (0000-0001-5774-7971); Tatyana N Popova (0000-0002-9660-3054); Yana G Boltysheva (0000-0001-6817-7652).

Author contributions: Popova TN and Agarkov AA participated equally in designed and coordinated the research and performed the majority of experiments and analyzed the data, wrote the paper; Boltysheva YG performed the molecular investigations and participated in treatment of animals.

Institutional review board statement: The results of the study were reviewed meeting of the Scientific and Technical Council Voronezh State University.

Institutional animal care and use committee statement: The results of the study were reviewed at a meeting of the Ethical Review Committee for Biomedical Research of the Voronezh State University.

Conflict-of-interest statement: Potential conflicts of interest not detected.

Data sharing statement: No additional data are available.

ARRIVE guidelines statement: The ARRIVE Guidelines have been adopted.

Aleksander A Agarkov, Tatyana N Popova, Yana G Boltysheva, Department of Medical Biochemistry and Microbiology, Voronezh State University, Voronezh 394018, Russia

Corresponding author: Aleksandr A Agarkov, PhD, Assistant Professor, Department of Medical Biochemistry and Microbiology, Voronezh State University, 1 Universitetskaya pl., Voronezh 394018, Russia. agalalek@mail.ru
Telephone: +7-473-2281160-1110
Fax: +7-473-2208755

Abstract

BACKGROUND

It is known that under conditions of tissue tolerance to insulin, observed during type 2 diabetes mellitus (DM2), there is an increased production of reactive oxygen species. Moreover, the free radicals can initiate lipid peroxidation (LPO) in lipoprotein particles. The concentration of LPO products can influence the state of insulin receptors, repressing their hormone connection activity, which is expressed as a reduction of the glucose consumption by cells. It is possible that reduction in glucose concentration during administration of 10-(6-plastoquinonyl) decyltriphenylphosphonium (SkQ1) to rats with DM2 may be related to the antioxidant properties of this substance.

AIM

To establish the influence of SkQ1 on free-radical homeostasis in the heart and blood serum of rats with streptozotocin-induced hyperglycemia.

METHODS

To induce hyperglycemia, rats were fed a high-fat diet for 1 mo and then administered two intra-abdominal injections of streptozotocin with a 7-d interval at a 30 mg/kg of animal weight dose with citrate buffer equal to pH 4.4. SkQ1 solution was administered intraperitoneally at a 1250 nmol/kg dose per day. Tissue samples were taken from control animals, animals with experimental hyperglycemia, rats with streptozotocin-induced glycemia that were administered SkQ1 solution, animals housed under standard vivarium conditions that were administered SkQ1, rats that were administered intraperitoneally citrate buffer equal to pH 4.4 once a week during 2 wk after 1-mo high-fat diet, and animals that were administered intraperitoneally with appropriate amount of solution without SkQ1 (98% ethanol diluted eight times with normal saline solution). To determine the intensity of free radical oxidation and total

Manuscript source: Unsolicited manuscript

Received: July 26, 2019
Peer-review started: July 26, 2019
First decision: August 19, 2019
Revised: October 20, 2019
Accepted: October 27, 2019
Article in press: October 27, 2019
Published online: December 15, 2019

P-Reviewer: Gabriel S, Tangvarasittichai S
S-Editor: Tang JZ
L-Editor: Filipodia
E-Editor: Liu MY

antioxidant activity, we used the biochemiluminescence method. Aconitate hydratase (AH), superoxide dismutase, and catalase activities were estimated using the Hitachi U-1900 spectrophotometer supplied with software. The amount of citrate was determined by means of the Natelson method. Real-time polymerase chain reaction was carried out using an amplifier ANK-32.

RESULTS
It was found that the mitochondrial-directed antioxidant elicits decrease of biochemiluminescence parameter values that increase by pathology as well as the levels of primary products of LPO, such as diene conjugates and carbonyl compounds, which indicate intensity of free radical oxidation. At the same time, the activity of AH, considered a crucial target of free radicals, which decreased during experimental hyperglycemia, increased. Apparently, increasing activity of AH influenced the speed of citrate utilization, whose concentration decreased after administering SkQ1 by pathology. Moreover, the previously applied antioxidant during hyperglycemia influenced the rate of antioxidant system mobilization. Thus, superoxide dismutase and catalase activity, as well as the level of gene transcript under influence of SkQ1 at pathology, were changing to the direction of control groups values.

CONCLUSION
According to the results of performed research, SkQ1 can be considered a promising addition to be included in antioxidant therapy of DM2.

Key words: Diabetes mellitus; Free radical oxidation; Antioxidants; 10-(6-plastoquinonyl) decyltriphenylphosphonium

Core tip: The results of this research suggest that the mitochondria targeted antioxidant 10-(6-plastoquinonyl) decyltriphenylphosphonium (SkQ1) might be a potential substance for incorporation into the antioxidant therapy of type 2 diabetes mellitus. The ability of this compound to lower the intensity of free-radical processes, acting as the key component of the pathogenesis of the type 2 diabetes mellitus, serves as the basis for this conclusion. Thus, after the introduction of SkQ1 to the animals with streptozotocin induced hyperglycemia, the values of the biochemiluminescence parameters reflecting the free-radical oxidation intensity, the concentration of diene conjugates and carbonyl products of protein oxidation, aconitate hydratase activity, and citrate content approached those of control values. At the same time, the activity level of the antioxidant enzymes superoxide dismutase and catalase approached those of normal values.

Citation: Agarkov AA, Popova TN, Boltysheva YG. Influence of 10-(6-plastoquinonyl) decyltriphenylphosphonium on free-radical homeostasis in the heart and blood serum of rats with streptozotocin-induced hyperglycemia. *World J Diabetes* 2019; 10(12): 546-559
URL: https://www.wjgnet.com/1948-9358/full/v10/i12/546.htm
DOI: https://dx.doi.org/10.4239/wjd.v10.i12.546

INTRODUCTION

Type 2 diabetes mellitus (DM2) is a pandemic metabolic disease and is becoming a serious problem for health protection due to the global increase of its prevalence. Endocrinopathic complications, such as nephropathy, retinopathy, brain angiopathy, myocardial angiopathy, and lower limbs angiopathy, prove to be the major reason for incapacity, disability, or patient mortality. It is known that diabetic cardiomyopathy develops in patients with insulin resistance and DM regardless of diagnosed coronary heart disease or hypertension[1].

The crucial target is vascular endothelium, which is affected by a number of metabolic, hemodynamic, and immunologic factors that characterize the development of the disease[2]. It has been shown in DM2 that the delivery of fatty acids to the myocardium is intensified and glycolysis is slowed down[3]. At the same time, the

concentration of reactive oxygen species (ROS) have a damaging effect on the lipids of cardiomyocyte membranes and contribute to the mitochondrion mechanism malfunction and, as a result, to the inhibition of ATP elaboration. This leads to calcium imbalance in cardiomyocytes and results in muscular relaxation and contraction. Hyperglycemia as well contributes to the development and progression of fibrotic degeneration of cardiomyocytes due to the increased deposition of collagen in the interstitium[4].

Taking into account the most important factors of free radical oxidation activation in the pathogenesis of DM, as well as in the development of its complications, antioxidant therapy should be considered among the modern medical endocrinopathy treatment technologies. In this context, there is an urgent need for effective substances that would protect cellular structures from oxidative stress.

Ten-(6'-plastoquinonyl) decyltriphenylphosphonium (SkQ1) is an aromatic cation (triphenylphosphonium) conjugated with a 10-12 atom aliphatic compound as well as plastoquinone, which is an active molecular component of this substance[5].

Several Sk-compounds with modified lipophilic and antioxidant parts were synthesized and tested by varying the length of the aliphatic linker. All these compounds have abbreviated names derived from the surname of Russian academician Skulachev VP (Sk), the letter to designate ubiquinone (Q), and the letter or numerical symbol to designate the modification.

When used in nanoconcentrations, this substance participates in the ROS balance regulation as it has the ability to neutralize free radicals (FR), including OH radicals in aqueous solutions. This may protect cells from apoptosis and necrosis induced by ROS[6].

The goal of this study was to evaluate the influence of SkQ1 on biochem-iluminescence (BCL) parameters, which reflect the free radical processes reactions rate, the total activity of the antioxidant system (AOS), the level of primary lipid peroxidation (LPO) products such as diene conjugates (DC), the activity of aconitase, which is the sensitive target of FR action and citrate content, the degree of protein oxidative modification, the activity of superoxide dismutase (SOD) and catalase, and the level of their genes' transcripts in heart and blood serum of the rats with hyperglycemia induced by the administration of streptozotocin (STZ).

MATERIALS AND METHODS

Experimental animals

To conduct the study, laboratory rats were selected of nursery rat males from Federal State-financed Organization of Health Service "Voronezh Hygiene and Epidemiology Center". The animals were divided through stratified randomization by their weight and age. The rats used for the study weighed 200-250 g and aged 3-5 mo. The experimental animals were kept for 14 d before the start of the study under the following conditions: 12-h light day, temperature 21-25 °C, and food *ad libitum*. The experiment was carried out in accordance with European legislation on the protection of animals (Directive 2010/63/EC).

Hyperglycemia induction in animals

Hyperglycemia was induced by feeding rats a high-fat diet for 1 mo, followed by two intra-abdominal injections of STZ with a 7-d interval at a 30 mg/kg of animal weight dose with citrate buffer equal to pH 4.4[7].

Hyperglycemia in rats was verified by measuring glucose level in the blood serum using a glucose oxidase test. The blood was collected twice with a day-interval from caudal vein after the second administration of STZ and 1-d food deprivation. The reagent kit used for the study was purchased from Vital Diagnosticum, Saint-Petersburg, Russia.

At 2 wk after STZ administration, drugged animals were devitalized for further research. The laboratory rats were divided into four groups: Group 1 (n = 20), animals housed under standard vivarium conditions (control group); group 2 (n = 20), animals with STZ injection-induced hyperglycemia; group 3 (n = 12), animals with STZ-induced glycemia that were administered SkQ1 solution intraperitoneally at a 1250 nmol/kg dose per day, starting from the second week; and group 4 (n = 8), animals housed under standard vivarium conditions that were administered with SkQ1 at a 1250 nmol/kg dose per day, during the second week of conducting the experiment. Group 2 also included rats (n = 8) that were administered intraperitoneally with appropriate aliquot quantity of citrate buffer equal to pH 4.4 once a week during 2 wk after 1-mo high-fat diet. Group 3 included animals (n = 8) that were administered intraperitoneally with appropriate amount of solution without SkQ1 (98% ethanol

diluted eight times with normal saline solution).

Preparation of materials for the study

To obtain tissue homogenate, heart tissue sample was homogenized in triple amount of cooled medium (0.1 mol/L Tris-HCl buffer (pH 7.8) containing 1 mmol/L EDTA, 1% beta-mercaptoethanol) and centrifuged for 10000 *g* for 15 min. The serum was obtained from venous blood collected in test tubes without anticoagulant. For this purpose, the blood was thermostated at a temperature of 37 °C until phase immiscibility, and supernatant fluid was centrifuged for 4000 *g* for 10 min. The obtained serum was used for further examination.

Evaluation methods of the intensity of free radical oxidation

The free-radical oxidation and total antioxidant status processes intensity was measured by applying the Fe^{2+}-induced biochemical luminescence method. The principle of the method is based on catalytic degradation of peroxide by transition valence metal ions (Fe^{2+}) in accordance with the Fenton reaction. Catalytic degradation leads to the formation of FR that enter free-radical oxidation initiation process in the examined biotic substrate. Recombination of RO_2 radicals results in unstable tetroxide formation that causes liberation of light quantum when it degrades. Biochemicoluminescence kinetic curve was recorded for 30 seconds using BCL-07 with software (Medozons OOO, Nizhny Novgorod, Russia), and the following parameters were measured: Chemicoluminescence light sum (S) and flash intensity (I_{max}) that characterized free-radical oxidation intensity and slope of curve magnitude ($tg\alpha_2$) depicting total antioxidant status.

The medium for estimating BCL intensity contained 0.4 mL of 0.02 mol/L potassium phosphate buffer (pH 7.5); 0.4 mL of 0.01 mol/L $FeSO_4$, and 0.2 mL of 2% H_2O_2 solution that had been added immediately prior to measurement. The test material had been added in an amount of 0.1 mL prior to measurement.

The amount of DC was measured by means of spectrophotometric method at 233 nm[32].

The oxidative modification of proteins valuation method is based on the interaction between oxidized amino acid residues and 2.4-dinitrophenylhydrazine (2.4-DNPH) that forms 2.4-DNPHs[10]. Protein load was identified by the biuret test.

The concentration of DC was analyzed spectrophotometrically at 233 nm[8].

For the analysis of protein oxidative modification (POM), we used the method based on the interaction between oxidized amino acid residues and 2.4-DNPH using the Hitachi U-1900 spectrophotometer (Hitachi High-Technologies, Tokyo, Japan)[9].

Enzyme analysis

Aconitate hydratase (AH) activity was estimated using the Hitachi U-1900 spectrophotometer supplied with software at 233 nm in the medium that contained 0.05 mmol/L of Tris-HC1-buffer (pH 7.8) and 4 mmol/L of sodium citrate (PanReac, Barcelona, Spain)[10].

The amount of citrate was determined by means of the Natelson method[11].

SOD activity was determined by the nitroblue tetrazolium recovery rate inhibition in the non-enzymatic system of phenazine methosulfate (PMS) and NADH.

The incubation medium, with a total volume of 3 mL, contained 0.1 M phosphate buffer (pH 7.8), 0.33 mmol/L EDTA, 0.41 mmol/L NBT, 0.01 mmol/L PMS, and 0.8 mmol/L NADH. The activity was measured spectrophotometrically according to the extinction augmentation after 5 min using the Hitachi U-1900 spectrophotometer at 540 nm[12].

Catalase activity was determined at a wavelength of 410 nm using the method based on the ability of hydrogen peroxide to form stable colored complex with ammonium molybdate[13].

The amount of the enzyme that was required for the conversion of 1 mM of substrate per min at 25 °C was defined as the enzyme unit (E). Biuret method was used to determine the protein content.

Total RNA extraction

Total RNA was isolated from heart tissues and blood cells of experimental animals using Extran RNA reagent kit (Syntol Company, Moscow, Russia). The severity of RNA degradation was determined *via* 1% denaturing agarose gel electrophoresis. The amount of RNA was determined by measuring the absorption at a wavelength of 260 nm using a Hitachi U-1900 spectrophotometer.

A process of reverse transcription

M-MuLV Reverse Transcriptase (Fermentas, Vilnius, Lithuania) was used to carry out reverse transcription. DNA, or complementary mRNA, was obtained *via* Oligo(dT) 18

Primer. The reaction was carried out at 40 °C for 1 h with the following inactivation of reverse transcriptase at 70 °C per 15 min. Ready-to-use cDNA was used for real-time amplification.

A real-time PCR amplification

The primers selected *via* a database of a web-based system Universal Probe Library (Universal Probe Library Assay Design Center) were applied to amplify the region of a gene.

PCR amplification was based on reagent kits containing the SYBR Green I (Syntol Company). Real-time PCR was carried out using an amplifier ANK-32 (Syntol Company) according to the following pattern: Per 5 min at 95 °C, then 40 cycles: 95 °C 15 s, 60 °C 15 s, 72 °C 30 s. The next step was to analyze the threshold cycle value obtained by PCR amplification. Among other scientific experiments, there was also a negative control for: (1) An impurity of foreign DNA set components; and (2) A purity level of sample preparation for the amplification. Negative control consisted of a separate test tube at each process of amplification with an equal amount of water instead of DNA test sample.

Reagents used in the research

During the study, the following chemicals were applied: STZ, Tris-HCl, citrate, nitroblue tetrazolium, PMS, NADH (Sigma, St Louis, MO, United States), SkQ1 synthesized according to the following method[5], EDTA (Reanal, Budapest, Hungary), and other chemicals of "chemically pure" or "analytically pure" grade purchased from Russian manufacturers.

Outcome analysis

Experiments were done in at least 8-20 biological and two analytical replicates. The results were compared with the control. The data were statistically analyzed using a software package STATISTICA 6.0 with numerical variables – arithmetical mean (M), mean error (m), and statistical significance level (P). Normal distribution data were compared by applying Student's t-test for Bonferroni correction in independent samples[14]. Significance level was set at $^{a}P \leq 0.0167$ and $^{b}P \leq 0.0167$.

RESULTS

The study showed that SkQ1 administration lowered glycemic level by 2.5 times, which was initially upregulated 2.7 times relative to the control (Table 1). The glucose level of the animals of the fourth experimental group was not significantly different from the stated value. Moreover, glucose concentration was within the stated value in rats of the second experimental group having been administered citrate buffer and of the third group having been administered an aliquot of 12% ethanol.

It is also established that S of BCL value increased by 2.2 times in rats' hearts under pathological conditions and in blood serum by 2.1 times. I_{max} BCL increased by 2.5 and 2.0, respectively, compared to the control group, demonstrating increased intensity of free radical oxidation. It is known that the processes of glucose autoxidation and its metabolic intermediates, glycosylation of protein and end-product accumulation of its modification, sorbitol exchange mobilization, glucose utilization *via* hexosamine pathway, and protein kinase C (PKC) activation may be free radical oxidation sources in DM2[15].

The values of BCL $tg\alpha_2$ increased in rats' hearts with pathology by 2.1 times and in blood serum by 2.3 times (Table 2), indicating compensatory mechanisms implementation and general antioxidant potential organism mobilization during the development of experimental hyperglycemia.

The administration of SkQ1 led to the S of BCL values decrease in rats' hearts by 1.3 times and in blood serum by 1.6 times and I_{max} BCL by 1.5 and 1.6, respectively (Table 2). BCL $tg\alpha_2$ parameter decreased in rats' hearts by 1.5 times and in blood serum by 1.4 times (Table 2).

No statistically significant BCL parameters changes in rats of the fourth experimental group and the animals belonging to the second experimental group that have been administered citrate buffer and to the third group that have been administered aliquot of 12% ethanol compared with control have been observed (Table 2).

The data received as a result of a research conducted upon the mitochondrial-directed antioxidant and its effect on biochemical luminescence parameters correspond with the results of the assessment of DC level and POM products. It has been shown that the level of DC in the heart and blood serum of animals of the third group has declined 1.4 and 1.7 times, correspondingly, in comparison with the

Table 1 Glucose concentration in rats' blood

	Glucose concentration in rats' blood, mmol/L	
	The 9th d after STZ administration	The 11th d after STZ administration
Control group	5.09 ± 0.081	5.41 ± 0.088
Animals with experimental hyperglycemia induced by streptozotocin	10.01 ± 0.166[a]	14.6 ± 0.241[a]
SkQ1 is administered to animals with pathology	6.04 ± 0.099[b]	5.87 ± 0.096[b]
SkQ1 is administered to animals at control group	5.1 ± 0.083	5.30 ± 0.086

[a]$P \leq 0.0167$ compared with control;
[b]$P \leq 0.0167$ compared with pathology. SkQ1: 10-(6-plastoquinonyl) decyltriphenylphosphonium; STZ: Streptozotocin.

pathology (Table 2). It was found that the concentration of primary products of LPO in the heart and blood serum of rats from the second group increased 2.4 and 3.3 times, correspondingly (Table 2). The progression of hyperglycemia with animals injected with STZ went along with the increase in POM products content: 2.7 times in the heart and 6.3 times in blood serum in comparison with the control group. After the injection of rats with pathology with SkQ1 carbonyl compounds, the level decreased 1.5 times in the heart and 2.0 times in blood serum in contrast with the pathology (Table 2).

DC and carbonyl compounds content in the heart and blood serum of rats under the standard mode of the vivarium and injected with SkQ1 and of animals from the second experimental group injected with citrate buffer and the third group that were administered with aliquot of ethanol with mass fraction of 12% did not change significantly in comparison with the control level (Table 2).

It is known that FR may have aconitase as a target of action. Decline in activity of aconitase is interrelated with the accumulation of citrate that, in turn, is an effective low molecular weight antioxidant due to its chelating properties in relation to ions Fe^{2+}[16].

It has been established that in case of hyperglycemia, specific activity of aconitase declines 1.9 times in the heart and 2.3 times in blood serum of rats in comparison with the control level (Figure 1). The slowdown in activity of aconitase within the pathology is clearly connected with intensification of ROS formation and the induction in the development of oxidative stress. It was found that FR participate directly in the oxidation and inactivation of the aconitase iron-sulfur cluster. The long-term exposure of FR leads to the dismantlement of [4Fe-4S] cluster, carbonylation, and degradation of the enzyme.

As a result of SkQ1 exposure, the specific activity of the given enzyme increased 1.4 times in the heart and 1.8 times in blood serum in comparison with the data received from experimental hyperglycemia (Figure 1). It appears that the administration of protector in the bodies of animals with pathology facilitated a decline in the level of ROS and, as a result, a decrease in the damage degree of the molecule of the enzyme and a change in aconitase activity towards control.

Along with the development of the examined pathology, citrate content increased 2.1 times in the heart and 2.5 times in blood serum (Table 2). Presumably, it was mediated by the inhibition of aconitase. In turn, citrate accumulation could be an adaptive process with the development of oxidative stress at pathology, due to the fact that citric acid chelates iron ions and decreases the Fenton's reaction rate. As a result, the possibility of hydroxyl radical formation declines.

It was found that the injection of SkQ1 leads to the decline of citrate content by 1.5 times in the heart and by 1.3 times in blood serum (Table 2). Presumably, the antioxidant effect provided by SkQ1 was manifested by the decline in the level of oxidative stress and by damage degree of the aconitase molecule. As a result, the activity of the given enzyme increased and led to the increase in citrate utilization rate.

The administration of SkQ1 to the animals of the fourth experimental group did not cause any statistically significant changes in aconitase activity and in heart and blood serum citrate levels in comparison with the control group. The administration of citrate buffer to the animals of the second group and of 12% ethyl solution to the third group did not cause such changes either.

The experiments showed that pathological conditions caused the increase in SOD and catalase specific activities in comparison with the control group of the animals. They were increased by 2.5 times in the heart and by 2.2 and 2.3 times in the blood serum, respectively (Figure 2 and Figure 3 respectively). It was noted that SOD gene

Table 2 Parameters reflecting the level of free radical processes and general antioxidant system activity

Parameters		Experiment conditions			
		Control group	Animals with experimental hyperglycemia induced by streptozotocin	SkQ1 is administered to animals with pathology	SkQ1 is administered to animals at control group
Biochemicoluminescence measurements					
Light sum, mV × c	Heart	485.01 ± 7.912	1062.76 ± 17.124*a*	818.76 ± 13.611*b*	478.33 ± 7.971
	Blood serum	307.70 ± 5.141	654.14 ± 10.114*a*	410.53 ± 6.713*b*	302.33 ± 5.012
Maximum flash intensity, mV	Heart	51.53 ± 0.851	126.93 ± 1.987*a*	83.10 ± 1.374*b*	47.33 ± 0.779
	Blood serum	25.20 ± 0.412	52.23 ± 0.864*a*	33.67 ± 0.559*b*	22.15 ± 0.362
Angle tangent of slope of kinetic curve of biochemicoluminescence pathway	Heart	7.10 ± 0.101	14.94 ± 0.241*a*	10.10 ± 0.165*b*	7.05 ± 0.112
	Blood serum	13.33 ± 0.223	30.43 ± 0.498*a*	21.71 ± 0.359*b*	12.93 ± 0.183
Content of conjugated dienes, μmol/mL	Heart	17.70 ± 0.281	41.90 ± 0.687*a*	29.76 ± 0.492*b*	17.22 ± 0.267
	Blood serum	7.55 ± 0.122	24.83 ± 0.401*a*	15.00 ± 0.247*b*	7.33 ± 0.113
Level of carbonyl compounds, nmol/L/mg of protein	Heart	0.072 ± 0.001	0.199 ± 0.003*a*	0.136 ± 0.002*b*	0.070 ± 0.001
	Blood serum	0.021 ± 0.0003	0.154 ± 0.002*a*	0.076 ± 0.001*b*	0.019 ± 0.0003
Citrate content, nmol/L	Heart	0.201 ± 0.003	0.43 ± 0.007*a*	0.28 ± 0.004*b*	0.204 ± 0.003
	Blood serum	0.57 ± 0.0097	1.45 ± 0.021	1.07 ± 0.016*b*	0.59 ± 0.0093

[a]$P \leq 0.0167$ compared with control;
[b]$P \leq 0.0167$ compared with pathology. SkQ1: 10-(6-plastoquinonyl) decyltriphenylphosphonium.

transcript and catalase gene transcript blood cell levels increased by 2.5 and by 1.6 times, respectively, and their heart levels increased by 2.3 and by 4.0 times, respectively (Figure 4). These enzyme activity changes in the case of hyperglycemia can probably be considered as a compensatory reaction to intensifying free-radical processes.

The administration of SkQ1 to the animals caused a decrease in SOD and catalase activities in comparison with pathological conditions. It was found that the impact of SkQ1 leads to the decrease in SOD and catalase heart and blood serum specific activities in comparison with the second group of animals. Thus, SOD heart and blood serum specific activities were decreased by 1.4 times and by 1.6 times, respectively (Figure 2), and catalase heart and blood serum activities were decreased by 1.5 and 1.4 times, respectively (Figure 3).

The identified studied enzyme activity is connected with the decrease in the number of their gene transcripts. Thus, the concentration of SOD1 and CAT gene products decreased by 1.5 and 1.3 times in the blood cells and by 1.4 and 1.3 times in the heart (Figure 4). Apparently, the reduction of free radical formation and, consequently, the reduction of oxidative stress, caused indirectly by SkQ1 antioxidant effect, were accompanied by decreased pressure on AOS, which was reflected in the approximation of SOD and catalase activities to the control values.

In comparison with the first group, the rats of the fourth experimental group, the rats of the second experimental group, to which citrate buffer was administered, and the rats of the third group, to which the aliquot of 12% ethyl alcohol solution was administered, did not have any statistically significant changes in SOD and catalase activities as well as in SOD and CAT gene transcript levels.

DISCUSSION

It is known that the inclusion of high fat content in rat diet contributes to the occurrence of animal tolerance to insulin[17]. Small dose administration of STZ leads to the moderate decline in insulin production, which is similar to a later stage of DM2[18]. Thus, the administration of STZ causes a significant basal increase in the blood glucose level. It also causes glucose tolerance, increase in the glycated hemoglobin level, significant reduction of insulin concentration, and resistance.

It should be noted that under conditions of tissue tolerance to insulin, observed

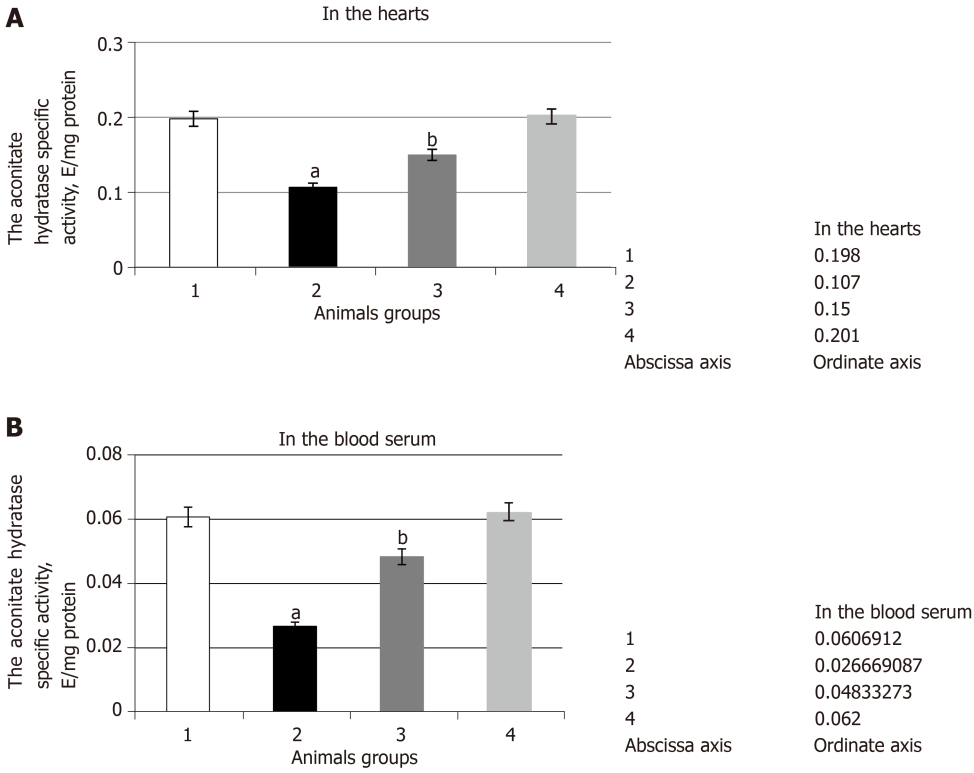

Figure 1 The aconitatehydratase specific activity, E/mg protein in the rats' hearts and the blood serum during the development of experimental hyperglycemia. A: The aconitatehydratase specific activity, E/mg protein in the rats' hearts during the development of experimental hyperglycemia; B: The aconitatehydratase specific activity, E/mg protein in the blood serum during the development of experimental hyperglycemia. 1: Control group; 2: Animals with experimental hyperglycemia induced by streptozotocin; 3: 10-(6-plastoquinonyl) decyltriphenylphosphonium (SkQ1) is administered to animals at pathology; 4: SkQ1 is administered to animals at control group. [a]$P \leq 0.0167$ compared with control; [b]$P \leq 0.0167$ compared with pathology. SkQ1: 10-(6-plastoquinonyl) decyltriphenylphosphonium.

during DM2, there is an increase in superoxide production by mitochondria[19], cytochrome P450, xanthine oxidase, and PKC-dependent NADPH oxidase activation. Moreover, the FR, which are generated during glucose autoxidation or glycosylation end products, can initiate LPO in lipoprotein particles[20]. The concentration of LPO products through an increase in hydrophilic hydrocarbon tails contents, in turn, can lead to formation of membrane pores and membrane stiffening through downregulation of unsaturated fatty acids, and thus it can influence state of insulin receptors, repressing their hormone connection activity, which is expressed as a reduction of the glucose consumption by cells[21]. It is possible that reduction in glucose concentration during administration of SkQ1 to rats with DM2 may be related to the realization of antioxidant properties of this substance[22].

It is well known that during several pathological states, including DM, LPO activation occurs and can lead to a number of defects, structural changes in membranes, and cell metabolic disturbance in particular. At the same time, ROS, including LPO products, act as the main POM inducers[23].

The use of SkQ1 may contribute to an inhibition of accumulation of LPO molecular products and a normalization of the structural condition of lymphocytes' membranes and their apoptosis level during oxidative stress[24].

Reviewing past literature, it is well known that through administration of SkQ1, the rate of development of such diseases as cataract, retinopathy, glaucoma, osteoporosis, hypothermia, and renal ischemia decreases[25]. Furthermore, in animal experiments, SkQ1 efficiency of correction of the several neurodegenerative states was shown[26]. The effect of SkQ1 led to acceleration of the end of the inflammatory phase, the formation of granulation tissue, vascularization, and epithelization of a wounded area[27]. Moreover, it was shown that in OXYS rats of an experimental model of accelerated aging, which is a famous animal model of human age-related macular degeneration, SkQ1 reduces clinical features of retinopathy[28].

According to the results obtained, it was found that administration of the antioxidant compound is accompanied by reduction in concentration of primary LPO products in both blood serum and heart closer to its control values.

During the experiment, it was found that an increase in activity of SOD and

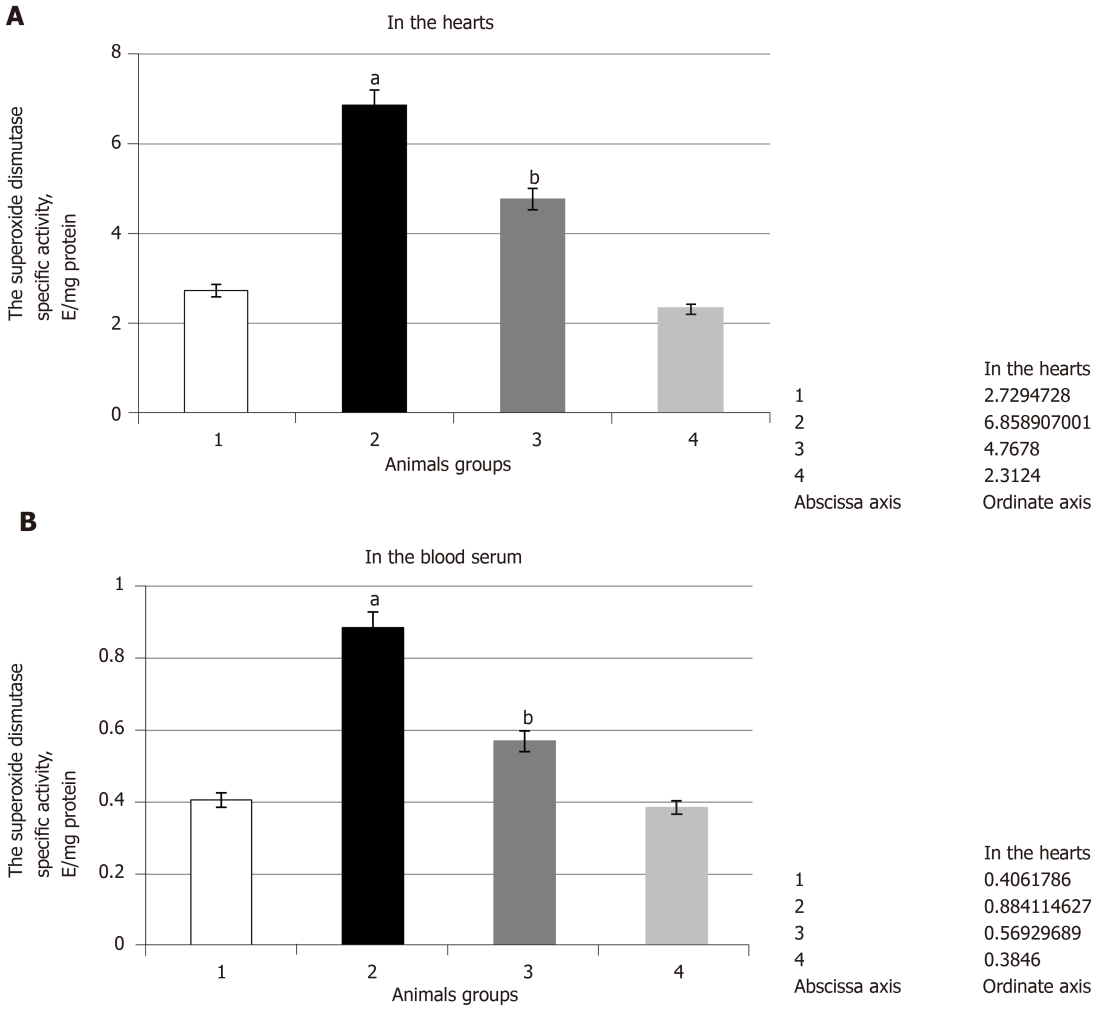

Figure 2 The superoxide dismutase specific activity, E/mg protein in the rats' hearts, and the blood serum during the development of experimental hyperglycemia. A: The superoxide dismutase (SOD) specific activity, E/mg protein in the rats' hearts during the development of experimental hyperglycemia; B: The SOD specific activity, E/mg protein in the blood serum during the development of experimental hyperglycemia. 1: Control group; 2: Animals with experimental hyperglycemia mellitus induced by streptozotocin; 3: 10-(6-plastoquinonyl) decyltriphenylphosphonium (SkQ1) is administered to animals at pathology; 4: SkQ1 is administered to animals at control group. $^{a}P \leq 0.0167$ compared with control; $^{b}P \leq 0.0167$ compared with pathology. SkQ1: 10-(6-plastoquinonyl) decyltriphenylphosphonium.

catalase in rats of the DM2 group may be related to induction of the synthesis of these enzymes under conditions of the oxidative stress formed in pathology.

Thus, according to the data provided by the literature, the regions reacting with nuclear factor kappa B (NF-kB) were discovered in the coding regions of all three SOD genes[29]. NF-kB is a redox-sensitive transcription factor and acts as a regulator of genes, playing a role of the actual defendant to injurious effects on a cell. It should be noted that H_2O_2, generated in the reaction that is catalyzed by Cu, Zn-SOD on the endosomal surface, can cause oxidation-reduction NF-κB activation. NF-κB activation leads to an increase in Cu, Zn-SOD expression[30].

It is evident that an increase in the dismutation rate of a superoxide anion radical leads to the accumulation of hydrogen peroxide. It is known that the amount of catalase is controlled by the presence of substrate[31].

It is stated that superoxide anion radicals activate various signaling systems. It includes Keap1 - Nrf2, which is responsible for the induction of a significant number of genes, including antioxidant enzyme genes[32]. Besides, c-jun N-terminal kinase, which is the main inducer activity of forkhead homeobox type O (FOXO) transcription factors, can be activated during hyperglycemia that contributes to the development of oxidative stress. FOXO can also be considered as messengers during the development of oxidative stress, since their activity is regulated by H_2O_2 and depends on the state of the cell[33].

It is known that protection against oxidative stress of human cardiac fibroblasts after myocardial infarction is mediated by expression of antioxidant enzymes regulated by FOXO, such as SOD, catalase, and peroxidase[34]. In addition, FOXO3a, a

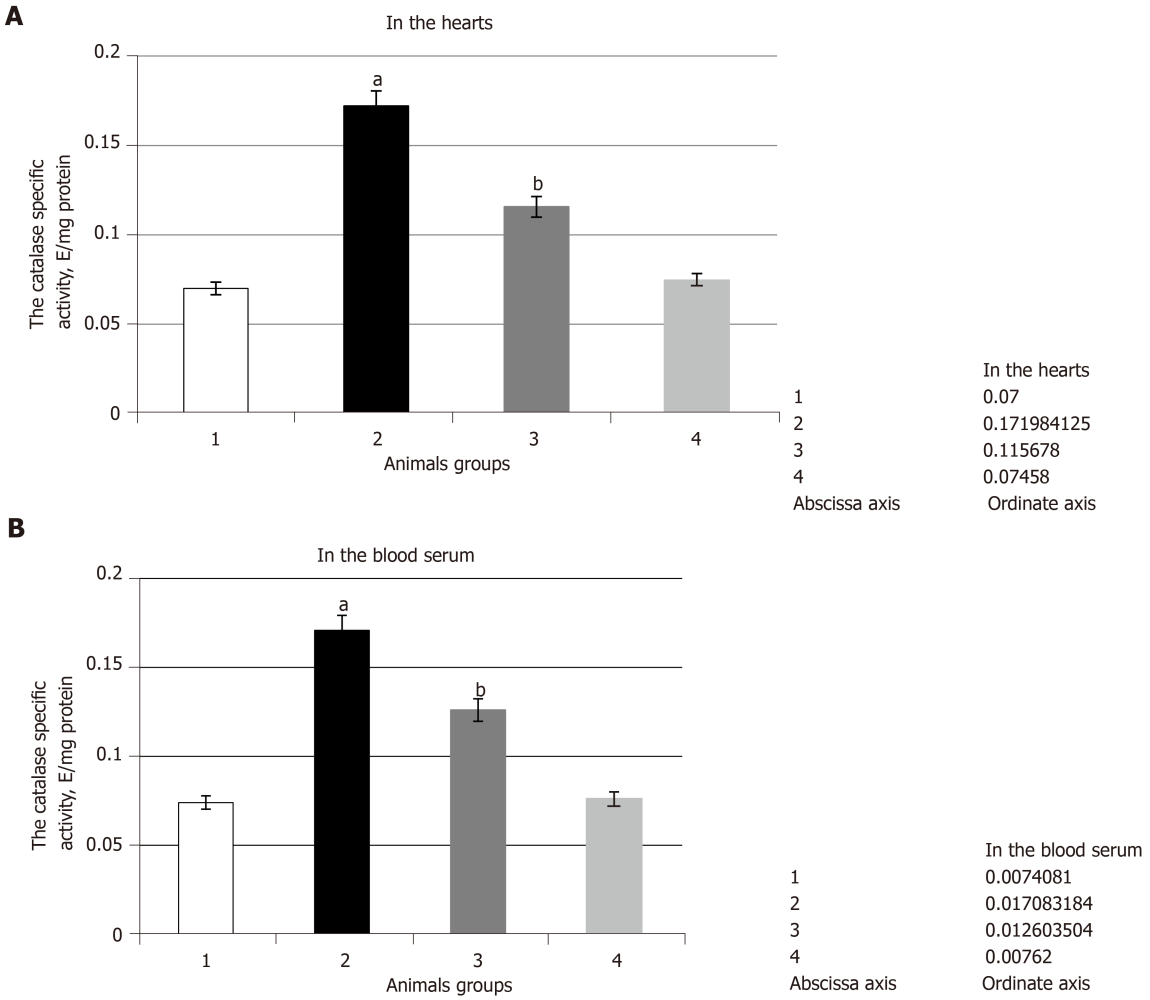

Figure 3 The catalase specific activity, E/mg protein in the rats' hearts, and the blood serum during the development of experimental hyperglycemia. A: The catalase specific activity, E/mg protein in the rats' hearts during the development of experimental hyperglycemia; B: The catalase specific activity, E/mg protein in the blood serum during the development of experimental hyperglycemia. 1: Control group; 2: Animals with experimental hyperglycemia induced by streptozotocin; 3: 10-(6-plastoquinonyl) decyltriphenylphosphonium (SkQ1) is administered to animals at pathology; 4: SkQ1 is administered to animals at control group. $^{a}P \leq 0.0167$ compared with control; $^{b}P \leq 0.0167$ compared with pathology. SkQ1: 10-(6-plastoquinonyl) decyltriphenylphosphonium.

member of the FOXO family, induces catalase gene expression in human cells[35]. Moreover, it activates the expression of Mn-SOD by regulating the SOD2 gene after exposure to resting cells with hydrogen peroxide[36].

The increase in the activity and level of transcripts of the studied antioxidant enzymes in pathology probably could be related to the considered molecular genetic mechanisms of the redox regulation of gene expression activity under conditions of excessive generation of ROS. A decrease in the intensity of free radical oxidation under the influence of SkQ1 led to a change in the studied parameters towards control values.

In conclusion, the results of this research suggest that the mitochondria targeted antioxidant SkQ1 might be a perspective substance for incorporation into the antioxidant therapy of DM2. The experimentally revealed ability of this compound to lower the intensity of free-radical processes, acting as the key component of the pathogenesis of the DM2, may serve as the reason for this conclusion. Thus, after the introduction of SkQ1 to the animals with STZ induced hyperglycemia, the values of the BCL parameters reflecting the free radical oxidation intensity, the concentration of DC and carbonyl products of protein oxidation, AH activity, and citrate content changed towards the control values. At the same time, the activity level of the antioxidant enzymes SOD and catalase changed to the direction of normal values.

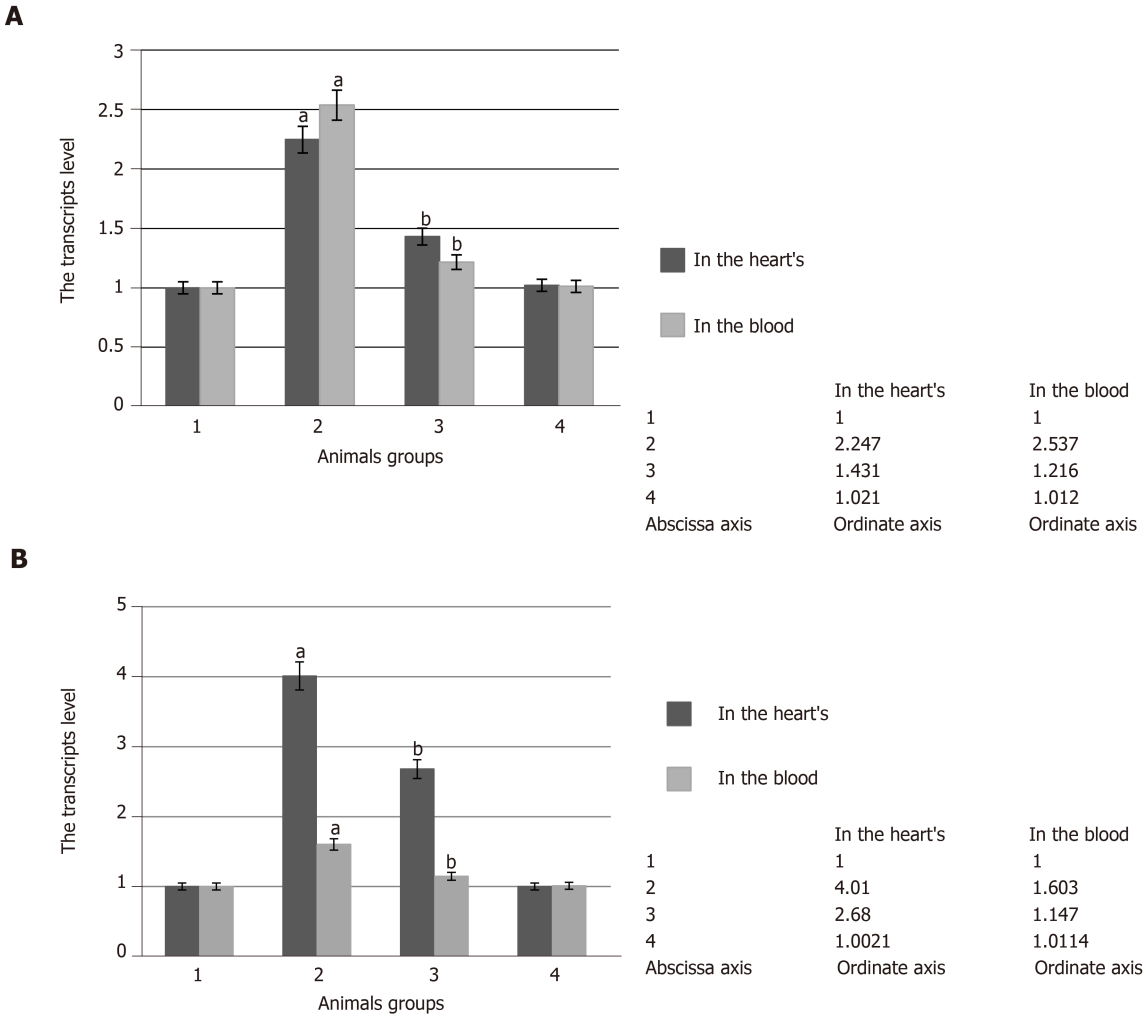

Figure 4 The relative level of the superoxide dismutase and catalase genes transcripts in the rats' hearts and the blood cells during the development of experimental hyperglycemia. A: The relative level of the superoxide dismutase genes transcripts in the rats' hearts and the blood cells during the development of experimental hyperglycemia; B: The relative level of the catalase genes transcripts in the rats' hearts and the blood cells during the development of experimental hyperglycemia. 1: Control group; 2: Animals with experimental hyperglycemia induced by streptozotocin; 3: 10-(6-plastoquinonyl) decyltriphenylphosphonium (SkQ1) is administered to animals at pathology; 4: SkQ1 is administered to animals at control group. [a]$P \leq 0.0167$ compared with control; [b]$P \leq 0.0167$ compared with pathology. SkQ1: 10-(6-plastoquinonyl) decyltriphenylphosphonium.

ARTICLE HIGHLIGHTS

Research methods

All treatments of the experiment were consistent with the requirements of the European legislation on the protection of animals (Directive 2010/63/EU).

The laboratory rats were divided into four groups: Group 1 (n = 20), animals housed under standard vivarium conditions (control group); group 2 (n = 20), animals with streptozotocin (STZ) injection-induced hyperglycemia; group 3 (n = 12), animals with STZ-induced glycemia that were administered with 10-(6-plastoquinonyl) decyltriphenylphosphonium (SkQ1) solution intraperitoneally at a 1250 nmol/kg dose per day, starting from the second week; and group 4 (n = 8), animals housed under standard vivarium conditions that were administered with SkQ1 at a 1250 nmol/kg dose per day, during the second week of conducting the experiment. Group 2 also included rats (n = 8) that were administered intraperitoneally with appropriate aliquot quantity of citrate buffer equal to pH 4.4 once a week during 2 wk after 1-mo high-fat diet. Group 3 included animals (n = 8) that were administered intraperitoneally with appropriate amount of solution without SkQ1 (98% ethanol diluted eight times with normal saline solution). The experimental unit was a single animal. Rats were kept in laboratory, and they were divided through stratified randomization by their weight and age.

Hyperglycemia was induced by feeding rats a high-fat diet for 1 mo. STZ was administered intra-abdominally at a 30 mg/kg of animal weight dose with citrate buffer equal to pH 4.4. Hyperglycemia was verified by measuring the glucose level in the blood serum with a glucose oxidase test. SkQ1 solution was administered intraperitoneally at a 1250 nmol/kg dose per day. Appropriate aliquot quantity of citrate buffer equal to pH 4.4 was administered intraperitoneally.

To conduct the study, laboratory rats were selected of nursery rat males from Federal State-financed Organization of Health Service "Voronezh Hygiene and Epidemiology Center". The rats used for the study weighed 200-250 g and aged 3-5 mo. Rats were kept at 12-h light day, room temperature, and access to water and food *ad libitum* for 2 wk before the study. Type of housing – plastic. Bedding material – sawdust. Number of cage companions - two rats per cage. The total number of animals used in experiment – 76 rats. The number of animals in each experimental group: Group 1 (n = 20 + 8); group 2 (n = 20 + 8); group 3 (n = 12); and group 4 (n = 8).

The number of animals was necessary for obtaining statistically significant results. The animals were divided through stratified randomization by their weight and age. The rats used for the study weighed 200-250 g and aged 3-5 mo.

The order in which the animals in the different experimental groups were treated and assessed: Group 2 compared with group 1; group 3 compared with group 2; and group 4 compared with group 1. Weight gain, increased water intake, and slowness in rats of the second group were seen. SkQ1 administration lowered glycemic level by 2.5 times, which was initially upregulated 2.7 times relative to the control. The glucose level of the animals of the fourth experimental group was not significantly different from the stated value. Moreover, glucose concentration was within the stated value in rats of the second experimental group, having been administered citrate buffer and of the third group, having been administered aliquot of 12% ethanol. The unit of analysis was group of animals.

Experiments were done at least in 8-20 biological and two analytical replicates. The results were compared with the control. The data were statistically analyzed using software package STATISTICA 6.0 with numerical variables – arithmetical mean (M), mean error (m), and statistical significance level (P). Normal distribution data were compared by applying Student's t-test for Bonferroni correction in independent samples. Significance level was set at $^{a}P \leq 0.0167$ and $^{b}P \leq 0.0167$.

Research results

It was found that influence of the mitochondrial-directed antioxidant elicits decrease of biochemiluminescence (BCL) parameters values that increase by pathology as well as the level of primary products of lipid peroxidation such as diene conjugates and carbonyl compounds, which indicate intensity of free radical oxidation. At the same time, the activity of aconitate hydratase (AH), considered as a crucial target of FR, which was decreasing during experimental hyperglycemia, increased. Apparently, increasing activity of AH influenced the speed of citrate utilization, whose concentration was decreasing after administering SkQ1 by pathology. Moreover, the previously applied anti-oxidant administration during hyperglycemia influenced the rate of antioxidant system mobilization. Thus, superoxide dismutase and catalase activity as well as the level of gene transcript under influence of SkQ1 at pathology were changing towards control groups values.

Research conclusions

The results of this research suggest that the mitochondria targeted antioxidant SkQ1 might be a perspective substance for incorporation into the antioxidant therapy of type 2 diabetes mellitus (DM2). The experimentally revealed ability of this compound to lower the intensity of free-radical processes, acting as the key component of the pathogenesis of the DM2, may serve as the reason for this conclusion. Thus, after the introduction of SkQ1 to the animals with STZ induced hyperglycemia, the values of the BCL parameters reflecting the free radical oxidation intensity, the concentration of diene conjugates and carbonyl products of protein oxidation, the AH activity, and citrate content changed towards the control values. At the same time, the activity level of the antioxidant enzyme SOD and catalase changed to the direction of normal values.

Research perspectives

The effects of SkQ1 on the stage of compensatory response occurrence in pathology may contribute to decrease of the degree of oxidative stress, normalization of antioxidant system functioning, and blocking of the development of decompensation, characterized by the inhibition of protective systems.

Thus, the mitochondria targeted antioxidant SkQ1 might be considered a perspective substance for incorporation into the antioxidant therapy of DM2.

ACKNOWLEDGEMENTS

The authors are very grateful to Academician of RAS, Prof. Vladimir P Skulachev for useful advice and attention to this study.

REFERENCES

1 **Jia G**, DeMarco VG, Sowers JR. Insulin resistance and hyperinsulinaemia in diabetic cardiomyopathy. *Nat Rev Endocrinol* 2016; **12**: 144-153 [PMID: 26678809 DOI: 10.1038/nrendo.2015.216]
2 **Ametov AS**. Diabetes mellitus type II. Problems and solutions. Moscow: GEOTAR-Media 2014; 1032
3 **Peterson LR**, Herrero P, Schechtman KB, Racette SB, Waggoner AD, Kisrieva-Ware Z, Dence C, Klein S, Marsala J, Meyer T, Gropler RJ. Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. *Circulation* 2004; **109**: 2191-2196 [PMID: 15123530 DOI:

10.1161/01.CIR.0000127959.28627.F8]
4 **Boudina S**, Abel ED. Diabetic cardiomyopathy revisited. *Circulation* 2007; **115**: 3213-3223 [PMID: 17592090 DOI: 10.1161/CIRCULATIONAHA.106.679597]
5 **Antonenko YN**, Avetisyan AV, Bakeeva LE, Chernyak BV, Chertkov VA, Domnina LV, Ivanova OYu, Izyumov DS, Khailova LS, Klishin SS, Korshunova GA, Lyamzaev KG, Muntyan MS, Nepryakhina OK, Pashkovskaya AA, Pletjushkina OYu, Pustovidko AV, Roginsky VA, Rokitskaya TI, Ruuge EK, Saprunova VB, Severina II, Simonyan RA, Skulachev IV, Skulachev MV, Sumbatyan NV, Sviryaeva IV, Tashlitsky VN, Vassiliev JM, Vyssokikh MYu, Yaguzhinsky LS, Zamyatnin Jr. AA, Skulachev VP. Mitochondria-Targeted Plastoquinone Derivatives as Tools to Interrupt Execution of the Aging Program. 1. Cationic Plastoquinone Derivatives: Synthesis and in vitro Studies. *Biochemistry (Mosc)* 2008; **73**: 1589-1606 [PMID: 19120014 DOI: 10.1134/S0006297908120018]
6 **Ter-Tatevosyan LP**, Sarkisyan LV, Yeranosyan LA, Arakelyan LN, Shirinyan EA, Galoyan AA. Enzymes of carbohydrate-phosphorus metabolism in the bone marrow and spleen after sympathectomy. Effects of neuropeptide PRP-1. *Neurochem J* 2009; **3**: 301–304 [DOI: 10.1134/S1819712409040102]
7 **Zhang M**, Lv XY, Li J, Xu ZG, Chen L. The characterization of high-fat diet and multiple low-dose streptozotocin induced type 2 diabetes rat model. *Exp Diabetes Res* 2008; **2008**: 704045 [PMID: 19132099 DOI: 10.1155/2008/704045]
8 **Recknagel RO**, Ghoshal AK. Lipoperoxidation of rat liver microsomal lipids induced by carbon tetrachloride. *Nature* 1966; **210**: 1162-1163 [PMID: 4960496 DOI: 10.1038/2101162a0]
9 **Reznick AZ**, Packer L. Oxidative damage to proteins: spectrophotometric method for carbonyl assay. *Methods Enzymol* 1994; **233**: 357-363 [PMID: 8015470 DOI: 10.1016/S0076-6879(94)33041-7]
10 **Popova TN**, Agarkov AA, Verevkin AN. Intensity of Free Radical Processes in Rat Liver under Type 2 Diabetes and Introduction of Epifamin. *Acta Naturae* 2013; **5**: 118-122 [PMID: 24455191 DOI: 10.32607/20758251-2013-5-4-118-122]
11 **Afanas'ev VG**, Zaytsev VS, Vol'fson TI. A micromethod of detecting citric acid in the blood serum by photoelectrocolorimeter. *Lab Delo* 1973; **2**: 115-116 [PMID: 4128330]
12 **White A**, Hendler F, Smith E, Hill R, Lehman I. Fundamentals of Biochemistry: In 3 volumes. V.3. Trans. from English. Moscow: Mir 1981; 7264
13 **Góth L**. A simple method for determination of serum catalase activity and revision of reference range. *Clin Chim Acta* 1991; **196**: 143-151 [PMID: 2029780 DOI: 10.1016/0009-8981(91)90067-M]
14 **Glantz S**. Medico-biological statistics. Moscow: Praktika 1998; 459
15 **Zanozina OV**, Borovkov NN, Shcherbatyuk TG. Free-radical oxidation at a diabetes mellitus of the 2nd type: sources of formation, components, pathogenetic mechanisms of toxicity. *Sovremennyye tekhnologii v meditsine* 2010; **3**: 104-112
16 **Matasova LV**, Popova TN. Aconitate Hydratase of Mammals under Oxidative Stress. *Biochemistry (Mosc)* 2008; **73**: 957-964 [PMID: 18976211 DOI: 10.1134/S0006297908090010]
17 **Chukanov CN**, Dvoracka M, Iskakova SS, Kurmambayev EZh. Modeling of Type 2 Diabetes Mellitus for the Study of Medicines with Antidiabetic Activity. *Nauka i zdravookhraneniye* 2004; **4**: 4-8
18 **Srinivasan K**, Viswanad B, Asrat L, Kaul CL, Ramarao P. Combination of high-fat diet-fed and low-dose streptozotocin-treated rat: a model for type 2 diabetes and pharmacological screening. *Pharmacol Res* 2005; **52**: 313-320 [PMID: 15979893 DOI: 10.1016/j.phrs.2005.05.004]
19 **Brownlee M**. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; **414**: 813-820 [PMID: 11742414 DOI: 10.1038/414813a]
20 **Inoguchi T**, Li P, Umeda F, Yu HY, Kakimoto M, Imamura M, Nawata H. High glucose level and free fatty acid stimulate reactive oxygen species production through protein kinase C-dependent activation of NAD(P)H oxidase in cultured vascular cells. *Diabetes* 2000; **49**: 1939-1945 [PMID: 11078463 DOI: 10.2337/diabetes.49.11.1939]
21 **Mikaelyan NP**, Potemkin VV, Frantseva EYu, Kulaeva IO. Functional state of the membrane-receptor apparatus of blood cells with newly diagnosed type 2 diabetes mellitus. *Problemy endokrinologii* 2012; **4**: 40-41
22 **Voronkova YG**, Popova TN, Agarkov AA, Skulachev MV. Effects of 10-(6'-plastoquinol)-decyltriphenylphosphonium (SkQ1) on oxidative status in rats with protamine sulfate-induced hyperglycemia. *Biochemistry (Mosc)* 2015; **80**: 1871-1879 [DOI: 10.1134/S0006297915120093]
23 **Dean RT**, Hunt JV, Grant AJ. Free radical damage to proteins: the influence of the relative localization of radical generation, antioxidants, and target proteins. *Free Radic Biol Med* 1991; **11**: 161-168 [PMID: 1937134 DOI: 10.1016/0891-5849(91)90167-2]
24 **Teixeira J**, Deus CM, Borges F, Oliveira PJ. Mitochondria: Targeting mitochondrial reactive oxygen species with mitochondriotropic polyphenolic-based antioxidants. *Int J Biochem Cell Biol* 2018; **97**: 98-103 [PMID: 29454114 DOI: 10.1016/j.biocel.2018.02.007]
25 **Skulachev VP**, Bogachev AV, Kasparinskiy FO. Membrane Bioenergetics. Moscow: Publishing House of Moscow University 2010; 365
26 **Lakomkin VL**, Kapel'ko VI. Protective effect of mitochondrial antioxidant SkQ1 at cardiac ischemia and reperfusion. *Kardiologiya* 2009; **49**: 55-60 [PMID: 19845521]
27 **Demyanenko IA**, Popova EN, Zakharova VV, Ilyinskaya OP, Vasilieva TV, Romashchenko VP, Fedorov AV, Manskikh VN, Skulachev MV, Zinovkin RA, Pletjushkina OY, Skulachev VP, Chernyak BV. Mitochondria-targeted antioxidant SkQ1 improves impaired dermal wound healing in old mice. *Aging (Albany NY)* 2015; **7**: 475-485 [PMID: 26187706 DOI: 10.18632/aging.100772]
28 **Perepechaeva ML**, Grishanova AY, Rudnitskaya EA, Kolosova NG. The Mitochondria-Targeted Antioxidant SkQ1 Downregulates Aryl Hydrocarbon Receptor-Dependent Genes in the Retina of OXYS Rats with AMD-Like Retinopathy. *J Ophthalmol* 2014; **2014**: 530943 [PMID: 25132985 DOI: 10.1155/2014/530943]
29 **Hoffmann A**, Natoli G, Ghosh G. Transcriptional regulation via the NF-kappaB signaling module. *Oncogene* 2006; **25**: 6706-6716 [PMID: 17072323 DOI: 10.1038/sj.onc.1209933]
30 **Rojo AI**, Salinas M, Martín D, Perona R, Cuadrado A. Regulation of Cu/Zn-superoxide dismutase expression via the phosphatidylinositol 3 kinase/Akt pathway and nuclear factor-kappaB. *J Neurosci* 2004; **24**: 7324-7334 [PMID: 15317858 DOI: 10.1523/JNEUROSCI.2111-04.2004]
31 **Miroshnichenko OS**. Biogenesis, physiological role, and properties of catalase. *Biopolym Cell* 1992; **8**: 3-25 [DOI: 10.7124/bc.00033C]
32 **Hayes JD**, Dinkova-Kostova AT. The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. *Trends Biochem Sci* 2014; **39**: 199-218 [PMID: 24647116 DOI: 10.1016/j.tibs.2014.02.002]

33 **Essers MA**, Weijzen S, de Vries-Smits AM, Saarloos I, de Ruiter ND, Bos JL, Burgering BM. FOXO transcription factor activation by oxidative stress mediated by the small GTPase Ral and JNK. *EMBO J* 2004; **23**: 4802-4812 [PMID: 15538382 DOI: 10.1038/sj.emboj.7600476]

34 **Storz P**. Forkhead homeobox type O transcription factors in the responses to oxidative stress. *Antioxid Redox Signal* 2011; **14**: 593-605 [PMID: 20618067 DOI: 10.1089/ars.2010.3405]

35 **Nemoto S**, Finkel T. Redox regulation of forkhead proteins through a p66shc-dependent signaling pathway. *Science* 2002; **295**: 2450-2452 [PMID: 11884717 DOI: 10.1126/science.1069004]

36 **Kops GJ**, Dansen TB, Polderman PE, Saarloos I, Wirtz KW, Coffer PJ, Huang TT, Bos JL, Medema RH, Burgering BM. Forkhead transcription factor FOXO3a protects quiescent cells from oxidative stress. *Nature* 2002; **419**: 316-321 [PMID: 12239572 DOI: 10.1038/nature01036]

World Journal of Diabetes

Submit a Manuscript: https://www.f6publishing.com

World J Diabetes 2019 December 15; 10(12): 560-580

DOI: 10.4239/wjd.v10.i12.560

ISSN 1948-9358 (online)

SYSTEMATIC REVIEWS

Correlating the global increase in type 1 diabetes incidence across age groups with national economic prosperity: A systematic review

Natalia Gomez-Lopera, Nicolas Pineda-Trujillo, Paula Andrea Diaz-Valencia

ORCID number: Natalia Gomez-Lopera (0000-0003-0094-6421); Nicolas Pineda-Trujillo (0000-0002-8342-2510); Paula Andrea Diaz-Valencia (0000-0001-8065-5629).

Author contributions: Gomez-Lopera N and Diaz-Valencia PA conducted the data collection and analyses; Gomez-Lopera N, Diaz-Valencia PA and Pineda-Trujillo N contributed to the writing of the manuscript. All authors read and approved the final manuscript.

Supported by doctoral scholarship (Natalia Gomez-Lopera) from Colciencias, No. 727.

Conflict-of-interest statement: The authors declare no conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 checklist.

Natalia Gomez-Lopera, Nicolas Pineda-Trujillo, Grupo Mapeo Genetico, Departamento de Pediatría, Facultad de Medicina, Universidad de Antioquia, Medellín 050010470, Colombia

Paula Andrea Diaz-Valencia, Epidemiology Group. School of Public Health. Universidad de Antioquia, Medellín 050010470, Colombia

Corresponding author: Natalia Gomez-Lopera, BSc, PhD, Academic Research, Research Scientist, Pediatrics, Departamento de Pediatría, Facultad de Medicina, Universidad de Antioquia, Carrera 51D No. 62-21, Medellín 050010470, Colombia.
natalia.gomezl@udea.edu.co
Telephone: +57-4-2106065
Fax: +57-4-2196069

Abstract

BACKGROUND

The global epidemiology of type 1 diabetes (T1D) is not yet well known, as no precise data are available from many countries. T1D is, however, characterized by an important variation in incidences among countries and a dramatic increase of these incidences during the last decades, predominantly in younger children. In the United States and Europe, the increase has been associated with the gross domestic product (GDP) per capita. In our previous systematic review, geographical variation of incidence was correlated with socio-economic factors.

AIM

To investigate variation in the incidence of T1D in age categories and search to what extent these variations correlated with the GDP per capita.

METHODS

A systematic review was performed to retrieve information about the global incidence of T1D among those younger than 14 years of age. The study was carried out according to the PRISMA recommendations. For the analysis, the incidence was organized in the periods: 1975-1999 and 2000-2017. We searched the incidence of T1D in the age-groups 0-4, 5-9 and 10-14. We compared the incidences in countries for which information was available for the two periods. We obtained the GDP from the World Bank. We analysed the relationship between the incidence of T1D with the GDP in countries reporting data at the national level.

RESULTS

We retrieved information for 84 out of 194 countries around the world. We found a wide geographic variation in the incidence of T1D and a worldwide increase

Manuscript source: Unsolicited manuscript

Received: March 8, 2019
Peer-review started: March 11, 2019
First decision: March 10, 2019
Revised: October 17, 2019
Accepted: October 27, 2019
Article in press: October 27, 2019
Published online: December 15, 2019

P-Reviewer: Koch TR
S-Editor: Wang J
L-Editor: A
E-Editor: Liu MY

during the two periods. The largest contribution to this increase was observed in the youngest group of children with T1D, with a relative increase of almost double when comparing the two periods (P value = 2.5 × e^{-5}). Twenty-six countries had information on the incidence of T1D at the national level for the two periods. There was a positive correlation between GDP and the incidence of T1D in both periods (Spearman correlation = 0.52 from 1975-1999 and Spearman correlation = 0.53 from 2000-2017).

CONCLUSION
The incidence increase was higher in the youngest group (0-4 years of age), and the highest incidences of T1D were found in wealthier countries.

Key words: Type 1 diabetes; Incidence; Children; Age categories; Gross domestic product per capita

Core tip: Currently, there is information on the incidence of T1D of 43.3% of the 194 countries of the world, of which only 44 countries have national coverage information. We found a wide geographic variation in the incidence of T1D and a worldwide increase in the two periods (1975-1999 and 2000-2017). Comparing the two periods, the relative increase in the incidence occurred in the 0-4 group (1.9 times), followed by the 5-9 group (1.8 times) and 10-14 group (1.4 times). There was a positive correlation between GDP per capita, and the incidence of T1D, where wealthier countries have higher values of incidence.

Citation: Gomez-Lopera N, Pineda-Trujillo N, Diaz-Valencia PA. Correlating the global increase in type 1 diabetes incidence across age groups with national economic prosperity: A systematic review. *World J Diabetes* 2019; 10(12): 560-580
URL: https://www.wjgnet.com/1948-9358/full/v10/i12/560.htm
DOI: https://dx.doi.org/10.4239/wjd.v10.i12.560

INTRODUCTION

Type 1 diabetes (T1D) is one of the most common endocrine diseases in childhood and adolescence. Additionally, the diagnosis of T1D has increased considerably in adults[1]. According to the International Diabetes Federation (IDF), it was estimated that more than 86000 children were living with T1D in 2015 around the world[2]. There is a wide geographic variation in the incidence of T1D, both among countries and within the different regions in these countries. In North America and Europe, the incidence varies between 4 and 41 per 100000. The countries that report the highest rates are Switzerland, Finland, Norway, the United Kingdom and Sardinia, with values > 20 per 100000 per year. In contrast, T1D is rare in Asian countries, such as China, where the incidence is approximately 0.1 case per 100000 people each year[3-5]. In Latin America, according to IDF, it is estimated that 45100 children younger than 15 years have T1D[2].(Table 1)

There are differences in the incidence rates among age categories (0-4, 5-9, 10-14) in almost all countries. According to DIAMOND[6], for the period between 1991-1996, it was noted that the incidence increased with age; children between 5 and 9 years had 1.62 times the risk of children 0-4 years, *i.e.*, a 62% excess risk, and the 10-14 age group had 1.93 times the risk of the 0-4 age group. Recently, there have been signs suggesting that this trend is changing. Records of the Patterson *et al*[7] between 1999 and 2008, showed that the incidence was highest in the youngest age group (0 to 4 years), with an increase of 5.4% compared to 4.3% in the 5-9 age group and 2.9% in the 10-14 age group.

In addition, the IDF has suggested the existence of a relationship between income level and the incidence of T1D[2]. In the United States, where the incidence of T1D in different socio-economic groups was studied, it was found that there was a higher incidence of T1D in the highest income groups[8]. The same pattern occurs in Europe, where it was shown that the incidence of T1D correlates strongly with the gross domestic product (GDP). GDP is most commonly used to measure the size of a

Table 1 Incidence of type 1 diabetes in individuals aged 0-14 years

Country	Area	Study period	Inc	Asce %	InfoSource	Datacollection	Ref.
Algeria							
	Oran	1990-1999	8.60	NA	PBDR	P or H	DIAMOND *et al*[6]
Argentina							
	Cordoba	1991-1992	7.00	90.0	PBDR	P or H	DIAMOND *et al*[6]
	Avellaneda	1990-1996	6.30	94.0	PBDR	P or H	DIAMOND *et al*[6]
	Tierra del Fuego	1993-1996	10.30	100.0	PBDR	P or H	DIAMOND *et al*[6]
	Corrientes	1992-1999	6.60	95.0	PBDR	P or H	DIAMOND *et al*[6]
Australia							
	NW[a]	2000-2011	23.6	97	PBDR	H	Hayne *et al*[18]
Austria							
	NW	2004-2008	17.50	97.2	PBDR	P	Patterson *et al*[19]
Bahamas							
	NW	2001-2002	10.10	NA	MBR	P	Peter *et al*[20]
Barbados							
	NW	1990-1993	2.00	NA	PBDR	P or H	DIAMOND *et al*[6]
Belarus							
	Gomel, Minsk	1997-2002	5.60	100.0	PBDR	NA	Zalutskaya *et al*[21]
Belgium							
	Antwerp	2004-2008	15.90	94.9	PBDR	P	Patterson *et al*[19]
Bosnia and Herzegovina							
	Tuzla Canton	1995-2004	6.93	100.0	PBDR	P	Tahirović *et al*[22]
	Republic of Srpska	1998-2010	8.13	100.0	PBDR	P	Radosevic *et al*[23]
Brazil							
	São Paulo[a] (Bauru)	1986-2015	12.8	97.7	PBDR	P	Negrato *et al*[24]
	Rio Grande do Sul (Passo Fundo)	1996-1999	7.00	82.5	PBDR	P or H	DIAMOND *et al*[6]
Bulgaria							
	Eastern	1989-1994	6.80	99.9	PBDR	P	Patterson *et al*[7]
	Varna	1990-1999	8.10	100.0	PBDR	P or H	DIAMOND *et al*[6]
	Western	1990-1999	10.70	99.5	PBDR	P or H	DIAMOND *et al*[6]
Canada							
	Toronto	1976-1978	9.00	97.2	PBDR	P, H	Ehrlich *et al*[25]
	Manitoba	1985-1993	20.65	95.0	PBDR	P	Blanchard *et al*[26]
	Prince Edward Island	1990-1993	24.50	100.0	PBDR	P or H	DIAMOND *et al*[6]
	Alberta (Edmonton)	1990-1996	23.30	85.5	PBDR	P or H	DIAMOND *et al*[6]
	Calgary	1990-1999	20.60	100.0	PBDR	P or H	DIAMOND *et al*[6]
	Québec	1989-2000	15.34	NA	PBDR	P	Legault *et al*[27]
	Newfoundland and Labrador	1987-2010	38.68	NA	PBDR	P, H	Newhook *et al*[28]
Chile							
	IX Region	1980-1993	1.37	97.0	PBDR	P	Larenas *et al*[29]
	Santiago of Chile (Communes of Metropolitan region)	2000-2005	6.30	100.0	PBDR	P	Torres-Avilés *et al*[30]
China							
	NW	1988-1994	0.47	93.0	PBDR	P, H	Yang *et al*[31]
	Zhejiang[a]	2007-2013	2.02	94,6	PBDR	H	Wu *et al*[32]
	Beijing[a]	1995-2010	1.7	NA	PBDR	H	Gong *et al*[33]
	Shanghai[a]	1997-2011	3.1	90	PBDR	H	Zhao *et al*[34]
Colombia							

	Bogotá	1990-1990	3.80	97.0	PBDR	P or H	DIAMOND *et al*[6]
	Cali	1995-1999	0.50	NA	PBDR	P or H	DIAMOND *et al*[6]
Croatia							
	NW[a]	2004-2012	17.2	96.69	PBDR	H	Rojnic Putarek *et al*[35]
Cuba							
	NW	1990-1999	2.30	62.5	PBDR	P or H	DIAMOND *et al*[6]
Cyprus							
	NW	1990-2009	12.34	50.0	PBDR	NA	Skordis *et al*[36]
Czech Republic							
	NW	2004-2008	19.30	97.4	PBDR	P	Patterson *et al*[19]
Dem. People's Republic of Korea							
	NW[a]	2012-2014	3.1	NA	PBDR	P or H	Kim *et al*[37]
Denmark							
	NW	2004-2008	25.10	99.2	PBDR	P	Patterson *et al*[19]
Dominican Republic							
	NW	1995-1999	0.50	53.0	PBDR	P or H	DIAMOND *et al*[6]
Egypt							
	Alexandria, Damanhour	1992-1992	8.00	NA	OPD	NA	Arab *et al*[38]
	Northern[a]	1996-2011	1.93	NA	MBR	H	El-Ziny *et al*[39]
Estonia							
	NW	1983-2006	13.09	98.0	PBDR	P, H	Teeäär *et al*[40]
Ethiopia							
	Gondar	1995-2008	0.33	NA	MBR	P	Alemu S *et al*[41]
	Jimma	2002-2008	0.33	NA	MBR	P	Alemu S *et al*[41]
Fiji							
	NW[a]	2001-2012	0.93	NA	PBDR	H	Ogle *et al*[42]
Finland							
	NW	2006-2011	62.42	NS	OPD	NA	Harjutsalo *et al*[43]
France							
	Franche-Comté	1980-1998	7.01	80.6	PBDR	H	Mauny *et al*[44]
	Aquitanie, Lorraine, Normandia Basse, Normandia Haut	1990-1994	8.50	97.0	PBDR	P or H	DIAMOND *et al*[6]
	Aquitaine	1998-2004	12.20	NA	OPD	NA	Barat *et al*[45]
	Languedoc-Roussillon[a]	2000-2010	16.2	NA	PBDR	NA	Trellu *et al*[46]
Georgia							
	NW	1998-1999	4.60	NA	OPD	NA	Arab *et al*[38]
Germany							
	NW[a]	2004-2008	22.9	97	PBDR	H	Bendas *et al*[47]
Greece							
	NW	1992-1992	6.03	NA	PBDR	P	Dacou-Voutetakis *et al*[48]
Hungary							
	18 of 19 countries (All, less Budapest)	2004-2008	18.30	98.7	PBDR	P	Patterson *et al*[19]
Iceland							
	NW	1989-1994	13.50	100.0	PBDR	P	Patterson *et al*[7]
India							
	Madras	1991-1994	11.00	90.0	PBDR	H	Ramachandran *et al*[49]
Iran (Islamic Republic of)							
	Fars	1991-1996	3.68	100.0	PBDR	P	Pishdad[50]
Ireland							
	NW[a]	2008-2013	28.3	96,8	PBDR	P	Roche *et al*[51]

Israel							
	NW[a]: Population: Arabs	2004-2010	9.14	NA	PBDR	P	Blumenfeld *et al*[52]
	NW[a]: Population: Jews	2004-2010	13	NA	PBDR	P	Blumenfeld *et al*[52]
Italy							
	Apulia[a]	2001-2013	17.99	NA	PBDR	P	Di Ciaula[53]
	Friuli-Venezia Giulia[a]	2010-2013	17.55	NA	MBR	H	Valent *et al*[54]
	Abruzzo[a]	1999-2008	14.30	95	PBDR	H	Altobelli *et al*[55]
	Veneto[a]	2006-2013	17.00	NA	PBDR	H	Marigliano *et al*[56]
	NW-39.7% population	1990-2003	12.55	NA	PBDR	P	Bruno *et al*[57]
Japan							
	NW[a]	2005-2012	2.14	NA	PBDR	H	Onda *et al*[58]
Jordan							
	NW	1992-1996	3.33	95.0	NS	P, H	Ajlouni *et al*[59]
Kuwait							
	NW[a]	2011-2013	41.7	96.7	PBDR	H	Shaltout *et al*[60]
Latvia							
	NW	1990-1999	7.40	NA	PBDR	P or H	DIAMOND *et al*[6]
Libyan Arab Jamahiriya							
	Benghazi	1991-1999	9.00	NA	PBDR	P or H	DIAMOND *et al*[6]
Lithuania							
	NW	2004-2008	14.20	NA	PBDR	P	Patterson *et al*[19]
Luxembourg							
	NW	2004-2008	19.00	100.0	PBDR	P	Patterson *et al*[19]
Malta							
	NW	2006-2010	23.87	100.0	PBDR	P	Formosa *et al*[61]
Mauritius							
	NW	1990-1994	1.30	67.5	PBDR	P or H	DIAMOND *et al*[6]
Mexico							
	NW	2000-2010	5.93	NA	PBDR	H	Gómez-Díaz *et al*[62]
Montenegro							
	NW[a]	1997-2011	18.6	100	PBDR	H	Samardžić *et al*[63]
Netherlands							
	NW[a]	1999-2011	25.2	NA	PBDR	H	Fazeli *et al*[64]
New Zealand							
	NW	1999-2000	18.00	95.0	PBDR	NA	Campbell-Stokes *et al*[65]
Norway							
	NW[a]	2004-2012	32.7	NA	PBDR	H	Skrivarhaug *et al*[66]
Oman							
	NW	1993-1995	2.59	96.0	PBDR	P	Soliman *et al*[67]
Pakistan							
	Karachi	1990-1999	0.50	51.0	PBDR	P or H	DIAMOND *et al*[6]
Papua New Guinea							
	NW	1996-2000	0.08	NA	MBR	P	Ogle *et al*[68]
Paraguay							
	NW	1990-1999	0.90	NA	PBDR	P or H	DIAMOND *et al*[6]
Peru							
	Lima	1990-1994	0.50	67.5	PBDR	P or H	DIAMOND *et al*[6]
Poland							
	NW	1989-2004	11.23	NA	PBDR	P	Jarosz-Chobot *et al*[69]

	Krakow and the Lesser Poland[a]	2004-2011	15.87	NA	PBDR	H	Wojcik *et al*[70]
	Podlasie, Silesia, Łódzkie, Pomorskie, Bydgoszcz[a]	2005-2012	20.22	NA	PBDR	H	Chobot *et al*[71]
Portugal							
	Algarve	1990-1994	14.60	87.0	PBDR	P or H	DIAMOND *et al*[6]
	Portoalegre	1990-1994	21.30	93.0	PBDR	P or H	DIAMOND *et al*[6]
	Coimbra	1990-1999	9.60	100.0	PBDR	P or H	DIAMOND *et al*[6]
	Madeira Island	1990-1999	6.90	100.0	PBDR	P or H	DIAMOND *et al*[6]
Qatar							
	NW	1992-1996	11.40	NA	OPD	NA	Al-Zyoud *et al*[72]
Republic of China (Taiwan)							
	NW[a]	2003-2010	5.45	NA	PBDR	H	Lin *et al*[73]
Romania							
	NW[a]	2002-2011	9.6	96,2	PBDR	H	Serban *et al*[74]
Russian Federation							
	Novosibirsk	1990-1999	6.90	93.5	PBDR	P or H	DIAMOND *et al*[6]
	Moscow	1996-2005	12.07	94.0	PBDR	P	Pronina *et al*[75]
Rwanda							
	capital and 6 regions[a]	2004-2011	2.7	NA	MBR	H	Marshal *et al*[76]
Saudi Arabia							
	Eastern Province	1986-1997	12.30	100.0	PBDR	NA	Kulaylat *et al*[77]
	Al-Madinah (North West)	2004-2009	30.88	NA	PBDR	P	Habeb *et al*[78]
Serbia							
	Belgrade	2000-2004	12.90	NA	OPD	NA	Vlajinac *et al*[79]
Singapore							
	NW	1992-1994	2.42	92.2	PBDR	P	Lee *et al*[80]
Slovakia							
	NW	1999-2003	13.60	100.0	PBDR	P	Patterson *et al*[19]
Slovenia							
	NW	1998-2010	13.83	100.0	PBDR	P	Radosevic *et al*[23]
Spain							
	Madrid	1985-1988	10.60	90.0	PBDR	H	Serrano Ríos *et al*[81]
	Cáceres	1988-1999	16.67	99.2	PBDR	H	Lora-Gómez *et al*[82]
	Badajoz	1992-1996	17.23	95.0	PBDR	P	Morales-Pérez *et al*[83]
	Navarre[a]	1975-2011	13.2	NA	PBDR	H	Forga *et al*[84]
	Catalonia	2004-2008	12.10	97.6	PBDR	P	Patterson *et al*[19]
	Castilla y León[a]	2000-2013	10.8	NA	PBDR	H	Vega *et al*[85]
	Biscay[a]	1990-2013	10.7	99,1	PBDR	H or P	Fernández-Ramos *et al*[86]
Sudan							
	Gezira	1990-1990	5.00	100.0	PBDR	P or H	DIAMOND *et al*[6]
	Khartoum	1991-1995	10.10	97.0	PBDR	NA	Elamin *et al*[87]
Sweden							
	NW[a]	2007-2011	42	99	PBDR	N	Rawshani *et al*[88]
Switzerland							
	NW	2004-2008	13.10	91.3	PBDR	P	Patterson *et al*[19]
TFYR Macedonia							
	NW	2004-2008	5.80	100.0	PBDR	P	Patterson *et al*[19]
Thailand							
	North-eastern	1996-2005	0.58	NA	MBR	H	Panamonta *et al*[89]

Tunisia							
	Beja, Monastir, Gafsa	1990-1994	6.69	96.0	PBDR	P	Ben Khalifa *et al*[90]
	Kairoan	1991-1993	7.60	NA	PBDR	P or H	DIAMOND *et al*[6]
	Beja	1990-1999	7.70	NA	PBDR	P or H	DIAMOND *et al*[6]
	Gafsa	1990-1999	8.50	NA	PBDR	P or H	DIAMOND *et al*[6]
	Monastir	1990-1999	5.80	NA	PBDR	P or H	DIAMOND *et al*[6]
Turkey							
	NW[a]	2011-2013	10.8	99	PBDR	H	Yeşilkaya *et al*[91]
Ukraine							
	NW	1985-1992	8.10	NA	OPD	NA	Timchenko *et al*[92]
United Kingdom							
	NW	1991-2008	19.32	NA	PBDR	P	Imkampe *et al*[93]
United Republic of Tanzania							
	Dar es Salaam	1982-1991	0.92	NA	MBR	P	Swai *et al*[94]
United States of America							
	Olmsted, Minnesota[a]	1994-2010	19.9	NA	MBR	H	Cartee *et al*[95]
	Five areas[a]	2002-2013	19.5	98,9	PBDR	H	Mayer-Davis *et al*[96]
Uruguay							
	Montevideo	1992-1992	8.30	97.0	PBDR	P or H	DIAMOND *et al*[6]
Uzbekistan							
	NW[a]	1998-2014	2.48	100	PBDR	H	Rakhimova *et al*[97]
Venezuela (Bolivarian Republic of)							
	Caracas	1990-1994	0.10	NA	PBDR	P or H	DIAMOND *et al*[6]

Update of the publications that report the incidence of type 1 diabetes from population-based studies.
[a]Updated studies. Area and NW: Study at the national level. ASCE%: Percentage of completeness between primary and secondary sources of registers. PBDR: Registration of population-based data; MBR: Medical-based record; OPD: Other population denominators; NS: Non-specified; P: Prospective -incident cases collected prospectively-; H: Historical -incident cases collected retrospectively-; NA: Information not available.

country's economy. However, there have been conflicting results. For example, an ecological study carried out in North Rhine-Westphalia, Germany showed that the risk of T1D was higher in children living in socially disadvantaged areas[9].

In a previous systematic review, we identified T1D incidence in 80 out of 194 countries and found significant associations between the geographical variation of incidence and a series of economic, climatic and environmental, and health conditions factors[10]. Among these factors, GPD per capita was highly correlated with the 0-14-year incidence of T1D (Spearman Correlation = 0.72, P value = $9.05 \times e^{-14}$).

Here, we focus on three age categories (0-4, 5-9, 10-14) and two periods (1975-1999 and 2000-2017). We searched, through a systematic review of the literature, the global variation in the incidence of T1D in these age categories and periods. We then searched to what extent these variations correlated with the GDP per capita in these countries.

MATERIALS AND METHODS

In this study, we updated the review on the global T1D incidence published by Diaz-Valencia *et al*[10] with new papers. Once the incidence data were obtained through the systematic review, we conducted an exploratory ecological analysis. Following the procedures mentioned by Morgenstern[11] for ecological studies, we analysed the relations of population rates of T1D incidence and the average GDP of these countries, retrieved from the World Bank database. This analysis was divided into two periods (1975-1999 and 2000-2017).

We extracted information on the incidence of T1D in children under 14 years from population-based studies conducted in clearly defined geographical areas at the local, regional or national level, published in original articles in English, Spanish or French, following the PRISMA recommendations. The databases used for the literature search

were Medline and Thomson Reuters (Web of Knowledge). Additionally, we explored Google Scholar. This study followed the protocol search deposited in the International Prospective of Systematic Reviews with the Registration Number: CRD42012002369. Figure 1 presents the flow diagram of the bibliographic search.

During this systematic review, several procedures were standardized to minimize the possibility of incurring biases in the identification of literature, selection and the interpretation of evidence. To reduce potential biases during the design and execution of the systematic review, a team was created; initially, this team was formed by a senior expert researcher (AJV) and a researcher (PAD). During the update of this systematic review, the team consisted of two researchers (NGL and PAD). The initial search was undertaken between November 2011 and January 2014 and the update between January and June 2017. For this systematic review a query equation was used, which implemented the same strategy as that validated by Diaz-Valencia *et al*[10] (Supplementary material).To build the original query equation, we performed an exploratory search, from which 92 references were selected that reported on the incidence of T1D. From these 92 references, we analysed the MeSH terms and incorporated them into a preliminary search equation. Using this equation, we excluded the MeSH terms of references that did not report the incidence of T1D in the search equation. We repeated this process until the search equation included the 92 references used initially.

For all query equations, studies were excluded if (1) The main objective was not to study the incidence of T1D (*e.g.*, genetic factors, complications, treatments); (2) The study was not population-based and instead it was performed in selected groups, such as studies based on volunteer subjects or people belonging to a specific health insurance organization; (3) The study did not report using the World Health Organization (1985 or 1999) or American Diabetes Association (1997 or 2011) diagnosis criteria; (4) The study described the incidence of T1D as a general topic, with no description by year and age at diagnosis; (5) We could not translate the article; or (6) The full text of the article was unavailable.

Quality assessment

The quality of the included studies was evaluated independently by 2 reviewers (NGL-PAD) using the evaluation criteria proposed by Loney *et al*[12] as an external validation. We also implemented an internal quality assessment. The external validation consisted of eight criteria, (1) Was the target population clearly described? (2) Were cases ascertained either by survey of the entire population or by probability sampling? (3) Was the response rate > 70%? (4) Were the non-responders clearly described? (5) Was the sample representative of the population? (6) Were data collection methods standardized? (7) Were validated diagnostic criteria or approaches used to assess the presence/absence of disease? and (8) Were the estimates of incidence given with confidence intervals? An article's score was obtained by adding up the number of criteria it satisfied. Every satisfied criterion was given 1 point. There was no cut-off score for rating low-quality studies; we arbitrarily considered 0-4, 5-6 and 7-8 points as high, medium and low risk of bias, respectively.

The internal validation was based on 5 criteria. (1) The percentage of completeness between primary and secondary sources of registers. A percentage greater than 90 scored a 1, less than 90 scored a 0.5 and unavailable information scored a 0; (2) Information source: If the data came from the registration of population-based data, it was assigned a 1; if the data came from medical-based records or population denominators it was assigned a 0.5; and if the source was non-specified, it scored a 0; (3) Data collection: If the cases were collected prospectively (P) or retrospectively (H) was assigned a 1; and if the information was not available, it scored a 0; (4) Clear criterion for diagnosis scored a 1; And (5) if the study was population-based, it scored a 1. We arbitrarily considered 0-3, 3.5 and 4-5 as high, medium and low risk of bias, respectively.

Data collection

Two reviewers (Diaz-Valencia PA and Gomez-Lopera N) extracted and reached agreement on the data from included articles using a standard data collection form. We included in this systematic review the most updated and comprehensive data. In each of the articles analysed, we extracted the following information: (1) Identification of the study: Authors, title, journal, year of publication; (2) Period and country of study: Countries were categorized by region according to the United Nations[13]; (3) Geographical coverage of the study: Nationwide (when the study was conducted across the whole nation) or local (when it was restricted to a region, city or geographically defined population); (4) Incidence rates expressed as new cases per 100000 people (both sexes) per year in the age categories 0-4, 5-9, 10-14, and 0-14. The rates were retrieved from either tables or graphs. If we found incidence values in the

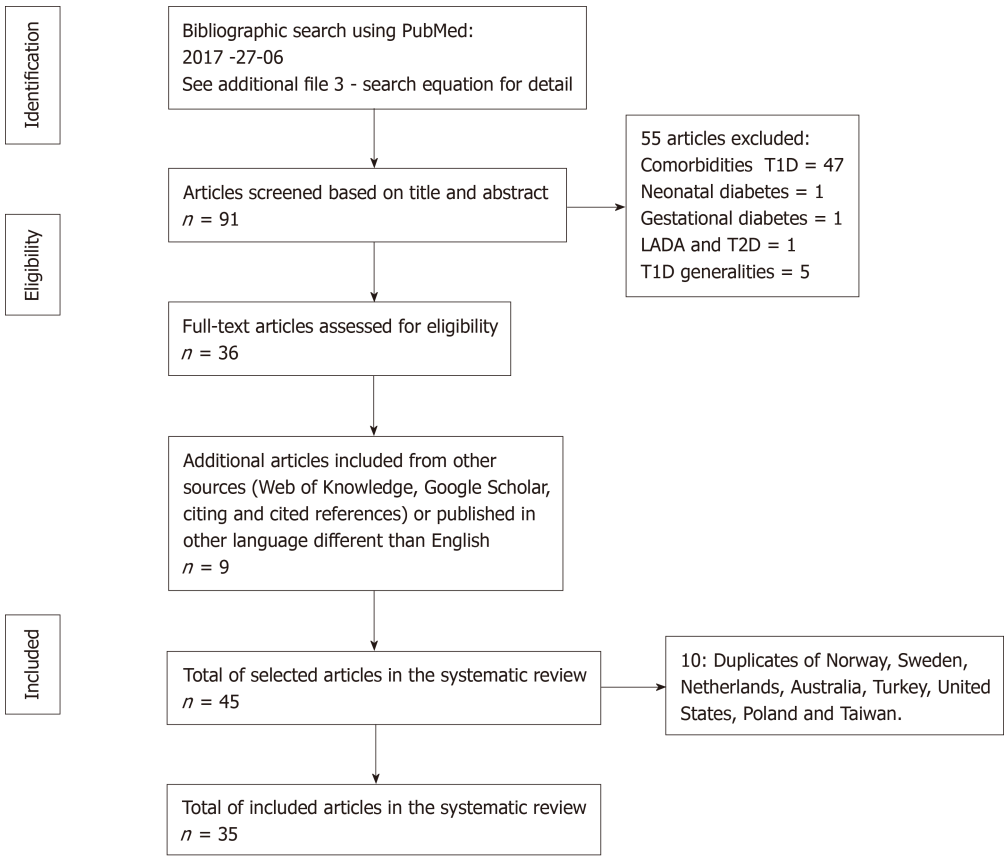

Figure 1 Flow diagram of the bibliographic search strategy. T1D: Type 1 diabetes; T2D: Type 2 diabetes; LADA: Latent autoimmune diabetes in adults.

graphics, we extracted them using GraphClick[14]. This program allows the user to automatically retrieve the original data from the *x* and *y* coordinates of images. Efforts were made to obtain the value of incidence of T1D for each country at the national level. When no information was retrieved at the national level, local studies were considered. In the database, we identified the level of coverage as national or local; (5) The incidence information from two periods was searched: The first was between 1975-1999, and the second was between 2000-2017. We based this separation on a bimodal trend observed in the years of the publications identified in the previous systematic review[10]; And (6) We collected the percentage of completeness/ascertainment when available.

GPD per capita

The GDP per capita was used to carry out an exploratory ecologic analysis of the relationship between the change in the incidence of T1D and the differences in socio-economic levels during two periods (1975-1999 and 2000-2017). The World Bank database[15] was used to extract the information for GDP per capita that indicated the relationship between the total value of all the goods and services generated during a year by the economy of a nation or state and the number of its inhabitants in that year. For each study period, we calculated the average of the values of the T1D incidence. In addition, for homogeneity in our analysis, we only chose countries with data at the national level.

Statistical analysis

We presented all the collected data graphically on maps that contain the information obtained from countries at the national level, in two timeframes (1975-1999 and 2000-2017) using the software Tableau[16]. We compared the incidence of T1D for countries that have information from 1975-1999 and 2000-2017 at the national level in the categories of ages 0-4, 5-9 and 10-14, comparing the means of paired samples.

We performed a correlation to analyse the relationship between the change in incidence of T1D and the change in GDP per capita using the Spearman test and linear regression models to predict the change in the incidence of T1D according to change in the GDP per capita by countries at the national level. Model assumptions for linear models were checked by visual inspection of the residuals. We used the

program R version 3.3.3[17] to perform the statistical analysis and create graphics related to the study. In all cases, we considered that a *P* value less than 0.05 was statistically significant.

RESULTS

This systematic review of the literature presented information available at the global level on the incidence of T1D and retrieved data for 84 countries, representing 43.3% of the 194 countries of the world. We included 35 additional studies from the previous systematic review[10]. Among these 35 new papers, we retrieved information for 25 countries; some of them reported data at the national and others at the local level (Figure 1). Updated studies were identified by superscript letters (a) in Table 1. It was possible to update the information published by Diaz-Valencia *et al*[10] for 21 countries and obtain data for 4 additional countries: Fiji, Turkey, Rwanda and Republic of China (Taiwan). Of the 84 countries, data were collected at the national level for 44 and the local level for 40.

The median study quality score for studies reporting on the incidence of T1D was high in both cases, with a mean quality score of 7.18 of 8 possible [standard deviation (SD): 0.80] using the external validation, and with a mean quality score of 4.37 of 5 possible [standard deviation (SD): 0.71] using the internal validation. All studies described the target population in detail and used validated diagnostic criteria to assess the presence of disease. Most studies used standardized data collection methods and reported estimates with their accompanying confidence intervals. We found 93.94% concordance between the internal and external validation.

We observed a wide geographical variation in the incidence of T1D at the global level (Table 1). In general, the incidence of T1D was highest in Europe (> 15 per 100000 per year), followed by North America, Australia, Asia, Central and South America. In children from 0-14 years-old, the lowest incidence at the national level (< 1 per 100000 per year) occurred in Thailand; Papua, New Guinea; Fiji; the Dominican Republic; and Paraguay. In contrast, the highest incidence at the national level occurred in Finland, Sweden, Norway and Kuwait, with 62.42, 42, 32.7 and 41.7 per 100000 inhabitants per year, respectively.

We retrieved and compared 26 countries that had information at the national level regarding the incidence of T1D for the periods 1975-1999 and 2000-2017 in individuals from 0-14 years (Figures 2 and 3). In general, an increase in the incidence of T1D is noted at the global level. In the 26 countries, these values were almost double. For example, in Kuwait, the incidence value was 22.3 for the period of 1992-1997[98] and 41.7 for the period of 2011-2013[60] (equivalent to a ratio of 1.86).

Additionally, we analysed three distinct categories for age in 15 countries that had information at the national level in the two periods considered in this study (Table 2). We observed an increased in the incidence. In absolute numbers, the period 1975-1999 showed that the incidence increased with age, where the lowest incidence was found in children under the age of 5 years and the highest in children older than 10 years. In the period 2000-2017, there was a higher incidence in the category of 5-9 years, followed by 10-14, and the lowest was found in 0-4. However, comparing the two periods, the relative increase in the incidence of T1D occurred in the 0-4 group (1.9 times), followed by the 5-9 group (1.8 times) and 10-14 group (1.4 times). We performed an extra analysis of all countries reporting incidence values for each age category without taking into account whether they reported the incidence at the local or national level, finding equivalent results (data not shown).

GDP per capita

In general, there was a positive correlation between GDP per capita and the incidence of T1D. A positive correlation was found for the relation between the relative change in T1D incidence and the relative change in GDP for the countries reporting data at national level (Spearman correlation 0.35) (Figure 4).

Analysing the two periods, we found a positive correlation between incidence of T1D and GPD per capita among 26 countries (Spearman correlation = 0.52 between 1975-1999 and Spearman correlation = 0.53 between 2000-2017). Excluding Finland and Switzerland because of their extreme values in T1D incidence and GDP per capita, respectively, we retrieved a Spearman correlation = 0.69 between 1975-1999 and Spearman correlation = 0.62 between 2000-2017 (Figure 5). From the linear regression model, including the 26 countries, it was suggested that for 1991 the country-to-country variation in GDP explained 9% of the country-to-country variation in incidence (adjusted R^2 of the model 0.09), while, for the year 2006, it was 17% (adjusted R^2 of 0.17) (Table 3). We performed the same analysis excluding Finland and

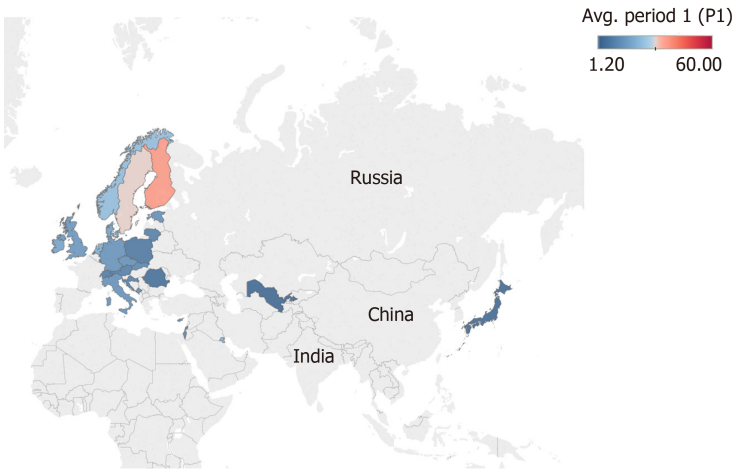

Figure 2 Map showing the mean incidence of type 1 diabetes in 26 countries from 1975-1999. The colour scale represents the level of incidence ranging from 1.20 in blue to 60 per 100000 individuals in red aged 0-14 years.

Switzerland. We found for 1991 that the change in the GDP explained 44% the change in incidence of T1D (adjusted R^2 of the model 0.44), while, for 2006, it was 22% (adjusted R^2 of 0.22) (Table 4).

DISCUSSION

In this study, we updated our previous results on the global incidence of T1D in individuals aged 0-14 years and its variation over time. We analysed the trend in two periods for age categories and GDP per capita. In general, there was a wide geographic variation in the 84 countries for which the incidence of T1D was reported. This variability could be explained to some extent by ethnic differences in allele and haplotype frequencies of risk alleles between populations, for example, in the HLA region, which explains almost 50% of the genetic component of the disease[99]. There has been a strong association between a high frequency of pre-disposition for HLA haplotypes and a high incidence of T1D. For example, research in the United States, based on the presence of two high-risk haplotypes of HLA-DR3/DR4, revealed that Caucasians have a higher risk of developing T1D than other ethnic groups[100]. It has been demonstrated that unlike Europeans, DR susceptibility alleles in Asian populations (whose incidence is lower) are in strong linkage disequilibrium with DQ neutral alleles or even protectors, and it is believed that these effects contribute to the low incidence of T1D in these populations[101,102].

Although there is a consensus on the effect of the genetic susceptibility to T1D between different ethnic groups, these differences cannot fully explain the global variability and the increase in incidence. In this study, we observed an increase in the incidence of T1D worldwide when comparing the periods 1975-1999 and 2000-2017 (Figures 2 and 3). The mechanisms behind the enigma in the increase in the incidence are unknown. However, the mechanism have been attributed to external factors, such as those related to the environment and lifestyle, which may be involved in the epidemiology of the disease[103].

We also observed an increase in the incidence of T1D in all age categories (0-4, 5-9 and 10-14). In the period 1975-1999, the incidence increased with age, with a peak in children aged 10-14 years. This pattern could be attributed to the onset of puberty with resistance to insulin; therefore, the demand for insulin secretion increases[104]. In contrast, for the period 2000-2017, there appeared to be an increasing number of patients in the 5-9 age group and a greater relative rise in the 0-4 age group. The mechanisms underlying the increased incidence of T1D in the youngest children are unknown but have largely been attributed to environmental influences[55].

The environment may act in diverse ways, either by enhancing autoimmunity or modulating normal mechanisms of protection against the development of the disease[105]. It can be speculated that the plausible causes of temporal changes in the incidence of T1D are attributed to environmental factors, such as social, economic, dietary and health-related factors, which have changed rapidly over the last century.

An example of these changes is socio-economic factors. This study analysed the relationship between one socio-economic indicator (GDP per capita) and the incidence of T1D and found that the highest incidences of the disease were reported in wealthier

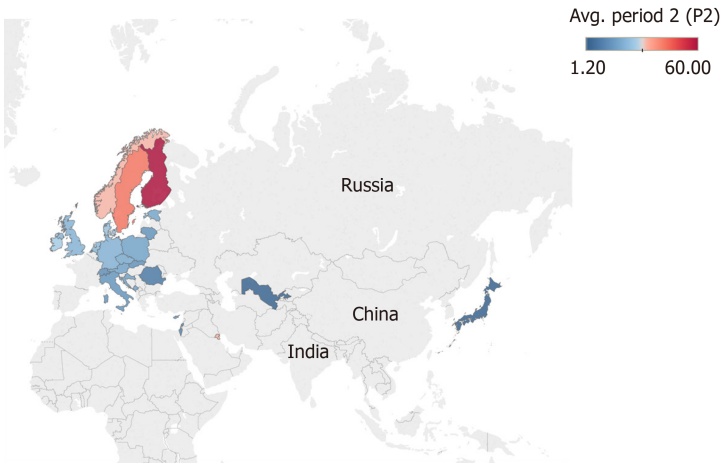

Figure 3 Map showing the mean incidence of type 1 diabetes in 26 countries from 2000-2017. The colour scale represents the level of incidence ranging from 1.20 in blue to 60 per 100000 individuals in red aged 0-14 years.

countries. This same pattern was found by Patterson *et al*[106] in a study conducted throughout Europe. Similarly, studies conducted at the country level in Sweden[107], United Kingdom[108], and Italy[109] described similar associations between T1D and the socio-economic variables. The influence of changes in GDP per capita on the incidence of the disease was higher for the average year 1991 than that after 2006. We wonder if this behaviour could be explained because 2006 was before the financial crisis of 2008 that provoked a fall in the economies of all regions[15].

The geographical associations between the socio-economic situation and the incidence of T1D could be attributed to spatial patterns in the composition of the population, which leads to differences in lifestyle and diet. A positive relationship has been demonstrated between the prosperity of the nation, as measured by GDP, with body mass index (BMI)[110]. Recently, the overload and accelerator hypothesis has been proposed for the increase in body size, BMI and insulin resistance, as well as risk factors for developing T1D[111]. This hypothesis suggests that the increase in BMI and a more sedentary lifestyle cause resistance to insulin, which leads to β-cells being overworked. This process results in apoptosis and increased production of antigens, which triggers an autoimmune response. Therefore, individuals with a genetic predisposition to T1D will develop an autoimmune response, further accelerating the loss of β-cells. Although an increase in weight contributes to insulin resistance, another consequence of overweight is the storage of ectopic fat with glucotoxicity associated with inflammation resulting in an inhibition of gene expression of insulin, which is also involved in the process of apoptosis of β-cells[112].

Additionally, the relationship of the socio-economic level with the incidence of T1D could be explained by the improvement of the standards of hygiene, low rates of infection in childhood and low social contact in early childhood, which are possibly experienced in wealthy countries. This theory is known as the hygiene hypothesis, proposed by Gale[113] in 2002. This hypothesis suggests that changes in hygiene and infection patterns in early childhood alter the development of the immune system and the normal mechanisms of protection against autoimmunity. A study in non-obese diabetic mice, showed that there was a 40%-50% increase in the incidence of T1D when the animals were raised in environments free of pathogens[114]. In general, there has been an inverse trend between the incidence of infectious diseases and the incidence of autoimmune and allergic diseases[115].

Other environmental factors potentially related to national economic prosperity must be mentioned. One of these is the nutritional component that has undergone major changes in many developed countries. Early nutrition seems to modulate the development of T1D, for example, the absence or short duration of breastfeeding and early introduction of cow's milk formulae are thought to be risk factors for this disease[116]. Also, rapid weight gain in infancy, associated with improper feeding, increases the risk of developing T1D[117]. Other possible factors that experiment in wealthier countries are a higher degree of urbanization, which are associated with an increased incidence of T1D, supporting the hygiene hypothesis[10]. In addition, there are differences in caesarean deliveries between low- and high-income countries, where wealthier countries have high levels of caesarean use without medical indication[118]. Delivered by caesarean section are at slightly increased risk of T1D, and it has been postulated that differences in the gut microbiota of these children

Table 2 Summary values for the comparison of the incidence of type 1 diabetes for countries with nationwide data by age category in the periods analysed in the study

	0-4 yr		5-9 yr		10-14 yr	
Period	1975-1999	2000-2017	1975-1999	2000-2017	1975-1999	2000-2017
Mean	6.68	12.59	11.92	21.99	14.04	19.54
95%CI	(4.49, 8.87)	(9.23, 15.96)	(7.95, 15.96)	(14.80, 29.18)	(9.72, 18.38)	(15.09, 23.99)
T student	-6.31		-4.58		-3.22	
P value	0.00002		0.00043		0.006	
Ratio periods	1.9		1.8		1.4	

CI: Confidence Interval.

compared with those born by normal vaginally delivery[103]. Also, the wealth of countries is associated with environmental pollution. An association between air pollution and T1D incidence has been described. Researchers proposed that chemical and air pollutant exposures have multiple effects that may directly affect the risk of T1D[119].

However, a single environmental factor or interaction between factors, has not been identified that could explain these changes in the incidence of T1D. Moreover, there are complex interactions between genetic and environmental factors that remain to be discovered. More epidemiological studies of T1D are needed to develop new hypotheses about the genetic and environmental factors that trigger the disease, which should be further tested.

Currently, there is information on the incidence of 43.3% of the 194 countries of the world, of which only 44 countries have national coverage information; most of them are European. Despite the efforts of the DIAMOND project[6] to describe the incidence of T1D at a global level, there is little information for countries in Africa, Central and South America. Moreover, the data are not entirely representative for some countries. To extrapolate this information for the whole country, there would be a substantial bias, as there may be variability within large nations in both the genetic component and environmental exposures that trigger the disease.

Another aspect to consider is the lack of continuity of the epidemiological studies. Only 21 countries have updated incidence rates in the systematic review conducted between 2014 and 2017. Moreover, this lack of continuity implies a limitation for our study since we retrieved available information to conduct comparisons in two periods, 1975-1999 and 2000-2017; only 26 countries had data at the national level, and age category data are even less available. These 26 countries are mainly from Europe (n = 23), and Asia (n = 3). Regrettably, we do not have information to conduct comparison in the two periods for countries in Africa, Oceania, and America. It is very important to generate more studies on the epidemiology of T1D. This approach will contribute to understanding the dynamic changes in the disease, which, together with studies in basic sciences such as genetics, could identify the factors that modify the risk to the disease and could probably slow down the current increase in the incidence of T1D.

Limitations of this study are worth noting. Although several procedures were standardized during this systematic review to minimize the possibilities of incurring biases in the identification of literature, selection and interpretation of evidence, we cannot rule out having missed relevant studies also due to publication bias. For example, studies that were published in languages other than English, Spanish or French were not included. An important limitation that is shared by all ecological studies is the possibility of making an ecological fallacy. The implication is that the associations we found are only at the group level, and we cannot assume that they are inferred to each individual in these groups. For example, our results do not necessarily imply that all wealthy countries have a higher incidence of T1D, and our findings only reveal potential associations between GPD and population rates of T1D incidence at the group level. Another limitation of our study is the heterogeneity of the different countries included in the statistical analysis. In addition, available secondary sources of GPD data may not have the same accuracy for all countries, leading to imprecise correlation with the incidence of T1D.

We found a wide geographic variation in the incidence of T1D and a worldwide increase in the two periods considered in this study. The greatest increase was observed in the youngest group of children with T1D (0-4 years), with a relative increase of almost double (P value = 2.47 × $e^{-0.5}$). Finally, there was a positive

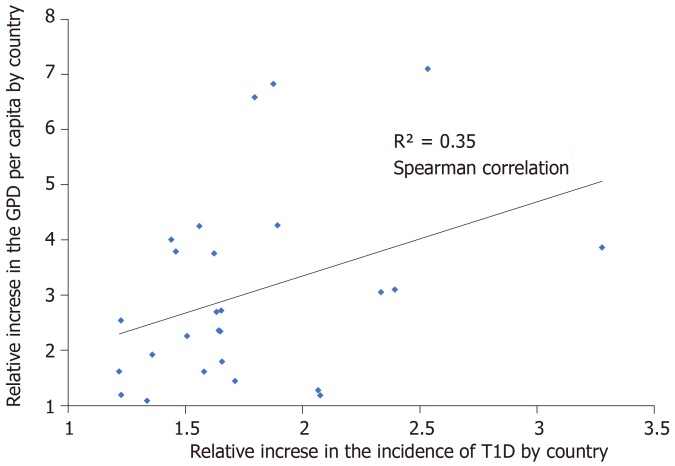

Figure 4 Observed relation between the ratios of the increase in incidence and gross domestic product in 26 countries.

correlation between the socio-economic level, as measured by GDP per capita, and the incidence of T1D, where wealthier countries have higher values of incidence.

Table 3 Models of change in the incidence of type 1 diabetes for 26 countries with nationwide data according to the change in gross domestic product

Model GDP per capita	Coefficient	Est	CI 2.5%	CI 97.5%	SE	*t* value	*P* value
Year 1991: Residual standard error: 6.63 Adjusted R^2: 0.09509; F-statistic: 3.312 on 1 and 21 DF; *P* value: 0.08307	Intercept	8.99	4.63	13.36	2.1	4.28	0.0003
	GDP per capita	0.0002	0.0000	0.0005	0.0001	1.8000	0.0830
Year 2006: Residual standard error: 8.6; Adjusted R^2: 0.176; F-statistic: 5.698 on 1 and 21 DF. *P* value: 0.02647	Intercept	13.5	7.34	19.66	2.96	4.56	0.0002
	GDP per capita	0.0000	0.0000	0.0000	0.0000	2.39	0.0260

Est: Estimator; CI: Confidence Interval; SE: Standard Error; Df: Degree freedom; GDP: Gross domestic product.

Table 4 Models of change in the incidence of type 1 diabetes for countries with nationwide data according to the change in gross domestic product, excluding Finland and Switzerland

Model GDP per capita	Coefficient	Est.	CI 2.5%	CI 97.5%	SE	*t* value	*P* value
Year 1991: standard residual error: 5.08; adjusted R^2: 0.44. F statistic: 19.37. 22 DF. *P* value: 0.0002	Intercept	5.82	2.27	9.36	1.71	3.40	0.002
	GDP Per capita	0.0005	0.0003	0.0008	0.0001	4.1220	0.0002
Year 2006: Standard residual error: 8.08; adjusted R^2: 0.22; F statistic: 7.62. 22 DF. *P* value: 0.01	Intercept	13.57	8.16	18.98	2.61	5.21	0.00003
	GDP Per capita	0.0002	0.00004	0.0003	0.0001	2.76	0.01

Est: Estimator; CI: Confidence Interval; SE: Standard Error; Df: Degree freedom; GDP: Gross domestic product.

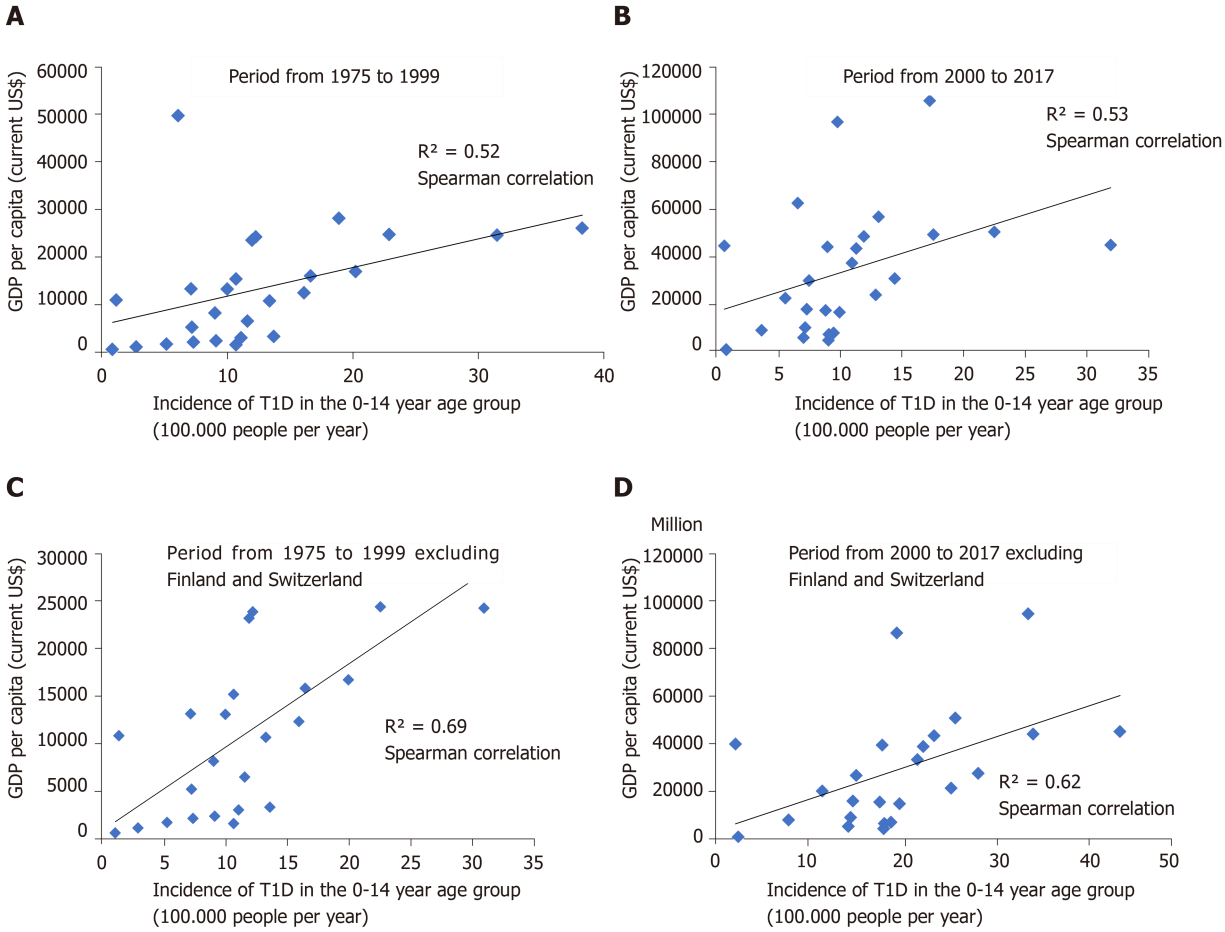

Figure 5 Correlation between incidence of type 1 diabetes and gross domestic product per capita for countries with information at the national level in two periods. A: Analysis for 26 countries period from 1975 to 1999; B: Analysis for 26 countries, period from 2000 to 2017; C: Analysis excluding Finland and Switzerland, period from 1975 to 1999; D: Analysis excluding Finland and Switzerland, period from 2000 to 2017.

ARTICLE HIGHLIGHTS

Research background

Type 1 Diabetes (T1D) is a complex disease resulting from the interplay of genetic, epigenetic, and environmental factors. There is a dramatic increase in the incidence of T1D, predominantly in younger children (0-4 years old) worldwide. The cause of this increase is still under study.

Research motivation

This work updates the current knowledge on the global incidence of T1D across age categories and its variation over time. The increase of incidence of T1D has been associated with socioeconomic factors, such as gross domestic product (GDP). However, there have been conflicting results about the relationship between income level and the incidence of T1D.

Research objectives

We searched the global variation in the incidence of T1D in the age categories and two periods (1975-1990 and 2000-2017). We then searched to what extent these variations correlated with the GDP per capita in these countries.

Research methods

We updated through a systematic review, our previous results on the global incidence of T1D in individuals aged 0-14 years. We first retrieved the incidence of T1D data in different age categories (0-4, 5-9, 10-14, 0-14) and divided the incidence information into two periods (1975-1999 and 2000-2017). Then, we conducted an exploratory ecological analysis about the relations of population rates of T1D incidence and the average GDP of these countries. Comparisons of means, correlations, linear regression were made.

Research results

We retrieved incidence data for 84 countries, most of them are European. We observed an increase in the incidence of T1D worldwide when comparing the periods 1975-1999 and 2000-2017. We also observed an increase in the incidence of T1D in all age categories (0-4, 5-9 and 10-

14). In the period 1975-1999, the incidence increased with age, with a peak in children aged 10-14 years. For the period 2000-2017, there appeared to be an increasing number of patients in the 5-9 age group and a greater relative rise in the 0-4 age group. Also, we found that the highest incidences of the disease were reported in wealthier countries.

Research conclusions

We found a wide geographic variation in the incidence of T1D and a worldwide increase in the two periods considered in this study, especially in younger children (0-4 years old); showing an early age at onset. Also, we confirmed that there was a positive correlation between the socio-economic level and the incidence of T1D. More studies are required to elucidate the interaction between environmental, immunological and genetic factor.

Research perspectives

This study showed the enormous differences in surveillance and epidemiological reports of T1D worldwide. Most of the countries retrieved from the systematic review are European and few studies were carried out in Central and Latin America, Central Asia and Sub-Saharan Africa. It is very important that the scientific community generates more studies on the epidemiology of T1D that contribute to understanding the changes in the dynamics of the disease.

ACKNOWLEDGEMENTS

We are very grateful to Professor Emmanuel Nieto for his advice in economics from Facultad de Salud Publica, Universidad de Antioquia and to Professor Valleron AJ, Membre de l'Académie des Sciences of France, for his critical reading of and helpful suggestions for this manuscript.

REFERENCES

1 **Diaz-Valencia PA**, Bougnères P, Valleron AJ. Global epidemiology of type 1 diabetes in young adults and adults: a systematic review. *BMC Public Health* 2015; **15**: 255 [PMID: 25849566 DOI: 10.1186/s12889-015-1591-y]
2 **International Diabetes Federation**. IDF DIABETES ATLAS. 6th ed; 2013
3 **Patterson C**, Guariguata L, Dahlquist G, Soltész G, Ogle G, Silink M. Diabetes in the young - a global view and worldwide estimates of numbers of children with type 1 diabetes. *Diabetes Res Clin Pract* 2014; **103**: 161-175 [PMID: 24331235 DOI: 10.1016/j.diabres.2013.11.005]
4 **Aschner P**. Diabetes trends in Latin America. *Diabetes Metab Res Rev* 2002; **18** Suppl 3: S27-S31 [PMID: 12324982 DOI: 10.1002/dmrr.280]
5 **Gómez-Díaz RA**, Garibay-Nieto N, Wacher-Rodarte N, Aguilar-Salinas CA. Epidemiology of type 1 diabetes in Latin America. *Curr Diabetes Rev* 2014; **10**: 75-85 [PMID: 24568292 DOI: 10.2174/1573399810666140223183936]
6 **DIAMOND Project Group**. Incidence and trends of childhood Type 1 diabetes worldwide 1990-1999. *Diabet Med* 2006; **23**: 857-866 [PMID: 16911623 DOI: 10.1111/j.1464-5491.2006.01925.x]
7 **Patterson CC**, Dahlquist GG, Gyürüs E, Green A, Soltész G; EURODIAB Study Group. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. *Lancet* 2009; **373**: 2027-2033 [PMID: 19481249 DOI: 10.1016/S0140-6736(09)60568-7]
8 **Grigsby-Toussaint DS**, Lipton R, Chavez N, Handler A, Johnson TP, Kubo J. Neighborhood socioeconomic change and diabetes risk: findings from the Chicago childhood diabetes registry. *Diabetes Care* 2010; **33**: 1065-1068 [PMID: 20150301 DOI: 10.2337/dc09-1894]
9 **du Prel JB**, Icks A, Grabert M, Holl RW, Giani G, Rosenbauer J. Socioeconomic conditions and type 1 diabetes in childhood in North Rhine-Westphalia, Germany. *Diabetologia* 2007; **50**: 720-728 [PMID: 17294165 DOI: 10.1007/s00125-007-0592-5]
10 **Diaz-Valencia PA**, Bougnères P, Valleron AJ. Covariation of the incidence of type 1 diabetes with country characteristics available in public databases. *PLoS One* 2015; **10**: e0118298 [PMID: 25706995 DOI: 10.1371/journal.pone.0118298]
11 **Morgenstern H**. Uses of ecologic analysis in epidemiologic research. *Am J Public Health* 1982; **72**: 1336-1344 [PMID: 7137430 DOI: 10.2105/ajph.72.12.1336]
12 **Loney PL**, Chambers LW, Bennett KJ, Roberts JG, Stratford PW. Critical appraisal of the health research literature: prevalence or incidence of a health problem. *Chronic Dis Can* 1998; **19**: 170-176 [PMID: 10029513]
13 **United Nations**. Standard country or area codes for statistical use (M49). Available from: https://unstats.un.org/unsd/methodology/m49/
14 **GraphClick**. Version 3.0. Arizona Software. 2008. Available from: http://www.arizona-software.ch/graphclick/
15 **The World Bank**. World Bank Open Data. Available from: https://data.worldbank.org/
16 **Reserved-TSAR**. Tableau Public. 2015. Available from: https://public.tableau.com/en-us/s/
17 **R Core Team (2017)**. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Austria: Vienna. Available from: https://www.R-project.org/
18 **Haynes A**, Bulsara MK, Bower C, Jones TW, Davis EA. Regular peaks and troughs in the Australian incidence of childhood type 1 diabetes mellitus (2000-2011). *Diabetologia* 2015; **58**: 2513-2516 [PMID: 26228717 DOI: 10.1007/s00125-015-3709-2]
19 **Patterson CC**, Gyürüs E, Rosenbauer J, Cinek O, Neu A, Schober E, Parslow RC, Joner G, Svensson J, Castell C, Bingley PJ, Schoenle E, Jarosz-Chobot P, Urbonaité B, Rothe U, Krzisnik C, Ionescu-Tirgoviste C, Weets I, Kocova M, Stipancic G, Samardzic M, de Beaufort CE, Green A, Dahlquist GG, Soltész G.

Trends in childhood type 1 diabetes incidence in Europe during 1989-2008: evidence of non-uniformity over time in rates of increase. *Diabetologia* 2012; **55**: 2142-2147 [PMID: 22638547 DOI: 10.1007/s00125-012-2571-8]

20 **Peter SA**, Johnson R, Taylor C, Hanna A, Roberts P, McNeil P, Archer B, SinQuee C, Roberts P. The incidence and prevalence of type-1 diabetes mellitus. *J Natl Med Assoc* 2005; **97**: 250-252 [PMID: 15712788]

21 **Zalutskaya A**, Bornstein SR, Mokhort T, Garmaev D. Did the Chernobyl incident cause an increase in Type 1 diabetes mellitus incidence in children and adolescents? *Diabetologia* 2004; **47**: 147-148 [PMID: 14658035 DOI: 10.1007/s00125-003-1271-9]

22 **Tahirović H**, Toromanović A. Incidence of type 1 diabetes mellitus in children in Tuzla Canton between 1995 and 2004. *Eur J Pediatr* 2007; **166**: 491-492 [PMID: 17047994 DOI: 10.1007/s00431-006-0257-2]

23 **Radosevic B**, Bukara-Radujkovic G, Miljkovic V, Pejicic S, Bratina N, Battelino T. The incidence of type 1 diabetes in Republic of Srpska (Bosnia and Herzegovina) and Slovenia in the period 1998-2010. *Pediatr Diabetes* 2013; **14**: 273-279 [PMID: 22925312 DOI: 10.1111/j.1399-5448.2012.00898.x]

24 **Negrato CA**, Lauris JRP, Saggioro IB, Corradini MCM, Borges PR, Crês MC, Junior AL, Guedes MFS, Gomes MB. Increasing incidence of type 1 diabetes between 1986 and 2015 in Bauru, Brazil. *Diabetes Res Clin Pract* 2017; **127**: 198-204 [PMID: 28391136 DOI: 10.1016/j.diabres.2017.03.014]

25 **Ehrlich RM**, Walsh LJ, Falk JA, Middleton PJ, Simpson NE. The incidence of type 1 (insulin-dependent) diabetes in Toronto. *Diabetologia* 1982; **22**: 289-291 [PMID: 7095330 DOI: 10.1007/BF00281308]

26 **Blanchard JF**, Dean H, Anderson K, Wajda A, Ludwig S, Depew N. Incidence and prevalence of diabetes in children aged 0-14 years in Manitoba, Canada, 1985-1993. *Diabetes Care* 1997; **20**: 512-515 [PMID: 9096971 DOI: 10.2337/diacare.20.4.512]

27 **Legault L**, Polychronakos C. Annual incidence of type 1 diabetes in Québec between 1989-2000 in children. *Clin Invest Med* 2006; **29**: 10-13 [PMID: 16553358]

28 **Newhook LA**, Penney S, Fiander J, Dowden J. Recent incidence of type 1 diabetes mellitus in children 0-14 years in Newfoundland and Labrador, Canada climbs to over 45/100,000: a retrospective time trend study. *BMC Res Notes* 2012; **5**: 628 [PMID: 23146327 DOI: 10.1186/1756-0500-5-628]

29 **Larenas G**, Montecinos A, Manosalva M, Barthou M, Vidal T. Incidence of insulin-dependent diabetes mellitus in the IX region of Chile: ethnic differences. *Diabetes Res Clin Pract* 1996; **34** Suppl: S147-S151 [PMID: 9015684 DOI: 10.1016/S0168-8227(96)90022-4]

30 **Torres-Avilés F**, Carrasco E, Icaza G, Pérez-Bravo F. Clustering of cases of type 1 diabetes in high socioeconomic communes in Santiago de Chile: spatio-temporal and geographical analysis. *Acta Diabetol* 2010; **47**: 251-257 [PMID: 20464570 DOI: 10.1007/s00592-010-0189-1]

31 **Yang Z**, Long X, Shen J, Liu D, Dorman JS, Laporte RE, Chang YF. Epidemics of type 1 diabetes in China. *Pediatr Diabetes* 2005; **6**: 122-128 [PMID: 16109067 DOI: 10.1111/j.1399-543X.2005.00116.x]

32 **Wu HB**, Zhong JM, Hu RY, Wang H, Gong WW, Pan J, Fei FR, Wang M, Guo LH, Yang L, Yu M. Rapidly rising incidence of Type 1 diabetes in children and adolescents aged 0-19 years in Zhejiang, China, 2007 to 2013. *Diabet Med* 2016; **33**: 1339-1346 [PMID: 26499360 DOI: 10.1111/dme.13010]

33 **Gong C**, Meng X, Jiang Y, Wang X, Cui H, Chen X. Trends in childhood type 1 diabetes mellitus incidence in Beijing from 1995 to 2010: a retrospective multicenter study based on hospitalization data. *Diabetes Technol Ther* 2015; **17**: 159-165 [PMID: 25545069 DOI: 10.1089/dia.2014.0205]

34 **Zhao Z**, Sun C, Wang C, Li P, Wang W, Ye J, Gu X, Wang X, Shen S, Zhi D, Lu Z, Ye R, Cheng R, Xi L, Li X, Zheng Z, Zhang M, Luo F. Rapidly rising incidence of childhood type 1 diabetes in Chinese population: epidemiology in Shanghai during 1997-2011. *Acta Diabetol* 2014; **51**: 947-953 [PMID: 24777734 DOI: 10.1007/s00592-014-0590-2]

35 **Rojnic Putarek N**, Ille J, Spehar Uroic A, Skrabic V, Stipancic G, Krnic N, Radica A, Marjanac I, Severinski S, Svigir A, Bogdanic A, Dumic M. Incidence of type 1 diabetes mellitus in 0 to 14-yr-old children in Croatia--2004 to 2012 study. *Pediatr Diabetes* 2015; **16**: 448-453 [PMID: 25080870 DOI: 10.1111/pedi.12197]

36 **Skordis N**, Efstathiou E, Kyriakides TC, Savvidou A, Savva SC, Phylactou LA, Shammas C, Neocleous V. Epidemiology of type 1 diabetes mellitus in Cyprus: rising incidence at the dawn of the 21st century. *Hormones (Athens)* 2012; **11**: 86-93 [PMID: 22450348 DOI: 10.1007/BF03401541]

37 **Kim JH**, Lee CG, Lee YA, Yang SW, Shin CH. Increasing incidence of type 1 diabetes among Korean children and adolescents: analysis of data from a nationwide registry in Korea. *Pediatr Diabetes* 2016; **17**: 519-524 [PMID: 26420382 DOI: 10.1111/pedi.12324]

38 **Arab M**. Diabetes mellitus in Egypt. *World Health Stat Q* 1992; **45**: 334-337 [PMID: 1299073]

39 **El-Ziny MA**, Salem NA, El-Hawary AK, Chalaby NM, Elsharkawy AA. Epidemiology of childhood type 1 diabetes mellitus in Nile Delta, northern Egypt - a retrospective study. *J Clin Res Pediatr Endocrinol* 2014; **6**: 9-15 [PMID: 24637304 DOI: 10.4274/Jcrpe.1171]

40 **Teeäär T**, Liivak N, Heilman K, Kool P, Sor R, Paal M, Einberg U, Tillmann V. Increasing incidence of childhood-onset type 1 diabetes mellitus among Estonian children in 1999-2006. Time trend analysis 1983-2006. *Pediatr Diabetes* 2010; **11**: 107-110 [PMID: 19496966 DOI: 10.1111/j.1399-5448.2009.00535.x]

41 **Alemu S**, Dessie A, Seid E, Bard E, Lee PT, Trimble ER, Phillips DI, Parry EH. Insulin-requiring diabetes in rural Ethiopia: should we reopen the case for malnutrition-related diabetes? *Diabetologia* 2009; **52**: 1842-1845 [PMID: 19565213 DOI: 10.1007/s00125-009-1433-5]

42 **Ogle GD**, Morrison MK, Silink M, Taito RS. Incidence and prevalence of diabetes in children aged <15 yr in Fiji, 2001-2012. *Pediatr Diabetes* 2016; **17**: 222-226 [PMID: 25597929 DOI: 10.1111/pedi.12257]

43 **Harjutsalo V**, Sund R, Knip M, Groop PH. Incidence of type 1 diabetes in Finland. *JAMA* 2013; **310**: 427-428 [PMID: 23917294 DOI: 10.1001/jama.2013.8399]

44 **Mauny F**, Grandmottet M, Lestradet C, Guitard J, Crenn D, Floret N, Olivier-Koehret M, Viel JF; Health Consequences of Chernobyl Fallout in Franche-Comté Study Group. Increasing trend of childhood type 1 diabetes in Franche-Comté (France): analysis of age and period effects from 1980 to 1998. *Eur J Epidemiol* 2005; **20**: 325-329 [PMID: 15971504 DOI: 10.1007/s10654-005-0329-z]

45 **Barat P**, Valade A, Brosselin P, Alberti C, Maurice-Tison S, Lévy-Marchal C. The growing incidence of type 1 diabetes in children: the 17-year French experience in Aquitaine. *Diabetes Metab* 2008; **34**: 601-605 [PMID: 18952477 DOI: 10.1016/j.diabet.2008.06.002]

46 **Trellu M**, Lacombe S, Morin D, Dalla-Vale F. [Epidemiology of diabetes in children in Languedoc-Roussillon (France)]. *Arch Pediatr* 2015; **22**: 241-246 [PMID: 25656455 DOI: 10.1016/j.arcped.2014.12.009]

47 **Bendas A**, Rothe U, Kiess W, Kapellen TM, Stange T, Manuwald U, Salzsieder E, Holl RW, Schoffer O,

Stahl-Pehe A, Giani G, Ehehalt S, Neu A, Rosenbauer J. Trends in Incidence Rates during 1999-2008 and Prevalence in 2008 of Childhood Type 1 Diabetes Mellitus in Germany--Model-Based National Estimates. *PLoS One* 2015; **10**: e0132716 [PMID: 26181330 DOI: 10.1371/journal.pone.0132716]

48 **Dacou-Voutetakis C**, Karavanaki K, Tsoka-Gennatas H. National data on the epidemiology of IDDM in Greece. Cases diagnosed in 1992. Hellenic Epidemiology Study Group. *Diabetes Care* 1995; **18**: 552-554 [PMID: 7497869 DOI: 10.2337/diacare.18.4.552]

49 **Ramachandran A**, Snehalatha C, Krishnaswamy CV. Incidence of IDDM in children in urban population in southern India. Madras IDDM Registry Group Madras, South India. *Diabetes Res Clin Pract* 1996; **34**: 79-82 [PMID: 9031809 DOI: 10.1016/S0168-8227(96)01338-1]

50 **Pishdad GR**. Low incidence of type 1 diabetes in Iran. *Diabetes Care* 2005; **28**: 927-928 [PMID: 15793198 DOI: 10.2337/diacare.28.4.927]

51 **Roche EF**, McKenna AM, Ryder KJ, Brennan AA, O'Regan M, Hoey HM. Is the incidence of type 1 diabetes in children and adolescents stabilising? The first 6 years of a National Register. *Eur J Pediatr* 2016; **175**: 1913-1919 [PMID: 27659662 DOI: 10.1007/s00431-016-2787-6]

52 **Blumenfeld O**, Dichtiar R, Shohat T; Israel IDDM Registry Study Group (IIRSG). Trends in the incidence of type 1 diabetes among Jews and Arabs in Israel. *Pediatr Diabetes* 2014; **15**: 422-427 [PMID: 24283719 DOI: 10.1111/pedi.12101]

53 **Di Ciaula A**. Type I diabetes in paediatric age in Apulia (Italy): Incidence and associations with outdoor air pollutants. *Diabetes Res Clin Pract* 2016; **111**: 36-43 [PMID: 26527558 DOI: 10.1016/j.diabres.2015.10.016]

54 **Valent F**, Candido R, Faleschini E, Tonutti L, Tortul C, Zanatta M, Zanette G, Zanier L. The incidence rate and prevalence of pediatric type 1 diabetes mellitus (age 0-18) in the Italian region Friuli Venezia Giulia: population-based estimates through the analysis of health administrative databases. *Acta Diabetol* 2016; **53**: 629-635 [PMID: 26997510 DOI: 10.1007/s00592-016-0854-0]

55 **Altobelli E**, Petrocelli R, Verrotti A, Chiarelli F, Marziliano C. Genetic and environmental factors affect the onset of type 1 diabetes mellitus. *Pediatr Diabetes* 2016; **17**: 559-566 [PMID: 26697762 DOI: 10.1111/pedi.12345]

56 **Marigliano M**, Tadiotto E, Morandi A, Sabbion A, Contreas G, Avossa F, Fedeli U, Maffeis C. Epidemiology of type 1 diabetes mellitus in the pediatric population in Veneto Region, Italy. *Diabetes Res Clin Pract* 2015; **107**: e19-e21 [PMID: 25641011 DOI: 10.1016/j.diabres.2014.12.009]

57 **Bruno G**, Maule M, Merletti F, Novelli G, Falorni A, Iannilli A, Iughetti L, Altobelli E, d'Annunzio G, Piffer S, Pozzilli P, Iafusco D, Songini M, Roncarolo F, Toni S, Carle F, Cherubini V; RIDI Study Group. Age-period-cohort analysis of 1990-2003 incidence time trends of childhood diabetes in Italy: the RIDI study. *Diabetes* 2010; **59**: 2281-2287 [PMID: 20566665 DOI: 10.2337/db10-0151]

58 **Onda Y**, Sugihara S, Ogata T, Yokoya S, Yokoyama T, Tajima N; Type 1 Diabetes (T1D) Study Group. Incidence and prevalence of childhood-onset Type 1 diabetes in Japan: the T1D study. *Diabet Med* 2017; **34**: 909-915 [PMID: 27925270 DOI: 10.1111/dme.13295]

59 **Ajlouni K**, Qusous Y, Khawaldeh AK, Jaddou H, Batiehah A, Ammari F, Zaheri M, Mashal A. Incidence of insulin-dependent diabetes mellitus in Jordanian children aged 0-14 y during 1992-1996. *Acta Paediatr Suppl* 1999; **88**: 11-13 [PMID: 10195848 DOI: 10.1111/j.1651-2227.1999.tb14334.x]

60 **Shaltout AA**, Wake D, Thanaraj TA, Omar DM, Al-AbdulRazzaq D, Channanath A, AlKandari H, Abdulrasoul M, Miller S, Conway N, Tuomilehto J, Davidsson L; Steering Group for the Study of Childhood Diabetes in Kuwait. Incidence of type 1 diabetes has doubled in Kuwaiti children 0-14 years over the last 20 years. *Pediatr Diabetes* 2017; **18**: 761-766 [PMID: 27981709 DOI: 10.1111/pedi.12480]

61 **Formosa N**, Calleja N, Torpiano J. Incidence and modes of presentation of childhood type 1 diabetes mellitus in Malta between 2006 and 2010. *Pediatr Diabetes* 2012; **13**: 484-488 [PMID: 22151907 DOI: 10.1111/j.1399-5448.2011.00839.x]

62 **Gómez-Díaz RA**, Pérez-Pérez G, Hernández-Cuesta IT, Rodríguez-García Jdel C, Guerrero-López R, Aguilar-Salinas CA, Wacher NH. Incidence of type 1 diabetes in Mexico: data from an institutional register 2000-2010. *Diabetes Care* 2012; **35**: e77 [PMID: 23093688 DOI: 10.2337/dc12-0844]

63 **Samardžić M**, Martinović M, Nedović-Vuković M, Popović-Samardžić M. Recent incidence of type 1 diabetes mellitus in montenegro: a shift toward younger age at disease onset. *Acta Clin Croat* 2016; **55**: 63-68 [PMID: 27333720 DOI: 10.20471/acc.2016.55.01.10]

64 **Fazeli Farsani S**, Souverein PC, van der Vorst MM, Knibbe CA, Herings RM, de Boer A, Mantel-Teeuwisse AK. Increasing trends in the incidence and prevalence rates of type 1 diabetes among children and adolescents in the Netherlands. *Pediatr Diabetes* 2016; **17**: 44-52 [PMID: 25377748 DOI: 10.1111/pedi.12232]

65 **Campbell-Stokes PL**, Taylor BJ; New Zealand Children's Diabetes Working Group. Prospective incidence study of diabetes mellitus in New Zealand children aged 0 to 14 years. *Diabetologia* 2005; **48**: 643-648 [PMID: 15759108 DOI: 10.1007/s00125-005-1697-3]

66 **Skrivarhaug T**, Stene LC, Drivvoll AK, Strøm H, Joner G; Norwegian Childhood Diabetes Study Group. Incidence of type 1 diabetes in Norway among children aged 0-14 years between 1989 and 2012: has the incidence stopped rising? Results from the Norwegian Childhood Diabetes Registry. *Diabetologia* 2014; **57**: 57-62 [PMID: 24149838 DOI: 10.1007/s00125-013-3090-y]

67 **Soliman AT**, al-Salmi IS, Asfour MG. Epidemiology of childhood insulin-dependent diabetes mellitus in the Sultanate of Oman. *Diabet Med* 1996; **13**: 582-586 [PMID: 8799664 DOI: 10.1002/(SICI)1096-9136(199606)13:6<582::AID-DIA114>3.0.CO;2-E]

68 **Ogle GD**, Lesley J, Sine P, McMaster P. Type 1 diabetes mellitus in children in Papua New Guinea. *P N G Med J* 2001; **44**: 96-100 [PMID: 12422979]

69 **Jarosz-Chobot P**, Polanska J, Szadkowska A, Kretowski A, Bandurska-Stankiewicz E, Ciechanowska M, Deja G, Mysliwiec M, Peczynska J, Rutkowska J, Sobel-Maruniak A, Fichna P, Chobot A, Rewers M. Rapid increase in the incidence of type 1 diabetes in Polish children from 1989 to 2004, and predictions for 2010 to 2025. *Diabetologia* 2011; **54**: 508-515 [PMID: 21165594 DOI: 10.1007/s00125-010-1993-4]

70 **Wojcik M**, Sudacka M, Wasyl B, Ciechanowska M, Nazim J, Stelmach M, Starzyk JB. Incidence of type 1 diabetes mellitus during 26 years of observation and prevalence of diabetic ketoacidosis in the later years. *Eur J Pediatr* 2015; **174**: 1319-1324 [PMID: 25894913 DOI: 10.1007/s00431-015-2537-1]

71 **Chobot A**, Polanska J, Brandt A, Deja G, Glowinska-Olszewska B, Pilecki O, Szadkowska A, Mysliwiec M, Jarosz-Chobot P. Updated 24-year trend of Type 1 diabetes incidence in children in Poland reveals a sinusoidal pattern and sustained increase. *Diabet Med* 2017; **34**: 1252-1258 [PMID: 28257151 DOI: 10.1111/dme.13345]

72 **Al-Zyoud M**, Al Ali M, Rahim A MI. Insulin dependant diabetes mellitus (IDDM) in children below 13

years of age in Qatar. *Diabetes Insights* 1997; **4**: 10
73 **Lin WH**, Wang MC, Wang WM, Yang DC, Lam CF, Roan JN, Li CY. Incidence of and mortality from Type I diabetes in Taiwan from 1999 through 2010: a nationwide cohort study. *PLoS One* 2014; **9**: e86172 [PMID: 24465941 DOI: 10.1371/journal.pone.0086172]
74 **Serban V**, Brink S, Timar B, Sima A, Vlad M, Timar R, Vlad A. An increasing incidence of type 1 diabetes mellitus in Romanian children aged 0 to 17 years. *J Pediatr Endocrinol Metab* 2015; **28**: 293-298 [PMID: 25581747 DOI: 10.1515/jpem-2014-0364]
75 **Pronina EA**, Petraikina EE, Antsiferov MB, Duchareva OV, Petrone A, Buzzetti R, Pozzilli P. A 10-year (1996-2005) prospective study of the incidence of Type 1 diabetes in Moscow in the age group 0-14 years. *Diabet Med* 2008; **25**: 956-959 [PMID: 18959609 DOI: 10.1111/j.1464-5491.2008.02508.x]
76 **Marshall SL**, Edidin D, Arena VC, Becker DJ, Bunker CH, Gishoma C, Gishoma F, LaPorte RE, Kaberuka V, Ogle G, Sibomana L, Orchard TJ. Prevalence and incidence of clinically recognized cases of Type 1 diabetes in children and adolescents in Rwanda, Africa. *Diabet Med* 2015; **32**: 1186-1192 [PMID: 25604893 DOI: 10.1111/dme.12701]
77 **Kulaylat NA**, Narchi H. A twelve year study of the incidence of childhood type 1 diabetes mellitus in the Eastern Province of Saudi Arabia. *J Pediatr Endocrinol Metab* 2000; **13**: 135-140 [PMID: 10711657 DOI: 10.1515/JPEM.2000.13.2.135]
78 **Habeb AM**, Al-Magamsi MS, Halabi S, Eid IM, Shalaby S, Bakoush O. High incidence of childhood type 1 diabetes in Al-Madinah, North West Saudi Arabia (2004-2009). *Pediatr Diabetes* 2011; **12**: 676-681 [PMID: 21418457 DOI: 10.1111/j.1399-5448.2011.00765.x]
79 **Vlajinac HD**, Bojović BM, Sipetić SB, Adanja BJ, Jarebinski MS, Radmanović SZ, Zdravković DS. Insulin dependent diabetes mellitus: incidence in childhood in Belgrade 1982-92. *J Epidemiol Community Health* 1995; **49**: 107-108 [PMID: 7706995 DOI: 10.1136/jech.49.1.107]
80 **Lee WW**, Ooi BC, Thai AC, Loke KY, Tan YT, Rajan U, Tan CL. The incidence of IDDM in Singapore children. *Singapore Med J* 1998; **39**: 359-362 [PMID: 9844497]
81 **Serrano Ríos M**, Moy CS, Martín Serrano R, Minuesa Asensio A, de Tomás Labat ME, Zarandieta Romero G, Herrera J. Incidence of type 1 (insulin-dependent) diabetes mellitus in subjects 0-14 years of age in the Comunidad of Madrid, Spain. *Diabetologia* 1990; **33**: 422-424 [PMID: 2401397 DOI: 10.1007/BF00404093]
82 **Lora-Gómez RE**, Morales-Pérez FM, Arroyo-Díez FJ, Barquero-Romero J. Incidence of Type 1 diabetes in children in Cáceres, Spain, during 1988-1999. *Diabetes Res Clin Pract* 2005; **69**: 169-174 [PMID: 16005366 DOI: 10.1016/j.diabres.2004.11.013]
83 **Morales-Pérez FM**, Barquero-Romero J, Pérez-Miranda M. Incidence of type I diabetes among children and young adults (0-29 years) in the province of Badajoz, Spain during 1992 to 1996. *Acta Paediatr* 2000; **89**: 101-104 [PMID: 10677067 DOI: 10.1080/080352500750029158]
84 **Forga L**, Goñi MJ, Ibáñez B, Cambra K, Mozas D, Chueca M. [Incidence of type 1 diabetes in Navarre, 2009-2012]. *An Sist Sanit Navar* 2014; **37**: 241-247 [PMID: 25189982 DOI: 10.4321/S1137-66272014000200007]
85 **Vega T**, Gil M, Lozano J. Age and sex differences in the incidence of diabetes mellitus in a population-based Spanish cohort. *J Diabetes* 2015; **7**: 411-417 [PMID: 24981073 DOI: 10.1111/1753-0407.12183]
86 **Fernández-Ramos C**, Arana-Arri E, Jiménez-Huertas P, Vela A, Rica I. Incidence of childhood-onset type 1 diabetes in Biscay, Spain, 1990-2013. *Pediatr Diabetes* 2017; **18**: 71-76 [PMID: 26782628 DOI: 10.1111/pedi.12354]
87 **Elamin A**, Ghalib M, Eltayeb B, Tuvemo T. High incidence of type 1 diabetes mellitus in Sudanese children, 1991-1995. *Ann Saudi Med* 1997; **17**: 478-480 [PMID: 17353609 DOI: 10.5144/0256-4947.1997.478]
88 **Rawshani A**, Landin-Olsson M, Svensson AM, Nyström L, Arnqvist HJ, Bolinder J, Gudbjörnsdottir S. The incidence of diabetes among 0-34 year olds in Sweden: new data and better methods. *Diabetologia* 2014; **57**: 1375-1381 [PMID: 24710965 DOI: 10.1007/s00125-014-3225-9]
89 **Panamonta O**, Thamjaroen J, Panamonta M, Panamonta N, Suesirisawat C. The rising incidence of type 1 diabetes in the northeastern part of Thailand. *J Med Assoc Thai* 2011; **94**: 1447-1450 [PMID: 22295730]
90 **Ben Khalifa F**, Mekaouar A, Taktak S, Hamhoum M, Jebara H, Kodia A, Zouari B, Chakroun M. A five-year study of the incidence of insulin-dependent diabetes mellitus in young Tunisians (preliminary results). *Diabetes Metab* 1997; **23**: 395-401 [PMID: 9416431]
91 **Yeşilkaya E**, Cinaz P, Andıran N, Bideci A, Hatun Ş, Sarı E, Türker T, Akgül Ö, Saldır M, Kılıçaslan H, Açıkel C, Craig ME. First report on the nationwide incidence and prevalence of Type 1 diabetes among children in Turkey. *Diabet Med* 2017; **34**: 405-410 [PMID: 26814362 DOI: 10.1111/dme.13063]
92 **Timchenko OI**, Kozachok GS, Turos EI, Omel'chenko EM. [The prevalence of diabetes mellitus in children of different regions of Ukraine]. *Tsitol Genet* 1996; **30**: 70-73 [PMID: 9139441]
93 **Imkampe AK**, Gulliford MC. Trends in Type 1 diabetes incidence in the UK in 0- to 14-year-olds and in 15- to 34-year-olds, 1991-2008. *Diabet Med* 2011; **28**: 811-814 [PMID: 21395679 DOI: 10.1111/j.1464-5491.2011.03288.x]
94 **Swai AB**, Lutale JL, McLarty DG. Prospective study of incidence of juvenile diabetes mellitus over 10 years in Dar es Salaam, Tanzania. *BMJ* 1993; **306**: 1570-1572 [PMID: 8329915 DOI: 10.1136/bmj.306.6892.1570]
95 **Cartee AK**, Owens LA, Lahr BD, Yawn BP, Murray JA, Kudva YC. Incidence of Type 1 Diabetes Is Not Increasing in a Population-Based Cohort in Olmsted County, Minnesota, USA. *Mayo Clin Proc* 2016; **91**: 1066-1073 [PMID: 27492913 DOI: 10.1016/j.mayocp.2016.05.019]
96 **Mayer-Davis EJ**, Lawrence JM, Dabelea D, Divers J, Isom S, Dolan L, Imperatore G, Linder B, Marcovina S, Pettitt DJ, Pihoker C, Saydah S, Wagenknecht L; SEARCH for Diabetes in Youth Study. Incidence Trends of Type 1 and Type 2 Diabetes among Youths, 2002-2012. *N Engl J Med* 2017; **376**: 1419-1429 [PMID: 28402773 DOI: 10.1056/NEJMoa1610187]
97 **Rakhimova GN**, Alimova NU, Ryaboshtan A, Waldman B, Ogle GD, Ismailov SI. Epidemiological data of type 1 diabetes mellitus in children in Uzbekistan, 1998-2014. *Pediatr Diabetes* 2018; **19**: 158-165 [PMID: 28097737 DOI: 10.1111/pedi.12495]
98 **Shaltout AA**, Moussa MA, Qabazard M, Abdella N, Karvonen M, Al-Khawari M, Al-Arouj M, Al-Nakhi A, Tuomilehto J, El-Gammal A; Kuwait Diabetes Study Group. Further evidence for the rising incidence of childhood Type 1 diabetes in Kuwait. *Diabet Med* 2002; **19**: 522-525 [PMID: 12109439 DOI: 10.1046/j.1464-5491.2002.00703.x]
99 **Morran MP**, Vonberg A, Khadra A, Pietropaolo M. Immunogenetics of type 1 diabetes mellitus. *Mol Aspects Med* 2015; **42**: 42-60 [PMID: 25579746 DOI: 10.1016/j.mam.2014.12.004]

100 **Lipton RB**, Drum M, Greeley SA, Danielson KK, Bell GI, Hagopian WA. HLA-DQ haplotypes differ by ethnicity in patients with childhood-onset diabetes. *Pediatr Diabetes* 2011; **12**: 388-395 [PMID: 21418452 DOI: 10.1111/j.1399-5448.2010.00712.x]

101 **Rønningen KS**, Keiding N, Green A; EURODIAB ACE Study Group. Europe and Diabetes. Correlations between the incidence of childhood-onset type I diabetes in Europe and HLA genotypes. *Diabetologia* 2001; **44** Suppl 3: B51-B59 [PMID: 11724418 DOI: 10.1007/PL00002955]

102 **Park Y**, Eisenbarth GS. Genetic susceptibility factors of Type 1 diabetes in Asians. *Diabetes Metab Res Rev* 2001; **17**: 2-11 [PMID: 11241886 DOI: 10.1002/1520-7560(2000)9999:9999<::AID-DMRR164>3.0.CO;2-M]

103 **Rewers M**, Ludvigsson J. Environmental risk factors for type 1 diabetes. *Lancet* 2016; **387**: 2340-2348 [PMID: 27302273 DOI: 10.1016/S0140-6736(16)30507-4]

104 **Regnell SE**, Lernmark Å. Early prediction of autoimmune (type 1) diabetes. *Diabetologia* 2017; **60**: 1370-1381 [PMID: 28550517 DOI: 10.1007/s00125-017-4308-1]

105 **Forlenza GP**, Rewers M. The epidemic of type 1 diabetes: what is it telling us? *Curr Opin Endocrinol Diabetes Obes* 2011; **18**: 248-251 [PMID: 21844707 DOI: 10.1097/MED.0b013e32834872ce]

106 **Patterson CC**, Dahlquist G, Soltész G, Green A; EURODIAB ACE Study Group. Europe and Diabetes. Is childhood-onset type I diabetes a wealth-related disease? An ecological analysis of European incidence rates. *Diabetologia* 2001; **44** Suppl 3: B9-16 [PMID: 11724424 DOI: 10.1007/PL00002961]

107 **Holmqvist BM**, Lofman O, Samuelsson U. A low incidence of Type 1 diabetes between 1977 and 2001 in south-eastern Sweden in areas with high population density and which are more deprived. *Diabet Med* 2008; **25**: 255-260 [PMID: 18201211 DOI: 10.1111/j.1464-5491.2007.02342.x]

108 **Cardwell CR**, Carson DJ, Patterson CC. Secular trends, disease maps and ecological analyses of the incidence of childhood onset Type 1 diabetes in Northern Ireland, 1989-2003. *Diabet Med* 2007; **24**: 289-295 [PMID: 17305789 DOI: 10.1111/j.1464-5491.2007.02080.x]

109 **Bruno G**, Spadea T, Picariello R, Gruden G, Barutta F, Cerutti F, Cavallo-Perin P, Costa G, Gnavi R; Piedmont Study Group for Diabetes Epidemiology. Early life socioeconomic indicators and risk of type 1 diabetes in children and young adults. *J Pediatr* 2013; **162**: 600-605.e1 [PMID: 23084710 DOI: 10.1016/j.jpeds.2012.09.010]

110 **Egger G**, Swinburn B, Islam FM. Economic growth and obesity: an interesting relationship with world-wide implications. *Econ Hum Biol* 2012; **10**: 147-153 [PMID: 22305524 DOI: 10.1016/j.ehb.2012.01.002]

111 **Islam ST**, Srinivasan S, Craig ME. Environmental determinants of type 1 diabetes: a role for overweight and insulin resistance. *J Paediatr Child Health* 2014; **50**: 874-879 [PMID: 24893825 DOI: 10.1111/jpc.12616]

112 **Wilkin TJ**. The accelerator hypothesis: a review of the evidence for insulin resistance as the basis for type I as well as type II diabetes. *Int J Obes (Lond)* 2009; **33**: 716-726 [PMID: 19506563 DOI: 10.1038/ijo.2009.97]

113 **Gale EA**. A missing link in the hygiene hypothesis? *Diabetologia* 2002; **45**: 588-594 [PMID: 12032638 DOI: 10.1007/s00125-002-0801-1]

114 **Bach JF**. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med* 2002; **347**: 911-920 [PMID: 12239261 DOI: 10.1056/NEJMra020100]

115 **Bach JF**, Chatenoud L. The hygiene hypothesis: an explanation for the increased frequency of insulin-dependent diabetes. *Cold Spring Harb Perspect Med* 2012; **2**: a007799 [PMID: 22355800 DOI: 10.1101/cshperspect.a007799]

116 **Cardwell CR**, Stene LC, Ludvigsson J, Rosenbauer J, Cinek O, Svensson J, Perez-Bravo F, Memon A, Gimeno SG, Wadsworth EJ, Strotmeyer ES, Goldacre MJ, Radon K, Chuang LM, Parslow RC, Chetwynd A, Karavanaki K, Brigis G, Pozzilli P, Urbonaite B, Schober E, Devoti G, Sipetic S, Joner G, Ionescu-Tirgoviste C, de Beaufort CE, Harrild K, Benson V, Savilahti E, Ponsonby AL, Salem M, Rabiei S, Patterson CC. Breast-feeding and childhood-onset type 1 diabetes: a pooled analysis of individual participant data from 43 observational studies. *Diabetes Care* 2012; **35**: 2215-2225 [PMID: 22837371 DOI: 10.2337/dc12-0438]

117 **Mejía-León ME**, Barca AM. Diet, Microbiota and Immune System in Type 1 Diabetes Development and Evolution. *Nutrients* 2015; **7**: 9171-9184 [PMID: 26561831 DOI: 10.3390/nu7115461]

118 **Petrou S**, Khan K. An overview of the health economic implications of elective caesarean section. *Appl Health Econ Health Policy* 2013; **11**: 561-576 [PMID: 24155076 DOI: 10.1007/s40258-013-0063-8]

119 **Butalia S**, Kaplan GG, Khokhar B, Rabi DM. Environmental Risk Factors and Type 1 Diabetes: Past, Present, and Future. *Can J Diabetes* 2016; **40**: 586-593 [PMID: 27545597 DOI: 10.1016/j.jcjd.2016.05.002]

Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
E-mail: bpgoffice@wjgnet.com
Help Desk:https://www.f6publishing.com/helpdesk
https://www.wjgnet.com