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МАЗМҰНЫ

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CONTENTS

Preface

Diabetes mellitus is a severe disease, and its prevalence is dramatically increasing world-wide. The complications associated with the disease include cardiovascular disease, blindness, amputations, end-stage renal disease, kidney dialysis, and kidney transplantations and present major public-health problems. Furthermore, diabetes costs are exceeding meanwhile billions of dollars annually and put tremendous burden on national health care systems. Recent years have seen a significant progress in basic knowledge on diabetes due to enormous research efforts, making possible the development of new technology and therapeutics for diabetes management and care.

It was just diabetes research, when Dr. G.G. Meyramov from the Karaganda State University joined me in 1977 in Karlsburg and started out to study how tryptophan metabolites could induce diabetes in animals. Since then we look back on a very fruitful cooperation between the Karaganda State University and the Institute of Diabetes Karlsburg.

It was a landmark decision of the Faculty of Biology of the University and the Publishing House of this journal to issue a volume focusing on problems in diabetes. Of note, this is the first time in the history of Kazakhstan and Central Asia that there is a special issue of this distinguished journal, exclusively devoted to diabetes research. The Editors of this journal, by inviting contributions from international as well as national diabetes experts, made an important step in enhancing and disseminating knowledge about diabetes but, beyond that, lay emphasis on care and management of diabetes in Kazakhstan.

We trust that readers will welcome the present issue and benefit from the contributions herein provided by experts in the field.

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Foreword

Welcome to the Diabetes issue – 2016 of this edition of the Bulletin of the Karaganda University, in which you will find again a spectrum of selected topics addressed in the following review articles. These contributions encompass subjects such as diabetes prevention, insulin pump therapy in type 1 and 2 diabetes, and cardiovascular complications.

Diabetes is a life-threatening disease and has become an epidemic of global dimension. As the International Diabetes Federation predicts, half a billion people will have this disease by 2030. There is no doubt that this will cause not only large-scale death and disability, but also impose massive costs on national healthcare systems and economies. Without targeted action, the socioeconomic burden will inevitably worsen. Despite extensive diabetes prevention programs, a radical rethinking of how we live, i.e. what we eat and how we behave, is required to stem the global epidemic. In other words, prevention at an individual level becomes important in our life more than ever.

Thus, in the review article of this edition, the focus is on strategies for diabetes prevention. The authors Peter E.H. Schwarz and Patrick Timple summarized outcomes of large randomized clinical trials and provided excellent evidence that diabetes is preventable and more than 50 % of the diabetes risk reduced and disease onset postponed. Translation of scientific evidence into clinical practice has not only proven that similar results are achievable in clinical practice but has also shown that implementation of prevention programs into different structures of care is feasible. Here, the responsibility of healthcare policies is required to use existing care structures and concepts for prevention programs. Meanwhile, effective strategies to identify people with increased diabetes risk are available. As the authors point out, changing physical activity and eating habit can be useful in the prevention of diabetes, but most active seem to be to «walk diabetes away» approach. Indeed, straightforward and inexpensive measures, such as daily physical exercise can be highly efficient and thus people should be encouraged to follow a healthy lifestyle.

Once diabetes has established and glycemic control is worsening, insulin becomes the life-saving drug. Continuous subcutaneous insulin infusion (CSII) is considered a standard therapy in patients with type 1 diabetes. Before the transition to this therapy, patients mostly receive multiple daily insulin injections (MDI). However, conversion of MDI to CSII can be troublesome and needs a time-consuming trial-and-error principle. Lutz Vogt and colleagues provide a practical approach, using the Karlsburg Diabetes Management System (KADIS) to adjust individual basal and bolus insulin dosing. For this purpose, they extended the original KADIS program for adjustment of insulin pump therapy (KADIS-CSII). In a pilot study, including patients with type 1 diabetes who had previously received MDI, the authors convincingly demonstrate that HbA1c values significantly improved already three months after initiation of KADIS-supported pump therapy. Along with HbA1c, glycemic control, as measured by time in hypoglycemia and glycemic variability significantly decreased. The authors are justified in their conclusion that this program represents a practical and efficient tool for adjusting insulin pump therapy.

Whereas continuous subcutaneous insulin infusion using an insulin pump has been proved to be very effective in patient with type 1 diabetes, it is not widely employed in patients with type 2 diabetes. Rudolf Chlup provides in his review evidence that pump therapy is beneficial for patients with type 2 diabetes, too. Insulin infusion therapy holds not only for patients with unstable glycemic control but also for those with newly diagnosed diabetes. Short-term intensive insulin therapy was shown to recover beta cell function and prevent further exhausting of the secretory reserve.

There is no doubt that good glycemic control is a prerequisite for prevention of late diabetes complications. Eckhard Zander and colleagues analyzed landmark studies to show that, although understanding in reducing the risk of micro- and macrovascular diabetes complications deepened, the dilemma for both type 1

and type 2 diabetic patients remains atherosclerosis with increased cardiovascular morbidities and mortality in comparison to the non-diabetic population. Results of the large randomized studies now provided evidence that strict glycemic control decreased the risk of cardiovascular complications and death. Whereas the «memory effect» of tight, long-lasting glycemic control and individual HbA1c target levels has shown to reduce micro- and macrovascular morbidity in type 1 diabetes; in type 2 diabetes, the effects of hyperglycemia are weaker than those of classical risk factors.

Smoking is a factor in increasing the risk of endothelial dysfunction and increase the risk of developing diabetes and cardiovascular diseases. Elena Laryushina and coll. analyzed the influence of active and passive smoking on the risk of developing diabetes and cardiovascular disease among population of industrial cities of Central Kazakhstan. It is established that a high risk of developing diabetes was observed in 31 % persons with passive type of smoking with prevalence of women in comparison with active type of smoking. A high cardiovascular risk among almost 80 % of persons with active type of smoking and high risk of diabetes in group with passive smoking.

Results investigation of mechanisms of diabetogenic activity of abnormal metabolits of tryptophan synthesized in animals and human as result of disturbances of tryptophan metabolism are presented by G.G. Meyramov, A.A. Kikimbaeva and coll. State of histostructure of pancreatic islets as mechanisms of damage of B-cells under influence of xanthurenic acid, a main diabetogenic metabolit of tryptophan were investigated as possible method of suppression of its endogenous synthesis.

L.G. Turgunova and coll. studied indicators of quality of life of patients with 2 type of diabetes depending of social and demographic factors among population of the Karaganda region. The research carried out according Scientific program «Environmental Risks and Health of the Population». Screening included using of elaborated by authors of questionnaire contained official consent of respondent (patient) as information about sex, age, data on social factors (level of the income, family status (married or not), education, employment, nature of work), availability or absence of chronic diseases were specified. For determination of risk groups of diabetes the questionnaire of FINDRISC (The Finnish Diabetes Risk Score) was used. For a quality of life estimation the short version of questionnaire of WHO (WHOQOL-BREF) which consists of 26 questions. The analysis of results of a scale of FINDRISC showed that at 24,6 % of respondents in the next 10 years moderate, high and very high risk of DM took place (12 points and more). More high quality of life at respondents with the higher education can be explained by more good social adaptation, smaller frequency of risk factors of DM as of developing of a chronic nonin- fectious diseases. A low parameters of quality of life were showed at respondents have low le- vel of education, financial problems and in unemployed.

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Histochemical Methods for Identification of Zinc ions in Pancreatic Islets, Prostate and in Salivary Glands

Authors have used two histochemical methods: 8PTSQ, a high specific fluorescent and Dithizon method for identification of Zinc in the frozen and paraffin sections of tissues of pancreas as in tissues of prostate and salivary glands. It was showed that 10–15 min past one injection to animals of diabetogenic chelators (DC) result accompanied by binding of Zn ions and by negative reaction for Zn in B-cells determined absence of free Zn ions for staining. In the contrary, 5–7 days past injection of DC reaction for Zn in B-cells was negative as result of destruction of cells and of almost complete disappearing of Zn ions from B-cells. Analogical negative reaction for Zn ions there are in B-cells past elimination of Zn by Glibenclamide. Meanwhile administration of Glibenclamide accompanied by elimination of Zinc ions from B-cells only, not from cells of prostate and from salivary glands. It was demonstrated that Dithizon method is more preferable for more detail investigation of location of Zinc in various parts of B-cells. The advantage of 8PTSQ fluorescent method determined by more high sensitivity in compared with Dithizon method. It is established that lifetime coloring of pancreatic B-cells of islets, of trailer part of epithelium cells of Prostate and salivary glands after administration of Ditizon to animals allows to study in detail in them location of Zinc using microscopy in the dark field.

Key words: pancreatic islets, prostate gland, salivary glands, zinc, dithizon, chelates.

Important role of Zinc in organism of animals and human determined by high biological activity. Biological significance of Zinc is determined as by component of some enzymes. Zinc take part in metabolism of nucleic acids and in processes of synthesis of proteins [1, 2].

Zinc takes part also in metabolism and realization effect of hormones of hypophysis, adrenal glands, pancreas, prostate and testicles [3]. The hypophysis, pancreas, eye retina, and prostate contains a large amount of Zinc [4].

A large amount of Zinc ions is revealed in pancreas and its prevalence in pancreastic islets is [5] determined by biosynthesis of insulin in B-cells. It is known that insulin is synthesized and stored in B-cells as insulin deposited crystal form Zinc-insulin complex in the ratio 2:6. Is supposed that releasing of crystal insulin from B-cells accompanied by dissolving of crystals and hexamer dissociate with forming of active monomers of insulin and ions of Zn^{+2} [4, 5].

The tissue of prostate gland contain more than 10 times high amount of Zinc comparatively with other tissues. A large amount of Zinc in prostate protect it, as supposed, of inflammation and improve local immunity against infections [6–8]. Zinc is need for normal function of organs of taste. He stimulates synthesis of a gustin — a protein contain histidine, a component of product of salivary glands. Pancreas, prostate and salivary glands cells carry not only accumulation of Zinc but of its secretion [9].

There are a various methods measuring of concentration of Zinc in biological liquids and in tissues. The following methods are the most widely used today: ardent nuclear and absorbing spectrometry, nuclear and

issue spectrometry with inductive connected plasma, the neutron-activation analysis, X-Ray-spectrometry, an anode inversion volt-amperometry [10, 11]. Along with their indisputable advantage for revealing of very small amount of chemicals in various objects, they are not suitable for to estimate dynamics of content of metals in cells and tissues of bodies in vivo and in vitro and also for identification of cytological bases mechanisms of development of pathological states caused by their deficiency.

Our attention was attention was drawn by methods of research which possess a high sensitivity for identification of Zinc and possibility to observe cells visually. Ditizon (diphenylthiocarbazon, DZ) is widely used in analytical chemistry for detection of heavy metals including Zinc with which he forms chelat complexes. It was showed by using of spectral analysis that maximum of absorbance of complex Zn^{+2}-DZ extracted from pancreatic islets of pancreas tissue is equal to 530 nm that correspond to maximum of absorbance of artificial complex Zn^{+2}-DZ formed in vitro as result of interaction of Zn ions with DZ [12–14].

E.A. Bozhevolnov reported about ability of 8 aren(sulphonylamino)quinolines to form complexes fluorescing under ultra-violet light with Zinc and Cadmium. One of these derivatives — a 8-para(toluenelsulphonilamino)quinoline (8PTSQ) — possess ability to form chelat complexes with Zn^{+2} ions as 1:1. This method of histochemical identification of Zn ions is high specific and very sensitive, allowing to reveal very low concentrations of Zn ions correspond to 10^{-7}–10^{-8} [15]. In ultra-violet light — wavelength equal of 360–370 nm — the Zn-8PTSQ complex fluoresces as brightly green light complex [8]. These chelat active chemicals possesses high chemical affinity to Zn ions and in the conditions of in vitro formed color chelat complexes Zn-8PTSQ visible at luminescent microscopy and a complex as Zn-Dithizon (DZ) visible as bright red granules using microscopy in the dark field [13, 14, 16]. One this base we suppose that these methods could be suitable for histochemical identi fication of Zinc in various bodies and tissues differing in his contents both at a physiological state and when modeling any pathology.

Research objective: to reveal of Zinc ions in pancreatic islets, prostate and in salivary glands of mammals by using of high specific histochemical Dithizon and 8PTSQ methods.

Research Methods

For experiences 26 rabbits males, 2450–2850 g, and 16 white mice 30–36 g were used. Animals have been distributed for 4 groups. Group 1: rabbits, mice; vital staining of tissues by intravenous injection of Dithizon and 8PTSQ. 10 min later past injection tissues of pancreas, prostate and salivary glands were frozen in cryostat. Sections of tissues 5 mcm were investigated in fluorescent microscope and using of dark microscopy.

Group 2: two models of experimental diabetes were induced in animals: 1) by intravenous injection to rabbits and mice of water-ammonia solution of a Dithizon («SERVA», Germany) 45–51 mg/kg and to rabbits — of ethanol solution of 8PTSQ (Institute for Pure Reagents, IREA, Moscow, Russia), 36–38 mg/kg.

Group 3. Peroral administration to animals of the Glibenclamide («Berlin-Chemie», Germany), 20–25 mg/kg daily during 3 days for maximal elimination of Zinc ions from cells.

Group 4. Control intact animals. Administration of equivalent volumes of physiological solution. Fixation of tissues of pancreas, prostate and salivary glands of animals of groups 2, 3, 4 at temperature of 0…–5 ºC in 70º etanol saturated with hydrogen sulfide.

For histochemical fluorescent staining of Zn ions 0,04 % acetone solution of 8PTSQ was used: 3–4 drops of solution placed on sections of tissues for 8–10 sec. following washing in the distilled water. Then sections were investigated using fluorescent microscopy [15].

Preparing of Ditizon solution. For preparation of solution of Ditizon: 30 ml of distilled water, 0,6 ml of 25 % of solution of NH_4OH and 400 mg of Ditizon were placed in vessel. Solution was mixed on a water bath (+70 ºC) within 10 min., filtered using of ashless filter. The filtrate contains approximately 1 % water-ammoniac solution of Ditizon which we used in our researches [13, 14].

Universal microscope Axioplan 2 for light and fluorescent microscopy, photometric system and digital millivoltmeter were used for measuring intensity of fluorescence or intensity of luminescence of B-cells on sections of pancreas with registration of intensity past staining of sections by 8PTSQ or by Dithizon respectively. Cytochemical indicators measuring of Zinc ions content were estimated as conventional units (c.u.) [17, 18].

For statistical analysis the Statistica 8,0 (Stat Soft Inc) and Microsoft Excel 2006 were used with calculation of M+m. After checking of distribution to a normality the importance of distinctions between groups was estimated by means t-criterium of Student's. Distinctions were reliable at 95 % a probability threshold ($p < 0,005$).

Results

For the first it was showed that intravenous administration to rabbits and to mice of Ditizon and 8PTSQ 5 min. later result formation of specific complexes Zn-8PTSQ and Zn^{+2}-DZ visible on frozen sections in cells contains a large amount of Zn ions: B-cells of pancreatic islets, cells of tissues of prostate and salivary glands (Fig. 1.1–1.3, 1.7, 1.8, 1.10–1.12). Same result we show in paraffin staining sections of fixed tissue of pancreas. Intensity of staining (Dithizon) and of fluorescence (8PTSQ) of tissues was measured in compared with control. The results showed a positive reaction for Zn as intensive red color of B-granules in B-cells past injection of Dithizon (Table: 1,94±0,05; 2,76±0,08; 2,89±0,08; Fig. 1.7, 1.8) as in cells of Prostate and in Salivary glands. In the contrary, we have observed negative reaction for Zn past staining by 8PTSQ past injection of Dithizon (Table 1: 1,07±0,03; 1,15±0,04; 1,09±0,05) that was determined by preliminary formation of complex Zn-Dithizon. As result, staining of sections by 8PTSQ not accompanied by forming of fluorescent complex Zn-8PTSQ due to absence of free Zn ions in B-cells for interaction with 8PTSQ.

Dithizon and 8PTSQ formed in B-cells chelat complexes with Zn that result destruction of cells and absence of Zn from B-cells (Fig. 1.6.). Taking into consideration this fact we tried to eliminate of Zinc ions from cells by Glibenclamide for try to protect B-cells of formation into cells of chelat complexes and by using of this way try to protect cells of destruction and of developing of diabetes. For realization of this purpose Glibenclamide was entered daily to animals of Group 3 which possess hypoglycemic effect due to ability to stimulate dissociation of Zinc-insulin complex in B-granules of B-cells and releasing of free insulin and Zinc ions in the blood. Results showed marked decreasing of content of Zinc ions in B-cells for 1,9–2 times in sections of pancreas tissue past staining by 8PTSQ and by Dithizon respectively ($p < 0,001$).

Elimination of Zn from B-cells by Glibenclamide accompanied by negative reaction for Zn using of both methods (Table; Fig. 1.4, 1.5, 1.9). In the contrary, using of Glibenclamide not accompanied by elimination of Zn from cells of Prostate and of Salivary glands (Table). Results showed that intensity of fluorescence of complex Zn-8PTSQ as intensity of color of complex Zn-Dithizon was approximately for 1,5–1,6 times more high comparatively with B-cells.

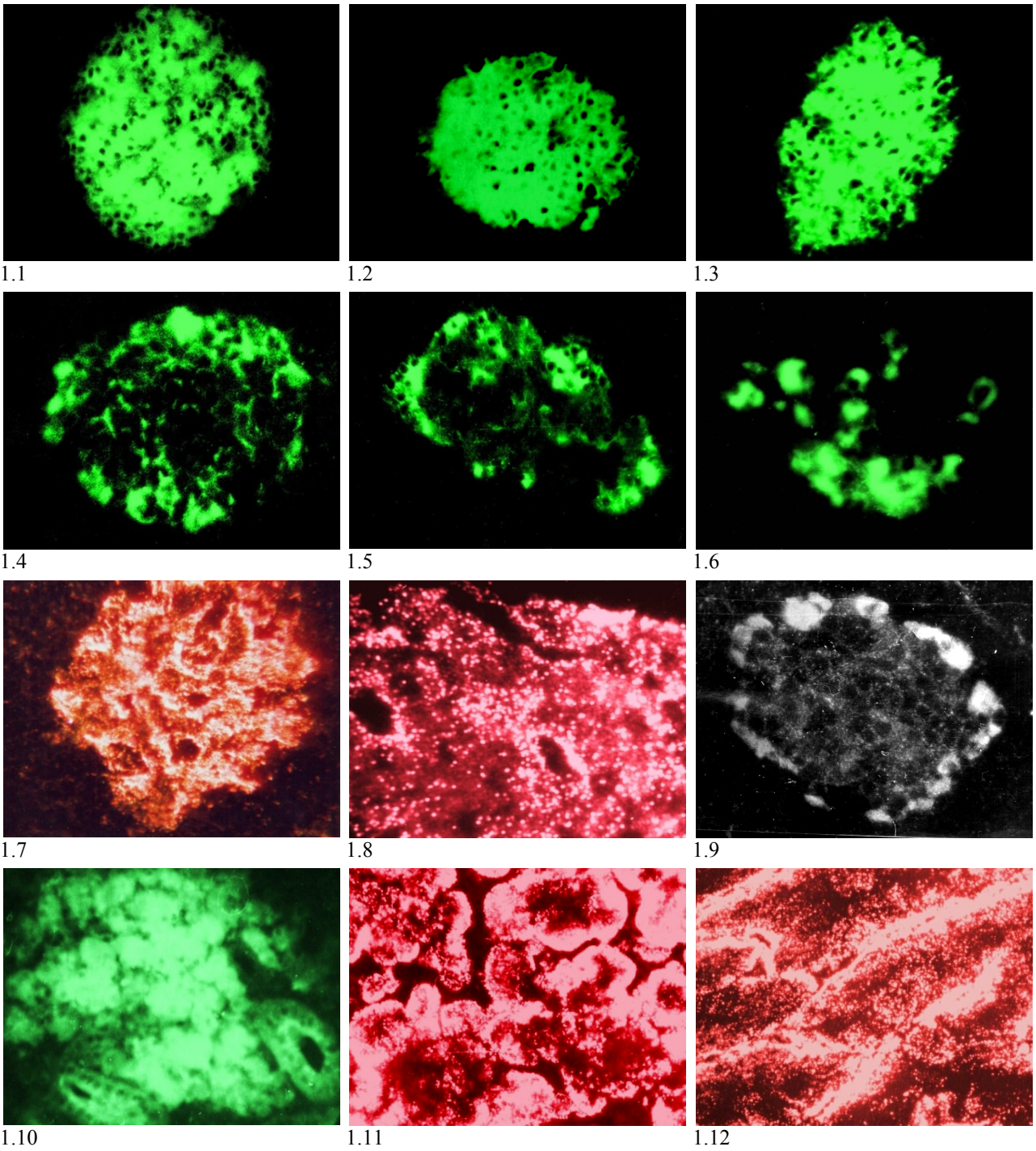
T a b l e

Histochemical methods for revealing of Zinc ions in Pancreas, Prostate and Salivary glands (M±m)

Groups of animals	Conditions of experience	Zinc ions content in tissues (c.u.)					
		Intensity of fluorescence			Intensity of staining		
		Staining of Zn by 8PTSQ			Staining of Zn by DZ		
		B-cells of pancreas	Prostate	Salivary gland	B-cells of pancreas	Prostate	Salivary gland
1	Dithizon, 50,2 mg/kg	1,07±0,03* *n*=16	1,15±0,04^{+} *n*=16	1,09±0,05** *n*=16	1,94±0,05 *n*=16	2,76±0,08 *n*=16	2,89±0,08 *n*=14
2	Experimental diabetes	1,04±0,05* *n*=14	3,04±0,12 *n*=14	3,32±0,11 *n*=18	1,03±0,07*** *n*=14	2,05±0,09 *n*=14	2,20±0,14 *n*=14
3	Glibenclamide, 25 mg/kg	1,05±0,04* *n*=19	2,95±0,11 *n*=19	3,40±0,20 *n*=19	1,06±0,08*** *n*=19	2,08±0,11 *n*=19	2,28±0,08 *n*=19
4	Intact animals (control)	2,07±0,08 *n*=14 *p*<0,005	3,12±0,09 *n*=21 *p*<0,001	3,35±0,12 *n*=16 *p*<0,001	1,92±0,06 *n*=12 *p*<0,001	2,95±0,09 *n*=15	3,05±0,06 *n*=12

It was especially interesting fact that we did not observe same changes of the Zinc ions content in cells prostate and salivary glands in which intensity of a fluorescence and luminescence significantly did not differ from analogical indicators in control sections. We have not found analogical changes of Zinc content in tissues of prostate and salivary glands Indicators of intensity of fluorescence and of luminescence significantly didn't differ from indicators in control (Table).

This fact demonstrates a selective influence of Glibenclamide on Zinc-insulin complex which is localized as depot form in the B-granules of pancreatic β-cells. Meanwhile, administration to animals as of diabetogenic chelat active chemicals as of Glibenclamide accompanied by negative reaction for insulin in B-cell only, not in A-cells. On the base of obtained results it is possible to suppose the presence of various conditions of metabolism of Zinc ions: regulation of metabolism by metalthioneins [10, 19, 20] of transport by transmembrane proteins[7, 21–23], deposition and of excretion [8, 24, 25].



1.1 Frozen section of pancreas tissue of Rabbit 10 min. past injection of 8PTSQ. Fluorescent reaction with 8PTSQ. Green fluorescence of Zn-8PTSQ complex; ×140;

1.2 Pancreatic islet of intact Rabbit. Histochemical revealing of Zinc ions by 8PTSQ; ×140;

1.3 Pancreatic islet of intact Mice. Histochemical revealing of Zinc ions by 8PTSQ; ×140;

1.4 Pancreatic islet of Rabbit 3 days past administration of Glibenclamide. Elimination of Zincions from B-cells; negative reaction or Zn in B-cells of central part of islet; staining by 8PTSQ.; ×140;

1.5 Pancreatic islet of Mice 3 days past administration of Glibenclamide. Elimination of Zinc ions from B-cells; negative reaction for Zn in B-cells of central part of islet; staining by 8PTSQ.; ×140;

1.6 Pancreatic islet of Rabbit 14 days past administration of Dithizon. Absence of Zinc ions in B-cells; staining by 8PTSQ; ×140;

1.7 Pancreatic islet of Rabbit 10 min. past administration of Dithizon. Red granules of complex Zn-DZ in B-cells. Dark microscopy; ×280;

1.8 Pancreatic islet of Mice 10 min. past administration of Dithizon. Red granules of complex Zn-DZ in B-cells. Dark microscopy; ×800;

1.9 Pancreatic islet of Rabbit Administration of Glibenclamide within 7 days + injection of Dithizon; absence of complex Zn-Dz in B-cells; dark microscopy; ×280.

1.10 Frozen section of salivary gland of rabbit past intravenous administration of 8PTSQ. Intensive green fluorescence of complex Zn-8PTSQ; fluorescent microscopy; ×140;

1.11 Frozen section of prostate of rabbit past intravenous administration of Dithizon. Red granules of complex Zn-Dithizon; dark microscopy; ×280;

1.12 Frozen section of salivary gland of rabbit past intravenous administration of Dithizon. Red granules of complex Zn-Diithizon; dark microscopy; ×280№

Figure 1. Histochemical methods staining of Zinc in cells

The histochemical method revealing of Zinc using of 8-para(toluenesulphonylamino)quinolin is a most high sensitive for Zinc ions, which forming with him the specific chelat complex fluorescing in ultraviolet light [13, 15]. The advantage of Dithizon method of histochemical identification of Zn ions based on ability to form the complexes having not diffusion coloring but brightly red granules of complex Zinc-DZ in the ratio 2:1 that allows to study metal cytotopography considering various concentration of localization granules in various parts of cells. Our results don't contradict data of other authors who also studied at the cellular level dynamics of Zinc content at animals under various experimental conditions [12, 14].

Thus, results of the comparative analysis of two histochemical methods staining of Zinc ions in cells of various bodies allow to confirm their high sensitivity, and possibility to use for cytologic researches.

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Ұйқы, қуық асты және сілекей бездерінде мырышты анықтаудың гистохимиялық әдістері

Тіндердің үлгілерін алу және кәдімгі гистологиялық әдістер арқылы ағза тіндердегі микроэлементтердің иондарын анықтауда гистохимиялық әдістер әрқашан оң нәтиже бере алмайтыны белгілі. Ұйқы безінің тіндеріндегі металдарды анықтаудағы люминесцентті әдістері үшін кәдімгі бекіту әдістері іс жүзінде жарамсыз болып табылады. Авторлар қуық асты, сілекей және ұйқы бездерінің В-жасушалардың кесілген бөліктерінің жаңа мұздатылған бөліктерінде мырышты анықтауда жоғары нақты дитизиондық және люминесцентті 8TCX гистохимиялық әдістер пайдаланған. Сусамыр (қант диабетінің) хелаттүзуші қуық асты және сілекей бездерінің В-жасушаларында мырыш теріс реакцияға әкелді: ол мырыш қатысуымен еркін мырыш теріс реакция жоқтығын растаған, осы әдістер В-жасушалардың мырыш бұғаттау эксперименттері ретінде көрсетілген. Кіріспе глибенкламид енгізгенде В-жасушаларынан мырышты шығарумен қатар, мырыш теріс реакциясының пайда болуы байқалды. Ұйқы безінің және В-жасушаларындағы мырыш иондарының орналасуы дитизиондық әдістің көмегімен зерделенді, ал 8TSKH әдісі жоғары сезімталдық артықшылығымен ерекшеленді.

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Гистохимические методы выявления цинка в панкреатических островках, предстательной и слюнных железах

Известно, что выявление ионов микроэлементов гистохимическими методами в тканях организма далеко не всегда дает положительный результат при использовании обычных гистологических методов фиксации и проводки образцов ткани. А для люминесцентных методов выявления металлов в ткани поджелудочной железы обычные методы фиксации вообще практически непригодны. Авторами использованы высокоспецифичные дитизоновый и люминесцентный 8TCX гистохимические методы выявления цинка в срезах не фиксированной, а свежезамороженной ткани предстательной и слюнных желез и в В-клетках поджелудочной железы. Результаты свидетельствуют о том, что в панкреатических островках животных с помощью обоих методов выявлена резко положительная реакция на цинк во всех исследованных тканях. Показано, что в опытах с блокированием цинка в В-клетках данные

методы подтвердили отсутствие свободного цинка наличием отрицательной реакции на цинк: однократное введение диабетогенных хелаторов приводило к отрицательной реакции на цинк в В-клетках, в предстательной и слюнных железах. Введение глибенкламида, сопровождающееся выведением цинка из В-клеток, приводит к появлению также отрицательной реакции на цинк. Показано, что дитизоновый метод позволяет детально изучить расположение ионов цинка в панкреатических островках и в В-клетках. 8ТСХ метод имеет преимущество в виде более высокой чувствительности.

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Quality of life of diabetic patients of the land «Karaganda» depending of social and demographic factors

Authors studied indicators of quality of life of patients with 2 type of diabetes depending on a risk of diabetes, socialand demographic factors among population of the Karaganda region. The research carried out according Sscientific program «Environmental Risks and Health of the Population». Screening included using of elaborated by authors of questionnaire contained official consent of respondent (patient) as information abouta sex, age, data on social factors (level of the income, family status (married or not), education, employment, nature of work), availability or absence of chronic diseases were specified. For determination of risk groups of diabetes the questionnaire of FINDRISC (The Finnish Diabetes Risk Score) was used. For a quality of life estimation the short version of questionnaire of WHO (WHOQOL-BREF) which consists of 26 questions. The analysis of results of a scale of FINDRISC showed that at 24.6 % of respondents in the next 10 years moderate, high and very high risk of SD took place (12 points and more).

Key words: diabetic patient, Karaganda region, quality of life, social and demographic factors.

Actuality

Now epidemic of chronic noninfectious diseases among which one of significant positions are belong to the diabetes mellitus (DM) is around the world observed. According prognosis of International Diabetes Federation prevalence of diabetes will increase to of 8.8 % by 2035 worldwide [1]. According to WHO data [2], prevalence of DM in Kazakhstan from 1980 to 2014 is increased from 72,000 registered patients (0.48 % of population) to 208,000 (1.4 %). Due to the existence by the long-lived preclinical stage, number of not diagnosed patients with DM cases of NIDDM fluctuate from 30 % to 90 % [3]. One of f way for to reduce the risk of development of DM is identification of the risk groups based on application the of questionnaires. The questionnaire developed by the Finnish diabetic association for assessment of ten-year risk of development of NIDDM was widely adopted.

DM is associated with high risk of development of cardiovascular complications, nephropathy, decreasing of working capacity and of quality of life (QL) [4]. Quality of life is one of important methods for assessment of effectiveness of treatment and p of health in the future prognosis of state disease [5–8].

The research objective: to study quality of life depending on of risk of a diabetes mellitus and its social and demographic determinants among the population of the Karaganda region.

Material and methods

The single-step transversal research in the form of screening among the population of the Karaganda region is carried out according scientific program named as «Environmental Risks and State of Health of the Population». Screening included questioning for which the questionnaire was elaborate. The questionnaire contain information for the participant as a sex, age, data on social factors (level of the income, marital status, education level, employment, the nature of work), existence or absence of chronic diseases were specified.

For definition of risk groups of DM the questionnaire of FINDRISC (The Finnish Diabetes Risk Score) was used. FINDRISC questionnaire with success is used in many countries and is recommended by the working group of the European society of cardiologists (European Society of Cardiology — ESC) and the European association for studying of a diabetes mellitus (EASD). The questionnaire of FINDRISC contains 8 questions of an age, the body weight index (BWI), the waist circle (WC), the physical activity (PA), using of fruit and vegetables in diet, anti-hypertensive therapy. Each answer is estimated on particular number of points which sum corresponds to risk of SD 2 types (maximum 26 points). For to estimate test of QL the short version of a questionnaire of WHO (WHOQOL-BREF) was used which consists of 26 questions. According to the recommended method number of points on scales of physical health, psychological perception, the social relations and a surrounding medium were counted; separately opinions of the respondent about quality of life and the state of health were estimated. 3684 patients at the age 18–65, a permanent resi-

dents of the Land KARAGANDA were examined. Patients gave the written consent for participation in examination.

Pregnant women, persons with a mental, serious neurologic illness were criteria of an exception. Material of 519 people (80.7 % men) were excluded as not completed. Among respondents women 2437 (77 %) were prevailed. All patients were invited for examination in Policlinic

Results and discussion

The analysis of results of the scale of FINDRISC showed that at 24.6 % of respondents have in the next 10 years a moderate, high and very high risk of DM (12 points and more) comparatively with 37.5 % at Moscow region (Russia) [9]. It was established that increasing of number of the points according a questionnaire the percent of patients with disturbances of carbohydrate metabolism were increased. In group the sum less than 5 points a disturbances of carbohydrate metabolism was minimal (at 23 % of patients) and prevalence of NIDDM — only 0.8 %. Among the persons with more than 20 points disturbances of carbohydrate metabolism was increased until 76.9 %, and prevalence of NIDD –until 23.1 %. Sensitivity of screening of 12 and more points made 73.5 %, and specificity — 66.7 %. By other authors it is showed that 31.7 % of adult population of Novosibirsk have on average a high and very high risk of development of NIDDM in the next 10 years [10].

In Greece 15 and more points were confirmed at 45 % of population and not diagnosed disturbances of carbohydrate metabolism were revealed in 33.1 % of population [11]. Sensitivity of FINDRISC scale — 81.9 % and specificity of 59.7 %. It should be noted that in this research [11] female persons (56.7 %) also prevailed with middle age 45.4±12.7 years in our work. In our research the highest risk (12 points and more points) was revealed among persons of 55 years and more (table 1); existence of genetic factor is noted at 53.1 % in group with moderate and high risk of DM. It is expected as the age and the burdened heredity is one of key not modified risk factor developing of 2 type DM. There are a tendency to increase in abundance of 2 type of DM at persons more young than age as 30 years. M.A. Sayed, H.Mantab showed that in age group of 20–29 years prevalence of DM 2 of type was 2.5 % among all population, in age group of 40–49 years this indicator increased to 3.7 % [12]. The risk of DM in our research among persons of 18–25 years is 4.2 %.

Within the Global strategy of prophylaxis of chronic noninfectious diseases and activity against fundamental risk factors of DM, cardiovascular diseases the percent of abundance of the modified factors in group with low risk of DM pays an attention. We showed that absence of daily 30th minute physical activity is confirmed at 61.6 % of respondents, absence of daily using of vegetables — at 74.9 %, an abdominal obesity — at 62.5 %, body weight and an obesity — at 74.6 % and 49.3 % patients of the same group. Considering that in group with absence and low risk of DM(0–11 points) persons of young and middle age prevailed, the optimization of a diet and of physical activity is extremely urgent and will promote strengthening of health of individuals and all population in general. Interrelations between risk of 2 type DM and social and demographic indexes are presented on Table 1.

Table 1

Interrelations between risk of 2 type DM and social and demographic indexes are presented in (*n*=3165)

Variable	N (%) Risk of DM (12 and more)	Risk of DM (0–11)	X^2	d.f.	P
1	2	3	4	5	6
Age, years			486.1		0.001
18–34	32 (4.2)	728 (95.8)			
35–44	77 (11.5)	593 (88.5			
45–54	260 (30.1)	605 (69.9)			
55+	411 (47.2)	459 (52.8)			
Gender			12.7	1	<0.001
Male	143 (19.6)	585 (80.4)			
Female	637 (26.1)	1800 (73.9)			
Ethnic background			25.9	2	<0.001
Kazakh	415 (21.5)	1513 (78.5)			
Russian	239 (29.8)	564 (78.2)			
Other	126 (29.0)	308 (71.0)			

1	2	3	4	5	6
Education			12.1	2	0.002
Secondary or less	299 (25.3)	882(74.7)			
Vocational	296 (27.3)	790 (72.7)			
Higher	185(20.6)	713 (79.4)			
Occupation			64.2	1	0.001
At work/study	440 (20.4)	1713 (79.6)			
Out of work	340 (33.2)	672 (66.4)			
Month salary:			3.63	2	0.162
Low	131 (28.1)	336 (71.9)			
Middle	249 (23.6)	807 (76.4)			
Middle and over	400 (24.4)	1242 (75.6)			
Marital status			1.05	1	0.31
Married	532 (21.1)	1673(75.9)			
Unmarried	248 (25.8)	712 (74.2)			

Percent of persons with moderate, high and very high risk of DM (12 and more points) was higher among women in comparison with men. Results studies of prevalence of 2 type of DM in two Moscow's administrative districts showed a dominance of women in comparison with men by 2.3 times is revealed [13]. The tendency to a moderate dominance of women among patients with 2 type of DM is observed also in other countries [14]. However so the significant differences most likely are determined maybe by more frequent requests of women for a medical care and also more high mortality and among men.

The most low frequency of risk of DM is confirmed among respondents of Kazakh nationality. In the research of A. Supiyevet al. [15] a dominance of abundance of 2 type of DM among of Russian persons, Belorussian, Ukrainen in comparison with Kazakhs is also revealed.

There are existence of interrelation between risk of DM and level of education. Persons with higher education have low risk of DM that is determined by a larger knowledge, motivation to keeping of a healthy lifestyle and nutrition. These data are confirmed by more high attention to treatment and self-control. The income level at a tendency to low risk of DM in group with more high level of the income, has statistically no significant influence on risk of DM ($p<0.162$). Increase number of persons who do not work and do not study in group of high risk of DM is caused by a dominance among them of the elderly people who are on pension.

The comparative analysis of quality of life (Table 2) showed that indexes of all scales, including the common evaluation test of life and health, were lower in group with moderate and high risk of DM (1 group).

Table 2

Indicators of quality of life (WHOQOL-BREF) in patients with different risk of diabetes

Indicators of QL of WHO	1 group (12 poits and more) (n=780) M+SD	2 group (0–11 points) (n=2385) M+SD	t	P
Assessment of QL, %	66.5±15.9*	68.8±16.3	–3.49	0.001
Assessment of state of health, %	48.9±24.7	56.5±23.5	–7.48	0.001
Physical health, %	55.8±13.2	58.0±1.5	–3.80	0.001
Psychological health, %	58.7±12.6	61.5±13.3	–5.17	0.001
Social relations, %	64.8±16.5	69.3±16.5	–6.54	0.001
Environment, %	47.6±11.9	49.6±12.3	–3.87	0.001

Decrease in indexes carried small, but statistically significant character; the greatest distinctions depending on degree of risk of DM were according to health (for 7.6 %) and to a scale «the social relations» — are 4.5 % lower in 1 group on comparison with the second.

The quality of life (QL) at patients with DM is depend not only of DM but s of the presence of factors as: satisfactions by treatment, complications, psychological adaptation of the patient as social and demographic factors (Table 3).

Table 3

Interrelation between quality of life (QL) and social and demographic factors

Variable	N (%) QL as «well» and «more better»	QL (%)as «not badly» and «not well»	X^2	d.f.	P
Age, years			26.2	3	0.001
18–34	594 (76.8)	179 (23.2)			
35–44	491 (72.5)	186 (27.5)			
45–54	587 (67.1)	288b (32.9)			
55+	590 (67.0)	290 (33.0)			
Gender			3.916	1	0.048
Male	546 (73.5)	197 (26.5)			
Female	1717 (69.7)	746 (30.3)			
Ethnic background			122.9	2	0.001
Kazakh	1512 (77.7)	434 (22.3)			
Russian	474 (58.2)	341 (41.8)			
Other	277 (62.2)	168 (37.8)			
Education			21.9	2	0.001
Secondary or less	815 $(67.9)_a$	386 (32.1)			
Vocational	754 (68.6)	345 (31.4)			
Higher	693$(76.6)_a$	212 (23.4)			
Occupation			10.2	1	0.001
At work	1576 (72.4)	602 (27.6)			
Out of work	687 (66.8)	341 (33.2)			
The monetary income of family:			140.9	2	0.001
Low	271 $(57.4)_a$	201 (42.6)			
Lower than average	670 $(62.3)_a$	405 (37.7)			
Average and above average	1322 $(79.7)_a$	337 (20.3)			
Marital status			41.1	1	0.001
Married	1653 (74.0)	581 (26.0)			
Unmarried	610 (62.8)	362 (37.2)			
BMI, kg/м^2			1.65	2	0.437
Till 24.9	859 (71.8)	338 (28.2)			
25–29.9	738 (70.5)	309 (29.5)			
30 and more	666 (69.2)	296 (30.8)			

Interaction between social and demographic factors of life quality are a differ depending on the contingent of the surveyed, social and economic level of society, psychological features of the person. QL is decreased after 45 years, is worse at women, at respondents among persons not having a good education which is not working or with low level of the income and lonely (Table 3). The received results of general estimation of QL depending on age correspond to regularities of the general population [16] (Table 4). More high QL at respondents with the higher education can be explained by more good social adaptation, smaller frequency of risk factors of DM as of developing of a chronic noninfectious diseases.

Table 4

Quality of life (QL) as «lower than «well» depending of social and demographic factors

Variable	cOR	95 % CI	p	aOR	a	P
1	2	3	4	5	6	7
Age, years			0.001			0.001
18–34	0.613	0.49–0.76		0.828	0.63–1.08*	
35–44	0.771	0.61–0.96		1.150	0.89–1.18*	
45–54	0.996	0.81–1.22*		1.380	1.10–1.73*	
55+	1	Reference		1	Reference	
Gender			0.048			,042
Male	1	Reference		1	Reference	
Female	1.48	1.20–1.81		1.25	1.0–1.56	

1	2	3	4	5	6	7
Ethnic background			0.001			0.001
Kazakh	0.67	0.53–0.85		0.69	0.54–0.88	
Russian	1.03	0.79–1.33*		0.98	0.75–1.28*	
Other	1	Reference		1	Reference	
Education			0.002			0.169
Secondary or less	0.91	0.75–1.09*		0.95	0.77–1.16	
Vocational	1	Reference		1	Reference	
Higher	0.69	0.56–0.85		0.81	0.64–1.01	
Occupation			0.001			0.001
At work	0.51	0.43–0.60		0.58	0.48–0.69	
Out of work	1	Reference		1	Reference	
Marital status			0.33			0.68
Married	0.92	0.77–1.09		0.96	0.79–1.16	
Unmarried	1	Reference		1	Reference	
Self-reported material deprivation			0.22			0.03
Low	1.18	0.93–1.48		0.86	0.67–1.10	
Below the average	0.95	0.79–1.13		0.77	0.63–0.94	
Average or higher	1	Reference		1	Reference	

For studying of possible communication of aggravation of QL with social and demographic factors the logistic regression analysis was carried out which showed that here are a relations with social, demographic factors, with age, a female, employment, level of the income and an ethnic origin remains (mentality, life style, nutrition). A low parameters of QL were showed at the respondents have low level of education, the financial position and in unemployed [16, 17].

Thus, results of our research showed that 24.6 % of respondents have an essential risk of development of DM which is followed by deterioration in all indexes of quality of life. Abundance of risk factors among persons with low risk of DM testifies to relevance of continuation of realization of the long-term priority activity on prevention of incidence of DM. The level of quality of life of patients with risk of development of DM assume need realization of preventive actions, first of all, among unemployed persons in age group 45 years are more senior.

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Л.Г. Тургунова, А.А. Турмухамбетова, Д.Т. Амирханова, А.Р. Алина

Қарағанды облысы тұрғындарының сусамыр (диабет) тәуекел деңгейіне байланысты өмір сүру сапасын және оның әлеуметтік-демографиялық детерминанттарын бағалау

Авторлар Қарағанды облысы тұрғындарының диабетке шалдығу деңгейіне және оның детерминанттарына байланысты диабеттің 2-түрімен ауыратын науқастардың тіршілік ету сапа көрсеткіштерін зерттеді. Зерттеу «Экологиялық қауіптілік және тұрғындар денсаулығы» атты ғылыми-техникалық бағдарлама шеңберінде өткізілді. Скринингтік зерттеулер үшін арнайы сауалнама жасалды. Онда зерттелушіге керек ақпарат және респонденттің келісімі шешуші болды. Сонымен қатар жынысы, жасы, әлеуметтік факторлар (табыс деңгейі, отбасылық жағдайы, білім деңгейі, жұмыс түрі), асқынған, созылмалы аурулар бар, жоқтығы көрсетілді. Қауіп тобын анықтау үшін FINDRISC (The Finnish Diabetes Risk Score) сұрақнамасы қолданылды. Тіршілік сапасына баға беру мақсатымен 26 сұрақтан тұратын ДДС сұрақнамасының қысқаша түрі келтірілді. FINDRISC сұрақнамасының нәтижесі респонденттердің 24.6 %-ға жуығы келер 10 жылда қалыпты, жоғары және өте жоғары (12 балл және одан жоғары) қант диабеті қауіпі болатынын растайды.

Л.Г. Тургунова, А.А. Турмухамбетова, Д.Т. Амирханова, А.Р. Алина

Оценка качества жизни в зависимости от степени риска сахарного диабета и его социально-демографические детерминанты у жителей Карагандинской области

Авторами изучены показатели качества жизни больных сахарным диабетом 2 типа в зависимости от степени риска и социально-демографических факторов среди населения Карагандинской области. Исследование проводилось в рамках выполнения научно-технической программы «Экологические риски и здоровье населения». Скрининг включал анкетирование, для проведения которого была разработана анкета для участника скринингового исследования, которая содержала информацию для участника исследования, информированное согласие респондента. Были указаны пол, возраст, сведения о социальных факторах (уровень доходов, семейное положение, уровень образования, занятость, характер труда), наличие или отсутствие хронических заболеваний. Для определения групп риска диабета использовался опросник FINDRISC (The Finnish Diabetes Risk Score). С целью оценки качества жизни была взята краткая версия опросника ВОЗ (WHOQOL-BREF), который состоит из 26 вопросов. Анализ результатов шкалы FINDRISC показал, что у 24.6 % респондентов в ближайшие 10 лет возможен умеренный, высокий и очень высокий риск СД (12 баллов и более).

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Use of the KADIS-CSII program for adjusting insulin pump therapy in type 1 diabetes

Continuous subcutaneous insulin infusion (CSII) has become a standard for treatment optimization of type 1 diabetes (T1D). However, the transition from Multiple Dose Injection (MDI) to CSII therapy can be challenging. The objective of the present study was to use KADIS, the Karlsburg Diabetes Management System, for individual basal and bolus insulin adjustments in patients with type 1 diabetes while switching from MDI to pump therapy. We describe the extended KADIS-CSII program and its practical application for adjustment of insulin pump therapy. We conducted a pilot study including 12 patients with T1D who had received MDI therapy consisting of short- and long-acting insulin injections. Baseline HbA1c was 8.2±0.8 %, age 31.3±11.1 years, and diabetes duration 15.7±6.7 years (mean±SD). Data derived from continuous glucose monitoring (CGM) during MDI therapy were processed by the KADIS algorithm in order to characterise the patient's specific metabolic parameters. Those were used to estimate individual basal infusion rate patterns as well as insulin boluses based on carbohydrate consumption for the transition to CSII. Three months after transitioning from MDI to CSII based on KADIS guided therapy, the mean HbA1c value was reduced to 7.6±0.5 % (–0.6 % vs. baseline, $p<0.05$) and remained at this level until the end of the 6-month study. Likewise, time <3.9 mmol/L ($p=0.008$), glycemic variability indexes, such as SD around mean glucose ($p=0.010$), MAGE ($p=0.001$), and CONGA ($p=0.007$), were all significantly lower at study end. Consistent with these data, quality of glycemia measured by the GRADE index and a recently developed Q-score was also improved. The proposed KADIS-CSII program could become a practicable and efficient tool to support adjusting insulin pump therapy.

Key words: diabetes, insulin pump therapy, KADIS-program therapy, glycemia, glucose metabolism, HbA1.

Introduction

Several studies have shown that diabetic patients with poor glycemic control who are assigned to insulin infusion therapy achieve better improvements in HbA1c levels than those that remain on multiple injection treatment [1–5]. Compared with Multiple Dose Injection (MDI), the essential advantages of continuous subcutaneous insulin infusion (CSII) include adjustable basal rates and flexible delivery of short-acting insulin boluses for meals according to individual lifestyle preferences. While currently available conventional insulin pumps may differ by some specific features, all of them provide similar basic functionality allowing users to deliver pre-programmed pattern of basal insulin adjustable for times of lower and higher insulin demand, like during exercise or acute illness. Boluses are given before meals based on actual blood glucose levels and the anticipated food intake. Pumps can also provide decision support by calculating the insulin bolus dose needed to cover for the amount of carbohydrates to be consumed. The flexible use of short-acting insulin boluses at mealtimes and continuous basal insulin infusion around the clock does represent an acceptable compromise, closely mimicking physiologic pattern of insulin secretion. Consequently, if handled adequately users can achieve near-normoglycemia without extensive glucose fluctuations and without increasing the risk for hypoglycemia.

The transition from MDI to insulin pump therapy does allow for therapy optimization by determining individualized basal insulin infusion rate pattern, which differ from patient to patient and vary within periods of the day. The basal insulin dose is usually calculated as a percentage of the total daily insulin requirement. In order to establish variable rate pattern one can introduce fasting periods and compensate changing blood glucose levels by adjustments of the basal rates. In practice this procedure of compensation is cumbersome

and usually requires several days until blood glucose levels remain relatively steady. After a 24-h basal insulin profile has been established, meal boluses can be refined considering respective carbohydrate intake. The whole process of building up basal rate profiles and determining meal boluses correctly is rather time-consuming and represents a challenge for most family physicians as well as their patients.

We have previously developed the personalized counseling program KADIS® (Karlsburg Diabetes Management System) [6–8]. The program is based on a mathematical model describing the glucose metabolism in the form of a coupled system of differential equations. The individual metabolic situation, including food intake, insulin therapy, anti-diabetic medication, physical activity, and lifestyle, is reflected by a so-called «Metabolic Fingerprint» for each patient. Endogenous factors, such as insulin sensitivity and insulin reserve are identified during the process and responsible for the individual expression of the fingerprint profile.

Based on CGM measurements and patients' metabolic control data, we have expanded the KADIS program for implementation in CSII therapy to determine individual basal insulin rates and meal boluses. Here we are presenting a pilot study using the expanded KADIS program supporting the optimization of basal/bolus insulin delivery by pump with focus on T1 while switching from MDI to CSII.

Research Design and Methods

KADIS-based adjustment of CSII therapy. For this purpose, the original KADIS-program was extended and implemented in the CSII therapy, as further referred to as KADIS-CSII. The KADIS-CSII therapy support was implemented as follows: First, CGM measurements and patient's self-control data (CHO-meals, insulin doses, time etc.) were entered into the KADIS software to generate the «Metabolic Fingerprint», as demonstrated in Figure 1*a*. The «Metabolic Fingerprint» represents an *in silico* copy of the patient´s metabolic status. Second, as shown in Figure 1*b*, an initial setting of the basal rate was performed on the computer, omitting meals and insulin boluses (switch off within the software). Taking the pharmacokinetic differences between basal insulin infusion and bolus injections into account, the basal insulin rate, sufficient of predicting the glycemic curve residing in the normal range, was calculated by the KADIS specific mathematical algorithm. Third, meal effects were included in the computer simulation estimating appropriate insulin boluses in relation to the carbohydrate intake (Fig. 1*c*).

Setting and Patients

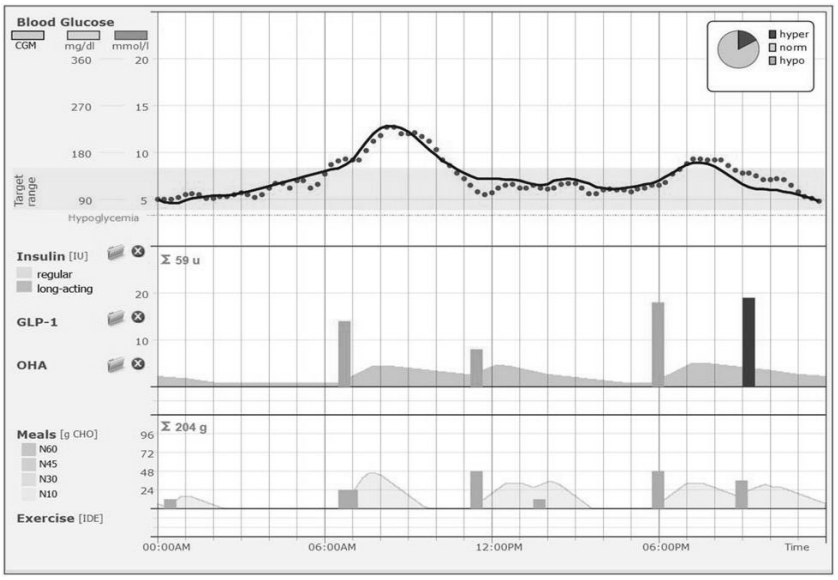
The pilot study was carried out at the Clinic of Diabetes and Metabolic Diseases Karlsburg, Germany, between February and December 2012. Twelve patients with type 1 diabetes on MDI therapy for a minimum of 2 years were included. MDI therapy consisted of either short-acting insulin Humalog (n = 4), Novorapid/Actrapid (n = 5), Liprolog (n = 2) or Huminsulin (n = 1) in combination with long-acting insulin Lantus (n = 9), Levemir (n = 2) or Huminsulin basal (n = 1). Exclusion criteria included clinically significant nephropathy, neuropathy, retinopathy, and women who were pregnant or breast feeding. Mean age of the participants was 31.3 ± 11.1 years, diabetes duration 15.7 ± 6.7 years, and baseline HbA1c 8.2 ± 0.8 %.

After hospital admission a continuous glucose monitoring was performed over 6 days, using the iPro system (Medtronic MiniMed). All participants performed a MDI therapy during this CGM. All participants signed informed consent prior to study entry. The main patient characteristics are shown in Table 1.

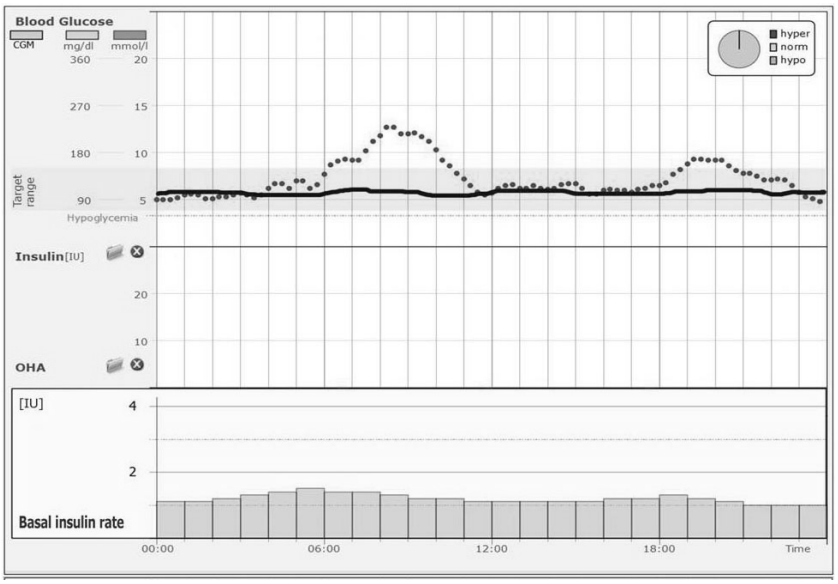
Table 1

Baseline characteristics of the study patients

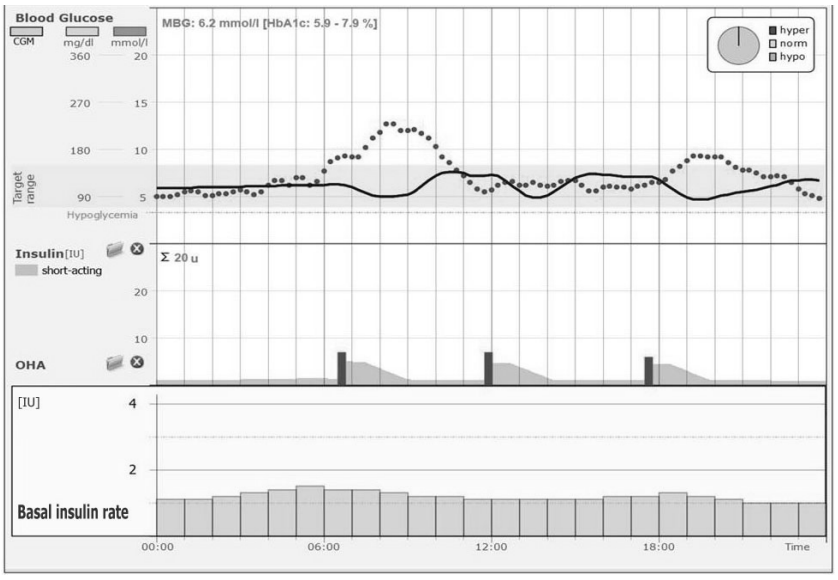
Patient	Age (years)	Gender	Diabetesduration (years)	HbA1c (%)	BMI (kg/m^2)	Insulinrequirement (U/day)
1	38	m	26	8.0	30.0	66
2	25	w	19	8.0	29.0	50
3	23	w	14	8.5	22.4	41
4	25	w	22	10.3	23.5	39
5	61	w	5	7.6	27.4	36
6	26	w	19	8.4	24.1	61
7	28	w	16	7.5	25.5	54
8	36	m	15	8.1	25.4	66
9	25	w	13	8.5	23.5	60
10	24	m	18	8.7	21.5	42
11	40	m	2	7.3	22.6	42
12	25	w	19	7.5	27.4	64
N = 12	31.3±11.1	8f/4m	15.7±6.7	8.2±0.8	25.2±2.7	51.8±11.4



a) **«Metabolic Fingerprint»** — After entering the measured data from continuous glucose monitoring (glucose curve with red dots), insulin dosing (3 x short-acting insulin, 1 x long-acting insulin; bar graph in the middle), and the meals as CHO (lower part of the figure), the model is fitted to the metabolic control of the patient and the glucose curve (blue) is finally simulated by the KADIS® model system



b) **KADIS®-based profile of the insulin basal rate** — After omitting the insulin bolus as well as meals, and considering the different pharmaco-kinetics of bolus insulin injections and continuous insulin infusion (CSII) is determined by simulation of the individual basal rate (bar graph)



c) **KADIS®-based transition to CSII therapy** — Meals are added again and the insulin boluses determined in relation to the amount of carbohydrates consumed. The expected glucose curve for the KADIS®-CSII setting of the individual basal rate and meal insulin boluses (red bar in the middle) is shown in blue

Figure 1. Procedure for KADIS® CSII-based assessment of the basal rate and the adjustment of boluses

The data flow for application of KADIS-CSII is shown in Figure 2. Comprising of:

(1) personalized mathematical adjustment to the acute individual metabolic situation «Metabolic Fingerprinting»;
(2) KADIS-based computer simulation of change of insulin injection from MDI to CSII therapy, taking pharmacokinetics under MDI and continuous insulin infusion into account;
(3) simulation of food omission and mathematical determination of individual basal insulin rate;
(4) simulation of meal insulin boluses dependent on food intake and changing circadian insulin sensitivity.

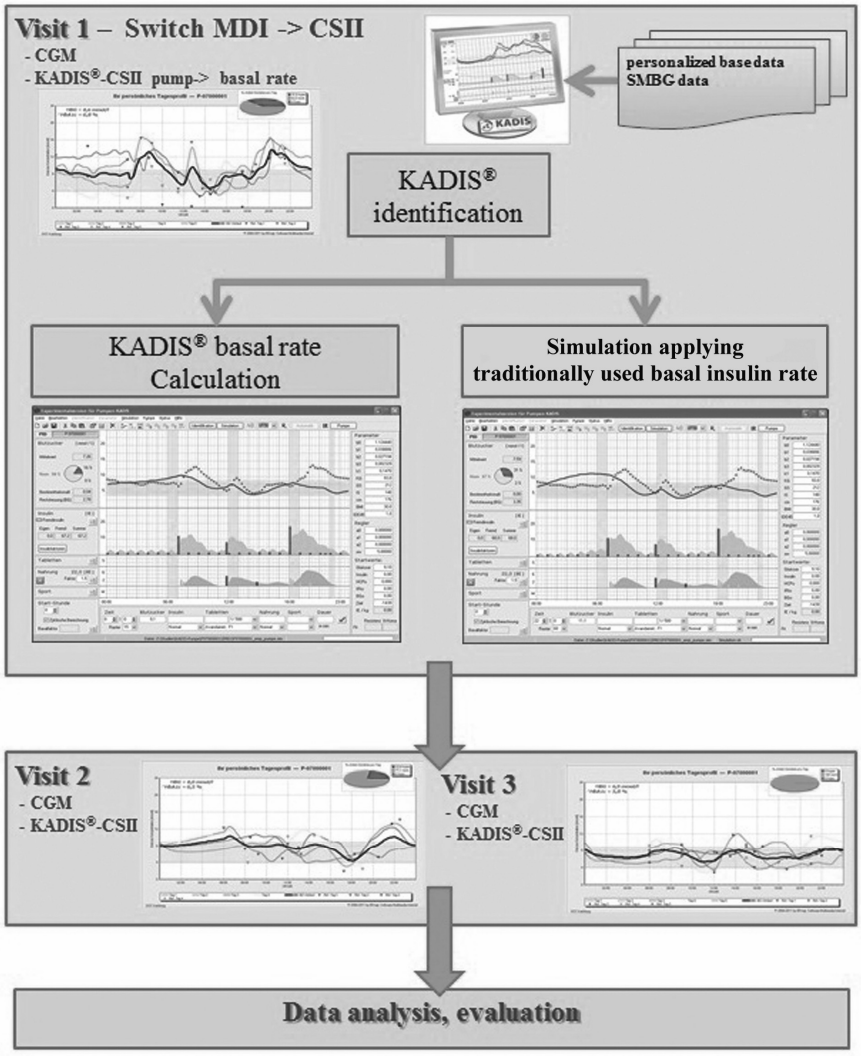


Figure 2. Flow chart of the KADIS-CSII study

Based on the result of the KADIS – CSII simulation a proposal was put forward to support the attending physician in adjustment of pump therapy.

Measures of glycemia

HbA1c levels were estimated from blood samples by standard procedure. The following measures were derived from CGM profiles: mean glucose concentration (MGC), standard deviation around mean glucose (SD), time spent in hypoglycemia and hyperglycemia, high blood glucose index (HBGI), low blood glucose index (LBGI), interquartile range, mean amplitude of glycemic excursion (MAGE), and continuous overall net glycemic action (CONGA). In addition, the quality of glycemic control was assessed by the Glycemic Risk Assessment Diabetes Equation (GRADE) score and a newly developed Q-score [9–10]. The Q-score does represent a combined value of various qualitative measures of glucose control that has been proven an effective determination of metabolic risk for an individual patient. Q-score evaluation criteria are depicted in Table 2.

Table 2

Q-Score evaluation criteria

Q-Score		Clinical evaluation of the quality of glycemic control
≥ 12.0	Poor	Glycaemia mostly outside the target range (>80 %), very high variability, presence of hypoglycaemic episodes
8.5–11.9	Fair	Glycaemia often outside the target range (50–80 %), high variability, hypoglycaemic episodes can occur
6.0–8.4	Satisfactory	Glycaemia partially outside the target range (20–50 %), reasonable variability
4.0–5.9	Good	Glycaemia mostly within the target range (80–100 %), low variability, no hypoglycaemic episodes
< 4.0	Very good	Glycaemia completely within the target range (80–100 %), negligible variability, no hypoglycaemic events

Primary outcomes were the HbA1c value and time in hypoglycemia (<3.9 mmol/L). Secondary outcomes included glycemic variability and quality of glycemic control.

Statistical analysis

Data are presented as mean±SD values unless otherwise specified. Individual comparisons within patients between MDI and CSII treatment were performed using the paired t-test and between group comparisons using analysis of variance. The mean area under the glucose curve (AUC) was calculated by the trapezoidal method. A P-value of <0.05 was considered statistically significant. Analyses were carried out using SPSS, version 12.0.

Results

Table 1 shows the baseline characteristics of the participants included in the study. Prior to CSII therapy HbA1c levels ranged from 7.3–10.3 % (56–89 mmol/mol). Switching to CSII therapy reduced HbA1c values by an average 0.6 % (p<0.052) during 3 month with no further decrease until the end of the study at 6 month. As shown in Table 3, CGM mean glucose was not significantly decreased, while time spent at glucose levels <3.9 mmol/L was reduced by a mean of 64 % (p = 0.008). This is consistent with a 62 % decrease in LBGI. The time glucose levels were in target range (3.9–8.9 mmol/L) increased overall from 73 to 86 % (p = 0.048). Four out of the 12 participants achieved 100 % with glucose levels spent in the target range. CSII therapy also decreased glycemic variability: SD 1.8 *vs.* 2.8 mmol/L (p = 0.010), MAGE 0.9 *vs.* 1.6 mmol/L (p = 0.001), and CONGA 2.7 *vs.* 4.3 (p = 0.007). It did not significantly decrease the GRADE score (5.6 *vs.* 7.3, p = 0.12) but did improve the quality of glycemic control as estimated by the Q-score (8.0 *vs.* 12.6, p = 0.001).

Table 3

Comparison of glycemic parameters at baseline and after 3 and 6 months duration

Parameter	MDI baseline	CSII at 3 months	CSII at 6 months	P Value
HbA1c, %	8.2	7.6	7.6	0.052
MGC, mmol/l (mg/dl)	7.5 [135]	8.3 [149]	7.3 [131]	0.065
SD, mmol/l (mg/dl)	2.8 [50]	2.2 [40]	1.8 [32]	0.010
MAGE, mmol/l (mg/dl)	1.63 [29]	1.09 [20]	0.91 [16]	0.001
Time > 8.9 mmol/l, h/day	6.87	8.22	5.54	0.359
AUChyper, mg/dl×day	19.50	17.03	12.31	0.166
Time < 3.9 mmol/l, h/day	2.87	0.65	1.02	0.008
AUChypo, mg/dl×day	2.35	0.41	0.54	0.010
Glucose levels in target range, %	72.7	74.5	86.0	0.048
Glucose Range, mmol/l (mg/dl)	10.5 [189]	8.6 [155]	6.9 [124]	0.006
HBGI	2.51	2.59	1.94	0.166
LBGI	1.70	0.42	0.65	0.011
GRADE	7.27	6.89	5.61	0.115
CONGA?	4.34	3.63	2.65	0.007
Q-Score	12.6	9.7	8.0	0.001

MGC, Mean Glucose Concentration; SD, Standard Deviation of Glucose Concentration; MAGE, Mean Amplitude of Glucose Excursion; Glucose Range (Max/Min), HBGI, High Blood Glucose Index; LBGI, Low Blood Glucose Index; GRADE, Glycemic Risk Assessment Diabetes Equation; CONGA, Continuous Overall Net Glycemic Action; Q-score, Quality of glycemic control.

Comparison of the basal rate estimates using the KADIS-CSII algorithm e.g. with the default scheme proposed by Renner [11, 12] for setting the basal insulin rate did reveale significant differences (Fig. 3). The differences consisted in dose, which were on average lower than by the traditional method, and in dynamics/distribution of the basal rate. Fig 4 demonstrates an example in case of identical basal insulin dose recommendation resulting in differences of distribution between KADIS-CSII and the Renner method. The method by Renner suggested an average 26.6 ± 6.6 IU daily amount of insulin, whereas CSII-KADIS suggested 21.7 ± 5.7 IU (p = 0.35). With minor modifications implemented by HCPs under everyday conditions, the mean basal insulin dose at the end of the 6months period consisted of 20.6 ± 4.8 U/day (p = 0.24).

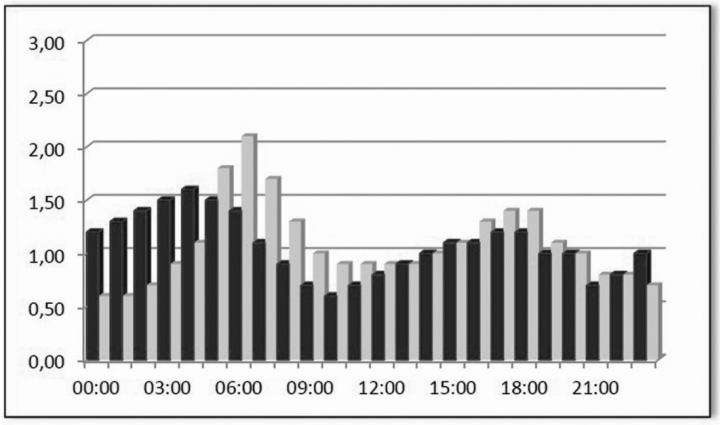


Figure 3. Basal rate profiles obtained for 26 IU with KADIS®-CSII adjustment (red) and after using the default profile by Renner et al. (light blue)

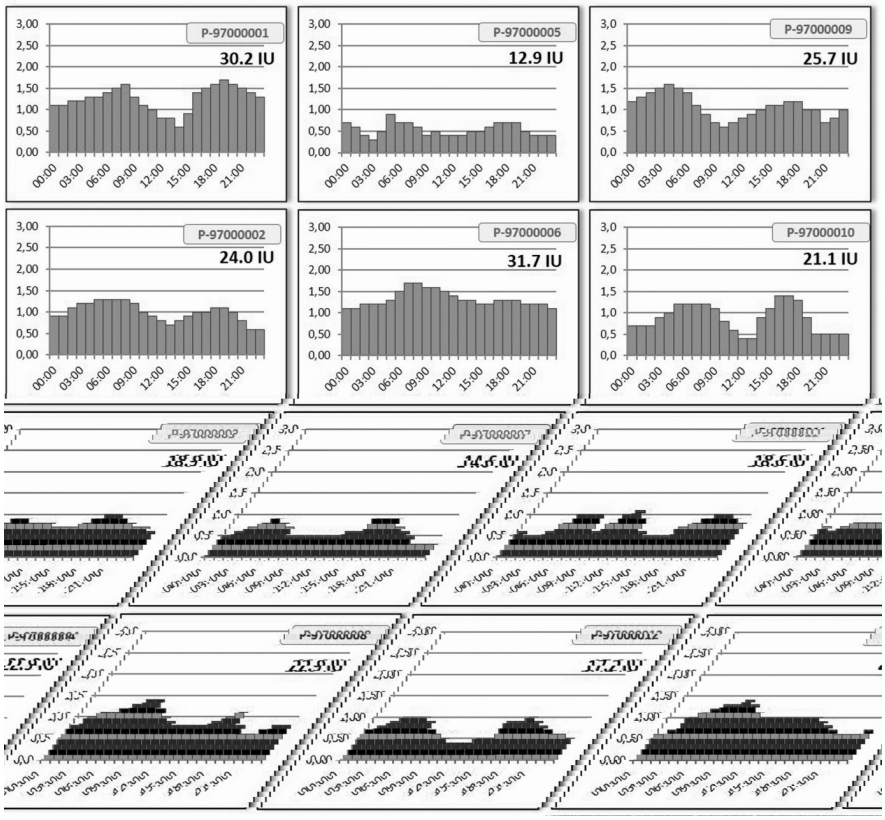


Figure 4. Samples of individual basal rate profiles with KADIS®-CSII of patients included in present study

Discussion

Our study shows that the KADIS-CSII program, which was specifically developed for recommendations of insulin pump therapy, is able to efficiently provide basal rates and insulin meal boluses. The capabilities of our algorithm outperform most widely used empirical approaches, which require several time-consuming meal omission tests until the basal insulin infusion profile can be established followed by adjusting meal boluses to minimize postprandial glucose excursions. The KADIS-CSII program, however, allows an instant assessment of basal insulin rate and meal boluses necessary to achieve glucose levels in target range by simulation, provided CGM profiles and respective inputs were recorded over a duration of several days. Herein, we have mainly used the iPro monitoring system to record glucose values over 6 days. It is conceivable that the longer the glucose monitoring time, usually 6–14 days, the more precise the «Metabolic Fingerprint» and thus estimation of basal and bolus insulin. Generating the «Metabolic Fingerprint» and calculation of the personalized basal rate setting for a patient by KADIS-CSII takes less than 10 minutes. This data does indicate that the use of KADIS would facilitate a successful transition from MDI to pump therapy within a much shorter period of time than considered traditionally. In addition, the use of KADIS by the clinician does offer checking out various treatment options or patient preferences by simulation in lieu of empirical implementation. It is also of note that the average daily insulin dose compared to MDI therapy could be reduced by 62 % (22 vs. 52 U/day) and was lower than suggested by the traditional method (22 vs. 26 U/day). Furthermore calculation of basal rates by KADIS-CSII results in personalized profiles/ distribution pattern for a patient whereas in case of the traditional method would result in identical pattern, including the same initial basal rate, for a given amount of insulin.

In addition, an important feature of the KADIS-CSII algorithm is the potencial to avoid hypoglycemia during adjustment of pump therapy. Using it is straightforward and requires users to input body weight, amount of carbohydrates, total daily insulin dose, and basal insulin infusion rate. Moreover, it is capable of discriminating between rapidly and slowly absorbed meals, and the variability in insulin sensitivity is assessed by model-based analysis. Limitations of the study are the small sample size, the dominance of female gender, and the broad age range (23–61 years) of participants.

The procedure of the program «KADIS®-CSII» on the identification of a «metabolic fingerprint» should be tested for other patients and age groups, which are known to have variable basal rate profiles. In particular, in children and adolescentsthis is known. The effectiveness of KADIS®-CSII in these groups of patients should be subject of further investigations.

In summary, introduction of the KADIS-CSII program into clinical practice circumvents time-consuming meal omission tests to build up individual basal insulin rates and cover prandial insulin deficiency. It may thus increase efficiency and flexibility when switch from MDI to pump therapy is required to optimize glycemic control. KADIS-CSII is a program that can be effectively used for the conversion of patients on CSII or the optimization of an existing CSII. For this purpose, a variant already has been created, which implements the calculation in an iPad (TeleDIAB). This makes it possible for the first time in the presence of CGM data and a corresponding user access to transfer patients to a CSII therapy to support online. The clinical relevance of KADIS-CSII is the immediate achieve optimum adjustment of the insulin pump parameters. The economic relevance relates to the time savings for the diabetes team, but also for the patients without burdening meal omission and other tests as well as access to a telemedicine solution. Finally KADIS-CSII provides personalized basal rates considering the typical daily life style of patients. These advantages are to be confirmed in a randomized, controlled clinical trial with a larger number of patients.

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1-Типті қант диабеті терапиясында инсулинді сорғышты қолдану үшін KADIS-CSII бағдарламасын пайдалану

1-Типті қант диабетін (T1D) емдеуде тері асты арқылы инсулинді (CSII) үздіксіз енгізуді оңтайландыру үрдісі стандартты болып табылады. Алайда бірнеше рет енгізген инъекциядан кейін CSII терапияға көшу қиынға соғады. Бұл зерттеудің мақсаты — инсулиндік сорғышта пайдаланатын инсулин терапиясының диабетті басқаратын KARLSBURG-KADIS жүйесін қолдану. Инсулин сорғыштарын пайдалану кезінде біз оның практикалық процесіндегі KADIS-CSII бағдарламасын ұсындық. Сондай-ақ инсулин қысқа және ұзақ мерзімді әсер ететін емнен тұратын MDI емін қабылдаған T1D-мен 12 науқастарды алдын ала зерттедік. HbA1c бастапқы деңгейі 8,2 ± 0,8 % құрады, емделушілердің жасы 31,3 ± 11,1 аралығында және қант диабетімен ауру ұзақтығы 15,7 ± 6,7 жылға тең болды. Науқастың нақтылы метаболитті көрсеткіштерін сипаттайтын MDI терапиясы кезінде глюкоза деңгейін үздіксіз бақылау (CGM) мәліметтері KADIS алгоритм көмегімен жүзеге асты. Үш ай өткен соң MDI-дан CSII-ға өту үшін негізгі терапия KADIS негізінде бақылынып, HbA1c орташа мәні 7,6 ± 0,5 % -ға төмендеді және алты айлық зерттеу соңына дейін осы деңгейде болды. Ұсынылған KADIS-CSII бағдарламасы инсулин сорғыш терапиясын өту үрдісінде нақты және тиімді нормативтік құрал бола алады.

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Применение программы KADIS-CSII для использования инсулинового насоса в терапии диабета 1 типа

Непрерывное подкожное вливание инсулина (CSII) стало стандартом в процессе оптимизации лечения диабета 1 типа (T1D). Однако переход от многократных инъекций к терапии CSII является непростым. Цель данного исследования состояла в том, чтобы использовать KADIS-KARLSBURG-систему управления диабетом при переводе терапии инсулином на использование метода его непрерывного введения. Нами представлена расширенная программа KADIS-CSII в процессе ее практического применения при использовании инсулиновых насосов. Проведено предварительное исследование, 12 па-

циентов с T1D получили терапию MDI, состоящую из инсулина короткого и длительного действия. Начальный уровень HbA1c составлял 8.2±0.8 %, возраст пациентов — 31.3±11.1 лет и продолжительность диабета — 15.7±6.7 года. Данные непрерывного контроля уровня глюкозы (CGM) во время терапии MDI были обработаны алгоритмом KADIS, чтобы характеризовать определенные метаболические параметры пациента. Спустя три месяца после перехода от MDI к CSII на основе управляемой терапии KADIS среднее значение HbA1c было снижено до 7.6±0.5 % и оставалось на этом уровне до конца шестимесячного исследования. Предложенная программа KADIS-CSII может стать реальным и эффективным регулирующим инструментом в процессе перехода к терапии инсулиновым насосом.

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Hyperglycemia and Cardiovascular Risk in Diabetes mellitus Type 1 and Diabetes mellitus Type 2

Diabetes mellitus is a chronic disease that through its complications seriously reduces quality of life and life expectancy in diseased people. There is a worldwide increase in the prevalence in diabetes mellitus type 2. Our understanding in reducing the micro- and macrovascular risk has increased in the last time. But, in contrast to microvascular morbidity the most persistent menace to the health in diabetic patients of both types remains atherosclerosis with increased cardiovascular morbidity and mortality when compared with the non-diabetic population. In the past, the role of hyperglycemia on CVD was not completely elucidated. It was the aim to review and to compare the role of hyperglycemia on cardiovascular morbidity and mortality both in type 2 and type 1 diabetes. Results from ADVANCE and UKPDS Studies in type 2 diabetes have shown that the effect of intensive glucose control was associated with decreased risk of cardiovascular disease and death from any cause in addition to reduction of microvascular disease. HbA1c targets lower than 7.5 % and near to 6.5 % and avoiding of hypoglycemia are recommended. DCCT-EDIC Study data in type 1 diabetes have demonstrated that an early intensive metabolic control near to normal level initiated in patients with short diabetes duration and without microangiopathic complications such as nephropathy significantly reduced micro- and macrovascular morbidity. The long lasting effect of intensive control is called «memory effect». Near normal HbA1c levels at least < 7.5 % and individually targeted in order to avoid hypoglycemia are required. When comparing both types of diabetes, in type 1 as well as type 2 diabetes intensified glucose control resulted in long-lasting effects, reducing significantly cardiovascular morbidity and mortality. Treatment has to be initiated early in the course of the disease. But considering meta-analyses of large randomized controlled trials of intensive vs. conventional glycemic control in type 2 diabetes, hyperglycemia has shown to be a weaker cardiovascular risk factor than increased cholesterol levels or hypertension.

Key words: diabetes mellitus type 1, diabetes mellitus type 2, hyperglycemia, glycemic control, cardiovascular disease.

Abbreviations:

ACCORD	—	Action to Control Cardiovascular Risk in Diabetes;
ADVANCE	—	Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled Evaluation;
DCCT/EDIC	—	Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications;
CAC	—	coronary artery calcification;
CVD	—	cardiovascular disease;
CHD	—	coronary heart disease;
CAD	—	coronary artery disease;
EURODIAB	—	European Prospective Complications Study IDDM Complications Study;
ROS	—	reactive oxygen species;
UKPDS-PTM	—	United Kingdom Prospective Diabetes Study-Post trial monitor;
VADT	—	Veterans Affairs Cooperative Study;
WESDR	—	Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Diabetes mellitus is a chronic disease that through its complications seriously influences the quality of life by shortening the life expectancy of people suffering from diabetes. A worldwide diabetes expansion from 285 million diseased people to expected 438 million in 2030 demands strengthening efforts to control and to prevent the disease expansion [1–3]. The worldwide accelerating increase in the prevalence of type 2 diabetes [4] enhances the risk for diabetic complications, indeed when considering also an alarming rise of type 2 diabetes already in young people. In the young populations there is also an increase of the type 1 diabetes incidence by about 2 % to 5 % per year worldwide [5, 6].

In the last years, our understanding about cardiovascular risk of hyperglycemia and other risk factors in reducing the micro- and macrovascular morbidity has enlarged. Prospective epidemiological studies have

shown to reduce the micro- and macrovascular morbidity and mortality by intensive metabolic control both in type 1 and type 2 diabetic patients [7, 8]. Over the past 40 years, a reduction in the mortality due to cardiovascular disease and coronary heart disease by about 70 % both in diabetic and in non-diabetic population has been reported [9].

But diabetic patients have not equally benefited from advances in reducing the coronary risk as the non-diabetic have. The traditional risk factors do not fully explain the excess risk for increased cardiovascular morbidity in diabetes [10]. In both types of diabetes an increased CVD risk in men and women has been reported. A significant increase in CVD mortality in diabetic patients compared to people without diabetes related to increasing HbA1c levels has been shown [10].

In the past the role of hyperglycemia as an independent risk factor for cardiovascular disease in both types of diabetes was still not fully enlightened [11, 12].

In previous cross-sectional studies we had found that cardiovascular risk factors are working also in type 1 diabetes [13]. We found CVD in type 1 diabetes to be associated with age, disease duration, increased insulin requirement, hyperglycemia, nephropathy, hypertension, lipid abnormalities, retinopathy and neuropathy [14]. As cardiovascular risk factor in type 1 diabetes were further considered arterial stiffness, coronary artery calcification, cardiac autonomic neuropathy and hypoglycemia [15].

Today our understanding about the cardiovascular risk of hyperglycemia in both types of diabetes has enlarged [8, 16].

Therefore, it was the aim of the present survey to compare the impact of the risk of hyperglycemia on the cardiovascular morbidity and mortality both in type 2 and in type 1 diabetes.

What is a risk factor?

A risk factor is an attribute or an exposure that is associated with increased probability of occurrence of a disease. This is not necessarily a causal factor. A risk factor represents more the likelihood that people who are exposed to certain factors subsequently develop a particular disease [17].

Hyperglycemia as mediator of cardiovascular complications in type 1 und type 2 diabetes

The pathogenesis of micro- and macrovascular complications in type 1 and type 2 diabetes is still not completely elucidated. The concept of an unifying mechanism of hyperglycemia in this process has been proposed by M. Brownlee in 2005 [18].

In diabetes, hyperglycemia is washing round all cells of every tissue, but there is a tissue damaging effect of hyperglycemia to a particular cell type, i.e. capillary endothel cells in the retina, mesangial cells in the renal glomerulus, neurons and Schwann cells in the peripheral nerves, and on endothel cells by generating diabetic macrovascular disease. These cells are not able to reduce the transport of glucose into the cells when they are exposed to hyperglycemia [19].

The increased glucose flux goes through the polyol pathway. When the glucose concentration in the cells becomes too high, glucose will be converted to sorbitol, which later will be oxidized to fructose.

Aldose reductase consumes the cofactor NADH, an essential cofactor for regeneration of antioxidants as glutathione, and thereby increases intracellular oxidative stress [20].

Increased intracellular production of AGE precursors appears to damage cells by modification of proteins involved in the regulations of gene transcription [21] and thereby causing cellular dysfunction [22]. The activation of PKC effects gene expression and leads to endothelial nitric oxid synthesis (eNOS) and increased vasoconstrictor endothelin-1 [23, 24].

An increased hexosamin pathway activity flux results from metabolizing glucose by glycolysis and the formation of UDP N-acethyl-glucoseamin.

This results in increased expression of transforming growth factor-β1 and plasminogen activator inhibitor-1 which is detrimental to blood vessels function [25, 26]. Hyperglycemia increases superoxide production by the mitochondria. The mitochondrial electron transport chain is the source of the hyperglycemia induced superoxide generation, as formation of reactive oxygen species (ROS) [18].

An increased FFA-oxidation in diabetic patients causes overproduction of ROS by the same mechanisms as it has been described for hyperglycemia, thus causing the same damaging pathways [18].

Hyperglycemia and CVD in type 2 diabetes

Regarding the worldwide increase in the prevalence of type 2 diabetes, we are faced with obesity, physical inactivity and aging as the main pathogenetic factors [27]. The most persistent menace to diabetic patients health and life has remained atherosclerosis. Type 2 diabetes is one of the pathological consequences of the metabolic syndrome with CHD, obesity, dyslipidemia and hypertension [28]. On the other hand, today

people with diabetes can live with growing confidence a complications free life. This, however, is requiring significant modifications in life style and a regular correction of risk factors for complications [29].

Cardiovascular morbidity and mortality are significantly increased in type 2 diabetes when compared with the age- and sex-matched non-diabetic population [30]. Classic cardiovascular risk factors are hypertension, hyperlipoproteinemia and smoking [31]. In addition to the classic risk factors, other factors are contributing to the increased cardiovascular mortality in type 2 diabetes, such as microalbuminuria [32], hemostatic abnormalities [33], endothelial dysfunction and chronic inflammation [34].

However, cardiovascular risk of hyperglycemia in type 2 diabetes was not fully supported [35–37]. Some studies have reported an increase of cardiovascular risk with the increase of hyperinsulinemia and glycated hemoglobin [38, 39]. But in prospective population based observational studies the effect of hyperinsulinemia on the development of CVD in type 2 diabetes was less pronounced than that of conventional risk factors [35]. The UKPD-PTM-Study was established to definitely answer the glycemic control controversy and to answer questions about the class of antidiabetic agents used to achieve control [40].

The UKPDS results have shown that the microvascular complications such as retinopathy, nephropathy, and possibly neuropathy were reduced by lowering blood glucose levels in type 2 diabetes with intensive treatment. A median HbA1c of 7.0 % was achieved in intensive treated patients when compared with conventional therapy with a median HbA1c of 7.9 %. Hereby, the overall microvascular complications decreased by 25 % [41, 42].

These data have provided statistical evidence that hyperglycemia causes these complications [43]. There, a continuous relationship between the risk of microvascular complications and glycemia was found. Every percentage point decrease in HbA1c showed a 35 % reduction in the risk of complications [43]. The risk of complications significantly decreased in the range of glycemic levels of HbA1 c <8.0 %. There was no evidence of any glycemic threshold for any of the microvascular complications above normal glucose level [43]. A significant effect of lowering blood glucose on cardiovascular complications was not found. There was a 16 % reduction of combined fatal and nonfatal myocardial infarction and of sudden death (P = 0.052) [41, 42]. Epidemiological analysis demonstrated a continuous association between the risk of cardiovascular complications and glycemia. Every percentage point decrease in HbA1c was associated with a 25 % reduction in diabetes related deaths, a 7 % reduction in all-cause mortality, and a 18 % reduction in combined fatal and nonfatal myocardial infarction [43]. Again, there was no glycemic threshold above normal glucose levels [43].

While lowering of blood pressure to a mean of 144/82 mm Hg reduced significantly strokes, diabetes related deaths, heart failure, microvascular complications and visual loss, there was no threshold for the complications above blood pressure of 130 mm Hg [44, 45].

The UKPDS-PTM-Study aimed to definitely answer the glycemic control controversy in type 2 diabetes:

Despite an early loss of glycemic differences between intensive and conventional therapy, a continued reduction in microvascular risk was registered, and a further risk reduction for myocardial infarction and death from any cause could be observed during 10 years of post trial follow-up. There was also a continuous decrease in complications among overweight patients undergoing metformin therapy [40].

Beyond UKPDS, it is established without any doubt that outcomes in those whose blood pressure and glycemic control were near normal were better, and it proved evidence base for the use of metformin.

The first years, following study initiation, were crucial to outcome. The authors of UKPDS-PTM suggested that this was no memory effect which was used by DCCT trial. Here, this was a legacy effect most likely related to atherosclerosis [40].

Other trials of glycemic control in type 2 diabetes however showed different results: ACCORD Study patients had longer disease duration 0f 11 years when comparing with the UKPDS population. The intensive group targeted HbA1c concentrations toward 6 %. At one year, stable HbA1c levels of 6.4 % and 7.5 % were achieved in the intensive group and the standard group, respectively. However, 257 patients in the intensive group died, and 203 patients in the standard therapy group. Hypoglycemia rates were three times higher in the intensive therapy groups as compared to control groups. Therefore, the trial was closed after 3.5 years because of 25 % increase in all-cause mortality in the intensive control group [46].

The ADVANCE trial is a randomized controlled international study of 11,140 patients with type 2 diabetes with glycemic intervention, comparing strategy of intensive blood glucose control (gliclazide) to a target on HbA1c of 6.5 %. In the ADVANCE trial no increase in cardiovascular mortality occurred, and there

was a 12 % decrease in mortality among the intensively treated patients [47]. Subsequent analyses showed a 25 % relative reduction in all-cause mortality for every 1 % point reduction in HbA1c [47].

The VADT Study was a multicenter trial that investigated the effects of intensive control at HbA1c targets of 6 % or less compared with standard glycemic control (HbA1c 8–9 %) on cardiovascular outcomes among 1.791 patients with type 2 diabetes [48]. Intensive HbA1c lowering in VADT and in ACCORD as well resulted in increased cardiovascular death rates and all-cause mortality rates when compared with ADVANCE and UKPDS [40, 47].

On the other hand, the results from ADVANCE [47] and UKPDS-PTM Studies [48] have shown that the effect of intensive glucose control was associated with decreased risk of myocardial infarction and death from any-cause in addition to reduction in the risk of microvascular complications in type 2 diabetes.

As shown by UKPDS data, intensive control should be started as early as possible at the time of disease manifestation.

UKPDS data have shown a so called legacy effect in reduction of cardiovascular morbidity that persisted for 10 years and after the loss of differences in HbA1 c levels [40].

Possible mechanisms behind the observed effect could be, that changes in glycation may alter the electric charges of proteins thus contributing to alterations in their properties and/or functions. As many proteins are sensitive to glycation, this may contribute to functional and structural consequences in many organs in the long term [49].

The therapeutic efforts in type 2 diabetes should not be focused only on glycemic control. Type 2 diabetes cannot simply be treated as a disease of abnormal glucose metabolism. Trial data show that lipid abnormalities and blood pressure should be treated in parallel [50, 51].

Targets of glycemia are an HbA1c lower than 7.5 % and near to 6.5 %, if achieved slowly and without hypoglycemia. Early interventions are beneficial. Late interventions and tight glucose control require a careful approach by avoiding hypoglycemias. Table shows a meta-analysis of intensified vs. conventional control including the major trials conducted in patients with type 2 diabetes.

Hyperglycemia and CVD in type 1 diabetes

The increased risk of CAD in type 1 diabetes has been recognized since long time [52, 53]. It was suggested that the most likely factor that primarily accounts for this increased risk is hyperglycemia [54], but the epidemiologic association between glycemia and CAD was rather weak [55]. Since long time an increased occurrence of CHD in type 1 diabetes has been reported [56, 57].

Over the past years, a reduction was observed in the mortality due to CVD both in the diabetic and non-diabetic population, presumably of the progress in cardiovascular risk management and interventional cardiology [58]. In type 1 diabetes, a decrease in mortality and an improvement in life expectancy occurred during the last years [59, 60].

However, the increased risk of CHD for people with type 1 diabetes compared to people without diabetes remained obvious. Increased CVD mortality was related to increasing HbA1c levels [61]. The benefits of improved diabetes care did not result in lowering CVD mortality [62].

On the other hand, an early and intensive metabolic control has been shown to reduce micro- and macrovascular morbidity and mortality, favouring the «imprinting « theory of metabolic control.

Nevertheless, in type 1 diabetes we have to consider still other pathogenetic factors: an excess CAC in type 1 diabetes is providing support for accelerated atherosclerosis [63, 64]. Here, angiographic and autopsy studies have shown more extensive disease. Of note, changes in arterial compliance, endothelial dysfunction and changes in vasculature structure and function occur early in the course of type 1 diabetes [65–68]. Type 1 diabetes is associated with increased risk for CHD and that is already evident at young age.

Beside the impact of hyperglycemia, there is a wide range of modifiable risk factors and indicators, such as blood pressure, lipid abnormalities and smoking and specific factors as renal disease. In the EDIC — Study inflammation, depressive symptomatology and insulin resistance were considered as CAD predictors; however, not hyperglycemia [69]. Similar data were found by the EURODIAB Study [70], and the WESDR Study [71]. In all these studies HbA1c showed only weak associations with CAD in type 1 diabetes [72]. However, another risk factor, i.e. diabetic autonomic neuropathy, implicated an increased CAD risk in type 1 diabetes [72].

Concerning lipids, HDL-cholesterol levels are generally higher in type 1 diabetes, thus reflecting an altered HDL metabolisms by enhanced lipoprotein lipase and reduced hepatic lipase activity due to systemic insulin administration.

Atherosclerosis is increasingly considered as an inflammatory disease. The oxidative modification of LDL, activation of macrophages, and endothelial cells, impaired nitric oxide and resulting vascular cytotoxicity may be involved in the pathogenetic process [73]. Other factors, for example, adhesion molecules and cytokines have still not extensively been studied in the development of CAD in type 1 diabetes [74].

The DCCT data have shown a durable effect of initially intensive metabolic control despite a loss of glycemic separation later on in the disease progress, an effect of metabolic memory. A reduction of early-stage complications during the course of DCCT has been demonstrated as well as a substantial reduction in severe complications and in cardiovascular disease [62].

The phenomenon of a durable reduction of complications by prior intensive metabolic control was named «metabolic memory». The effect lasted at least 10 years [62]. Major beneficial effects of intensive control on advanced complications included retinopathy, nephropathy and autonomic neuropathy. Measurements of atherosclerosis included carotid intima thickness and coronary artery calcification. Fatal and nonfatal myocardial infarctions were reduced by intensive treatment with 58 % after a mean of 18 years of follow-up [75]. The EDIC observational follow up confirmed the durability of DCCT effects [76].

T a b l e

Meta-analysis of intensified vs. conventional glycemic control

Trials	Annualeventrate (%)			
	Intensified	Conventional	(%)	Hazard ratio (95 %CI)
Major cardiovascular event				
ACCORD	352(2.11)	371(2.29)	–1.01	0.90 (0.78–1.04)
ADVANCE	557(2.15)	590(2.28)	–0.72	0.94 (0.84–1.06)
UKPDS	169(1.30)	87(1.60)	–0.66	0.80 (0.62–1.04)
VADT	116(2.68)	128(2.98)	–1.16	0.90 (0.70–1.16)
Overall	**1194**	**1176**	**–0.88**	**0.91 (0.84–0.99) (Q=1.32; P=0.72; I^2=0)**
Myocardialinfarction				
ACCORD	198 (1.18)	245 (1.51)	–1.01	0.77 (0.64–0.93)
ADVANCE	310 (1.18)	337 (1.28)	–0.72	0.92 (0.79–1.07)
UKPDS	150 (1.20)	76 (1.40)	–0.66	0.81 (0.62–1.07)
VADT	72 (1.65)	87 (1.99)	–1.16	0.83 (0.61–1.13)
Overall	**730**	**745**	**–0.88**	**0.85 (0.76–0.94) (Q=2.25; P=0.52; I^2=0)**
Cardiovasculardeath				
ACCORD	135 (0.79)	94 (0.56)	–1.01	1.35 (1.04–1.76)
ADVANCE	253 (0.95)	289 (1.08)	–0.72	0.88 (0.74–1.04)
UKPDS	71 (0.53)	29 (0.52)	–0.66	1.02 (0.66–1.57)
VADT	38 (0.83)	29 (0.63)	–1.16	1.32 (0.81–2.14)
Overall	**497**	**441**	**–0.88**	**1.10 (0.84–1.42) (Q=8.61; P=0.04; I^2=65.1 %)**
All-causemortality				
ACCORD	257 (1.41)	203 (1.14)	–1.01	1.22(1.01–1.46)
ADVANCE	498 (1.86)	533 (1.99)	–0.72	0.93(0.83–1.06)
UKPDS	123 (0.13)	53 (0.25)	–0.66	0.96(0.70–1.33)
VADT	102 (2.22)	95 (2.06)	–1.16	1.07(0.81–1.42)
Overall	**980**	**884**	**–0.88**	**1.04(0.90–1.20) (Q=5.71; P=0.13; I^2=47.5 %)**

Adapted from reference [80]: Turnbull et al. Diabetologia. — 2003. — Vol. 52. — P. 2288–2298.

Abbreviations: ACCORD — Action to Control Cardiovascular Risk in Diabetes; ADVANCE — Action in Diabetes and Vascular Disease Preterax and Diamicron controlled evaluation; UKPDS — United Kingdom Prospective Diabetes Study; VADT — Veterans Affairs Diabetes Trial; HbA1c — glycated hemoglobin.

Hazard ratios < 1.0 are favouring intensified glycemic control. Hazard ratios >1.0 are favouring conventional glycemic control.

It was convincingly demonstrated, that the glucose hypothesis was correct. Blood glucose control aimed to achieve glycemia close to non-diabetic levels as safely as possible, reduced microvascular and macrovascular complications. This suggests that long-lived proteins might account for this effect [62].

Introduction of these findings into clinical care has improved the long-term health of patients with type 1 diabetes [62]. A strong relation of glycemia with CAD was not seen in other studies [69–71]. However, the DCCT patients had shorter diabetes duration, and obese hypertensive and hypercholesterolemic patients were excluded. Consequently, sufficiently low HbA1c levels of 7.4 % were achieved [62].

Conclusions

This survey shows that early intensive metabolic control near to the normal level initiated in type 1 diabetes patients with short diabetes duration and without microangiopathic complications resulted in significantly reduced micro- and macrovascular morbidity. It caused long-lasting effect (memory effects) and resulted even in decreasing CAD morbidity and mortality [77, 78].

The Guidelines of the DDG in considering the results of the above mentioned studies suggest:

Type 1 diabetes

In patients with type 1 diabetes HbA1c concentrations <7.5 % are aimed. Guidelines recommend individually targeted HbA1c levels in order to avoid hypoglycemias and recommend blood glucose self control at least 4times daily, i.e. before meals and at bedtime [79, 80].

Type 2 diabetes

(1) For type 2 diabetes HbA 1c levels are aimed at 6.5 % to 7.5 % by taking into account individually targeted HbA1c concentrations [79], even though, meta-analysis of four large randomized controlled trials of intensive vs. conventional glycemic control in type 2 diabetes have shown an only modest but still significant cardiovascular benefit in intensively treated patients (Table). The effect of intensive glucose control resulted in a 15 % reduction risk (RR) of myocardial infarction [81].

The benefits of intensified blood glucose control in reducing cardiovascular disease should not be overestimated by giving records in terms of relative risk reduction (RR). They should rather be given in terms of absolute risk reduction or the corresponding NNT, i.e. the number of individuals who would require 5 years of treatment to prevent one event would be 44 with cholesterol lowering, 34 with blood pressure lowering and 119 with intensive blood glucose lowering [81].

(2) Intensive glucose control has to be started as early as possible (legacy effect), and hypoglycemia should be avoided [40].

(3) Hyperglycemia has shown to be a weaker cardiovascular risk factor than increased cholesterol or hypertension [81].

(4) Reducing the cardiovascular risk by decreasing elevated cholesterol levels and hypertension has shown to be more effective than intensive blood glucose control.

Common features

Comparing both types of diabetes the survey has shown type 1 and type 2 diabetes are different entities. Major epidemiological trials provided evidence that hyperglycemia causes the microangiopathic complications both in type 1 and type 2 diabetes, and intensified glycemic control decreases significantly the microangiopathic complications.

A special role both in type 1 and type 2 diabetes plays an increased cardiovascular morbidity and mortality. Patients of both types have an increased prevalence of cardiovascular complications. These complications appear earlier than in the non-diabetic population, the clinical course is accelerated and there are no sex differences.

When comparing both types of diabetes, the major epidemiological trials have brought the evidence that intensified glycemic control equally resulted in longlasting effects, thus reducing significantly cardiovascular morbidity and mortality in both types of diabetes. In both types of diabetes treatment has to be initiated early in the clinical course of the disease, and hypoglycemias have to be avoided.

Nevertheless, we have to consider that in both types of diabetes beneficial effects of intensified glycemic control in reducing the cardiovascular morbidity and mortality are considerably lower than those of reducing the classic cardiovascular risk factors.

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1- және 2-типті диабет кезіндегі жүрек-қан тамырлар ауруларының гипергликемиясы және даму қауіпі

Мақалада диабетпен ауыратын адамдар үшін ең елеулі және тұрақты қауіп ретінде атеросклероз және ЖҚТ аурулардың саны жоғарылауы және соның салдарынан өліммен аяқталу болып табылады. Жұмыстың мақсаты — 1- және 2-типті диабет кезінде гипергликемияның, жүрек-қан тамырлар ауруларының дамуы мен өлім көрсеткішіндегі рөлін зерттеу. 2-типті диабет кезіндегі ADVANCE және UKPDS зерттеулері ЖҚТ ауруларының дамуы мен капиллярлардың зақымдануына байланысты болған аурудың азаюымен қатар, олардың өлім көрсеткішінің азаюына алып келетінін көрсетті. Мақсат — HbA1 дәрежесін 7,5 %-дан төмен, 6,5 %-ға дейін төмендету мен гипогликемияны болдырмау. Нәтижелер 1-типті диабетпен ауыратындардың ерте басталған метаболитті қадағалау арқасында микрогангиопатияның, нефропатияның және микро- және макроваскулярлы қабынулардың санының азайғанын көрсетті. HbA1 дәрежесінің 7.5 % -ға тең болуы ұсынылды. Алайда нәтижелер көрсеткіші бойынша гиперхолестеринемия немесе гипертонияға қарағанда гипергликемия ЖҚТ аурулары ішінде ең әлсіз фактор болып табылады.

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Гипергликемия и риск развития сердечно-сосудистых заболеваний при диабете 1 и 2 типов

В статье отмечено, что наиболее серьезной и постоянной угрозой здоровью больных диабетом лиц остаются атеросклероз и повышенный риск развития сердечно-сосудистых заболеваний (ССЗ), наблюдается высокая смертность от них. Цель работы — исследовать роль гипергликемии в развитии ССЗ и смертности от этих заболеваний при диабете 1 и 2 типов. Исследования ADVANCE и UKPDS при диабете 2 типа показали, что интенсивный контроль за глюкозой приводил к снижению риска развития ССЗ и смертности от других причин в сочетании с уменьшением заболеваний, связанных с

поражением капилляров: наблюдалось снижение уровня HbA1c до 6,5 % и предотвращение гипогликемий. Результаты показали наличие снижения числа микроангиопатий, нефропатий и числа микро- и макроваскулярных расстройств у больных диабетом 1 типа при рано начатом метаболическом контроле. Рекомендуемый уровень HbA1c — 7,5 %. Между тем результаты показывают, что гипергликемия является более слабым фактором риска развития ССЗ, чем гиперхолестеринемия или гипертония.

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Diabetogenic Metabolits of Tryptophan

The analysis of results investigations of mechanisms of diabetogenic activity of metabolits of abnormal tryptophan metabolism as Xanthurenic acid (XA) are presented in review. Among more than 30 diabetogenic chemicals widely known today XA only is formed in animals and elderly human as result of disturbances of tryptophan metabolism. The influence of XA on histostructure of pancreatic islets and on insulin content in B-cells as mechanisms of diabetogenic action and of its prevention are investigated by authors. It was showed that Xanthurenic acid induced diabetes determined by: direct damage of B-cells by Xanthurenic acid accompanied by marked histological changes in islets as destruction and necrosis of B-cells, marked decreasing of insulin content in cytoplasm of cells; by forming of complex XA-insulin that result overstrain of B-cells; by alteration of islet's capillaries and of blood microcirsulation.

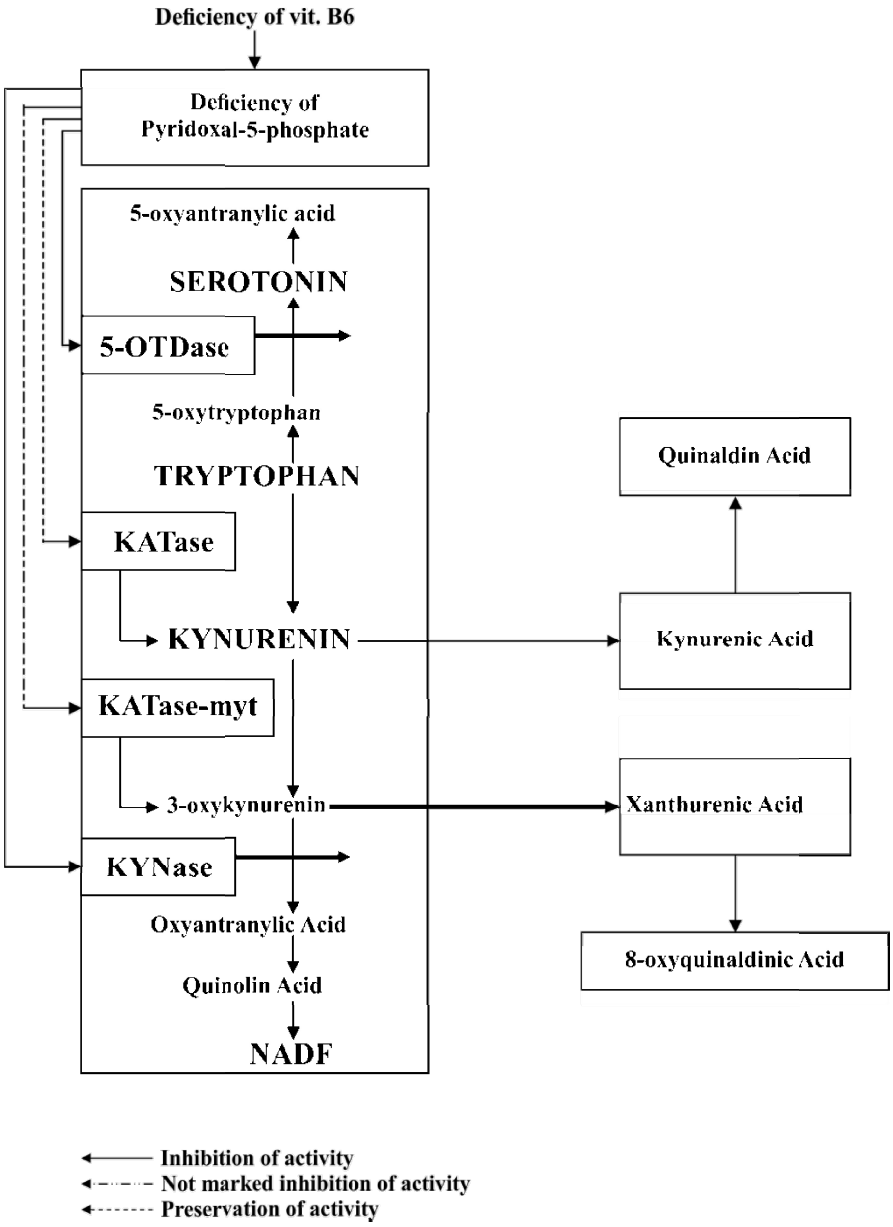
Key words: B-cells, Xanthurenic acid, experimental diabetes, tryptophan, pancreas.

In 1935 Musajo L. and coll. reported about synthesis of Xanthurenic acid (XA). This chemical was separated from urine of experimental animals and identified as 4,8-digidroxyquinolin-2-xarboxylic acid, a derivative of 8-oxyquinoline [1]. Formula: $C_{10}H_7NO_4$.

Accumulation in organism of large amount of fatty acids and tryptophan in the deficiency of vit. B6 (pyridoxine) result intensive synthesis of XA in tissue. It was followed by developing in animal symptoms of diabetes [2–8].

Xanthurenic acid is a product of disturbances of Tryptophan metabolism, in routine conditions is metabolised on serotonin and kinurenine ways (Fig. 1) which at the same time come to the end with forming of a 5-oxyindol-acetic acid and NADF [9, 10]. The deficiency of pyridoxal-5-phosphat (P-5-F) result inhibition of 5-oxytryptophan decarboxylase and of kinureninase that accompanied by inhibition of metabolisation on both paths. As result — 4 substances are formed: Xanthurenic acid and 8 oxyquinaldine — from 3-oxyquinurenine and kynurenic and oxyquinurenic acids — from kynurenine [10–12]. Main enzymes for synthesis of Xanthurenic acid are kynureninaminotransferase and oxykynurenine-tryptophandecarboxylase, a coenzymes of P-5-P [10, 13]. XA is formed from 3-oxykynurenine. Under influence of a kynureninaminotransferase from 3-oxykynurenine Xanthurenic acid is formed. In the deficiency of P-5-P synthesis of serotonin is decrease and synthesis of XA and of kynurenine acid is increased [2, 14]. However there is, apparently, a contradiction: why deficiency of P-5-P inhibit synthesis of serotonin and stimulate synthesis of XA? On the one hand this results based on fact that the pyridoxal enzymes of tryptophan metabolism differently react for deficiency of P-5-P: if activity of a kynureninase decrease by 83 %, then of kynureninaminotransferase — decrease for only 42 % [13, 15]. On the other hand, studying of localization of enzymes in cells of liver and kidneys it was established that the kynureninaminotransferase is both in mitochondria and in soluble part of cells whereas a kynureninase — only in a soluble part of cells. In the deficiency of P-5-P in organism the content of these two enzymes in soluble part of cells significantly decrease, and of mitochondrial kynureninaminotransferase remains at the previous level [16]. Increasing of excretion with urine of xanthurenic acid is explained by it. For the first time the high amount of Xanthurenic acid were found in the urine of the white rats who were contained on diet enriched with tryptophan and in deficiency of vit. B6.

Addition of Pyridoxine accompanied by disappearance of Xanthurenic acid from urine [9, 12, 17]. However, marked avitaminosis of B6 result decrease of activity of kynureninaminotransferase that accompanied by decrease of its excretion with urine [18; 32]. Later Xanthurenic acid was found in urine of rabbits, dogs, guinea pigs and human [3, 11, 19–22].



5-OTDase — 5-tryptophanedehydrogenase; KATase — kynureninaminotransferase;
KATase-myt — kynureninaminotransferase mytochondrial; KYNase — kynureninase

Figure 1. Disturbances of Tryptophan Metabolism

Increasing of excretion of Xanthurenic acid with urine is revealed at elderly patients with diabetes mellitus. At elderly people [23] there is increase amount of Xanthurenic and of kynurenine acids in urine. In spite of the fact that administration of Pyridoxin result decreasing of concentration in urine, there is not a complete normalisation of their excretion [23]. Average concentration in daily urine at healthy persons fluctuates from 2.1 mg to 8.8 mg [12].

Deficiency of P-5-F in organism developed as result of deficiency of vit. B6 and as result of inhibition of synthesis of P-5-P from vit. B6. Synthesis of Xanthurenic acid is increased using of diet enriched by saturated fatty acids and of casein. Two enzyme systems are known which provide biosynthesis of P-5-F: pyridoxynphosphatoxydase (PPO) and pyridoxinkynase (PK). The diet enriched by fatty acids, stimulate decrease of activity of PPO in liver [24] which can be restored by administration of vit. B2, a co-enzyme of PPO. Studying of disturbamces of tryptophan metabolism depending on age of patients showed that in the first four days of life derivatives of kynurenine not found in the urine of newborns [25].

During the period from the 5th to the 20th day of life there are a minimal concentrations of Xanthurenic acid in urine. Administration of α-tryptophan does not increase excretion of Xanthurenic acid [26, 27], but in-

crease it at children at age of 4–6 years [28]. In patients age 70 years and over formation of kynurenine is increased. Administration of 100 mg/kg of α-tryptophan is accompanied by marked excretion of Xanthurenic acid. Administration of pyridoxine result normalization of excretion at elderly people [29]. There are a changes of tryptophan metabolism at pregnant women [30–32]. Administration of α-tryptophan accompanied by active excretion Xanthurenic acid with urine [33–35]. Administration of α-tryptophan, 100 mg/kg at pregnant women followed by increasing of excretion not only of Xanthurenic acid but also of kynurenine acid [36].

At the same time, the increase of excretion of Xanthurenic acid was found within all period of pregnancy and increase excretion of kynurenic acid was observed in the first 3 months [36; 82]. A high excretion of Xanthurenic acid at pregnant women was decreased after administration of Pyridoxine [33, 34; 83, 84]. The increased excretion of Xanthurenic acid — is a symptom of deficiency of vit. B6 in patients with diabetes [37, 38].

Very often disturbances of Tryptophan metabolism are shown as dissociation of Tryptophan accompanied by forming of a large amount of Xanthurenic acid. Deficiency of P-5-P result developing of disturbances of Tryptophan metabolism [14].

Y. Kotake in 1957 [4] investigated processes of formation and of excretion of Xanthurenic acid in organism. He used administration of various sodium salts of fatty acids and of Tryptophan. The most marked effect of endogene synthesis and excretion with urine of Xanthurenic acid — as 10.49 of mg daily — was showed using of complex as Tryptophan + oleic acid. The least effect — 1.6 mg — past using of Tryptophan only. Excretion of Xanthurenic acid after administration of Tryptophan in combination with fatty acid: Tryptophan + acetic acid — 5.37 mg; Tryptophan + propionic acid — 8.79 mg; Tryptophan + oil acid — 9.87 mg; Tryptophan + valerianic acid — 9.64 mg; Tryptophan + palmitinic acid — 9.61mg; Tryptophan + stearinic acid of — 8.57 mg.

The specific diet stimulate endogene synthesis of Xanthurenic acid was recommended by Y. Kotake [4]. Percentage of components of diet: casein — 22, salt mixture McCollumn — 6, agar-agar — 3, yeast — 2, oil — 10, sugar — 5, amylum — 52. This diet include the majority of above-named fatty acids in the structure and each diet caused increasing of excretion of Xanthurenic acid with urine by 3,5–6,5 times in compared with diet contain only Tryptophan. It was showed that biosynthesis of P-5-P depends of content of fat or fatty acids in diet. And as conclusion: diet enriched by fats result decreasing of activity of pyridoxalaminotransferase in liver [24]. Due to acceleration of kynurenine way of Tryptophan metabolism its diabetogenic metabolites can collect at a stress [39, 40].

Meanwhile injection of vit. B6 10.0 mg in experimental conditions result decreasing of excretion of Xanthurenic acid till 2.03 mg [42] per 24 h in compared with 8.42 mg without vit. B6. Y. Kotake in 1968 established that fatty acids suppress synthesis of P-5-P that result more active endogene synthesis of Xanthurenic acid. Intraperitoneal administration to mice of 200 mg/kg of endogene formed Xanthurenic acid followed by developing of diabetes [43]. It was showed a temporary hyperglycemia at rabbits after administration of Xanthurenic acid [44]. However, synthetic Xanthurenic acid, a dose of 200 mg/kg did not caused developing of diabetes in dogs and rabbits [45].

At the same time, a large amount of fat in diet in combination with Xanthurenic acid or kynurenic acid followed hyperglycemia and developing of histological changes typical for the experimental diabetes [10, 46–48]. Meanwhile disturbances of carbohydrate metabolism not developed in rats and rabbits after administration of Xanthurenic acid or containing of animals on free of vit. B6 diet [49].

Using of diet contains Tryptophan, 10 mg/kg in combination with hypovitaminosis of B2 [4] was followed by developing of hyperglycemia and xanturenuria.

At the rats contained on diet by Y. Kotake hyperglycemia is increased for long period that accompanied by glucosuria and and of polyuria. Animals had a tendency to increase of body weight on average from 140 g to 220 g and until 260 g (obesity) as of xanturenyria for 2–3 mg/24 h [50, 51].

It was established that increase of blood glucose level besides Xanthurenic acid is caused by kynurenine acid [52] which final products is quinaldine acid [53]. In our experiences with use within 3 months of a diet of Y. Kotake also permanent increase in level of a glycemia was revealed which was, however, less expressed in comparison with observed after single-pass administration of diabetogenic doses of other derivatives 8-oxyquinolines. Its influence by the end of experience was followed also marked — at 7–10 times — increasing of xanthurenuria and decreasing of insulin content in B-cells. Xanthurenic acid is transformed in 8-oxyquinaldinic acid [17] which possess diabetogenic properties. Other metabolites of Tryptophan as kynaldine and kynurenic acids possess insulin releasing activity [17, 50]. It is shown a large release of insulin from the isolated islets at the first 30 min. after the beginning of incubation.

Results of investigation of state of histostructure of pancreas of experimental animals: vacuolization and destruction of cytoplasm, hydropic distrophya, destruction of nuclei [4, 5, 54, 55–57].

It was established that increase of blood glucose level besides Xanthurenic acid is caused by kynurenie acid [58] which final products of metabolism is quinaldine acid [53].

Presence of quinaldine acid almost completely suppresses the second phase of release of insulin [59]. Incubation of insulin and of Xanthurenic acid result forming of stable complex [51, 60]. By using of fluorimetric methods it was showed that two moles of Xanthurenic acid connected with one insulin dimer. Hormonal activity of this complex decrease until 49 % of activity of native insulin [51, 61] and is increased past administration in media of Zinc [60, 62].

E.Murakami [63–65] showed that incubation of Xanthurenic acid with insulin result formation of two complexes. In one of them insulin is bound to 1 mole of Xanthurenic acid and in the second — with 1.5 mole. Xanthurenic acid easily formed complex with insulin in blood serum, without breaking structure of insulin. This complex is stable [51]. It was supposed that chemical connection is carried out between atom of Zinc and imidazole radical in a molecule of insulin [51, 43]. Xanthurenic acid shows a high affinity for ions of Zinc [66]. Activity of insulin is restored after addition of ions of Zinc to blood serum contains of complex XA-insulin [67].

Presented data about diabetogenic properties of Xanthurenic acid are interesting first of all that contrary for other diabetogenic chemicals, Xanthurenic acid is synthesised in human and animals at disturbances of diet in combination with deficiency of Pyridoxin.

On the mechanisms of diabetogenic activity of Xanthurenic acid

More than 60 years ago Y. Kotake noted a strong likeness of chemical structure of molecule and of properties of Xanthurenic acid with other diabetogenic derivatives of 8-oxyquinoline (Fig. 2). He supposed that diabetogenic properties of Xanthurenic acid determined by the –OH radical located in position «8» of the molecule of Xanthurenic acid [68, 69]. Xanthurenic acid possess a high affinity for ions of Zinc [66]. In 1957 Y. Kotake and M. Kato confirmed that Xanthurenic acid possess diabetogenic properties only in case if –OH radical is fixed in the position «8» of a quinoline ring similar as other diabetogenic derivatives of 8-oxyquinoline (Fig. 2). Extraction or replacement of it followed by complete disappearing of diabetogenic properties of Xanthurenic acid [54, 69].

G. Weitzel and coll. confirmed [45] that Xanthurenic acid form with Zinc a chelate complex 1:1 and atom of Zinc is fixed between hydroxyl and carboxylic groups of a quinoline ring (Fig. 2). It is known that such type of complex of metal with derivatives 8-oxyquinolines is the most toxic for cells. E. Murakami and Y. Kotake investigated interaction between insulin and Xanthurenic acid. For the first time the evidence of ability of Xanthurenic acid to connect insulin in experiences of in vitro were presented by E. Murakami [65].

On the base of obtained results, Y. Kotake, T. Ueda and coll. (1975) proposed a follow mechanisms of diabetogenic properties of Xanthurenic acid (Fig. 3, left part).

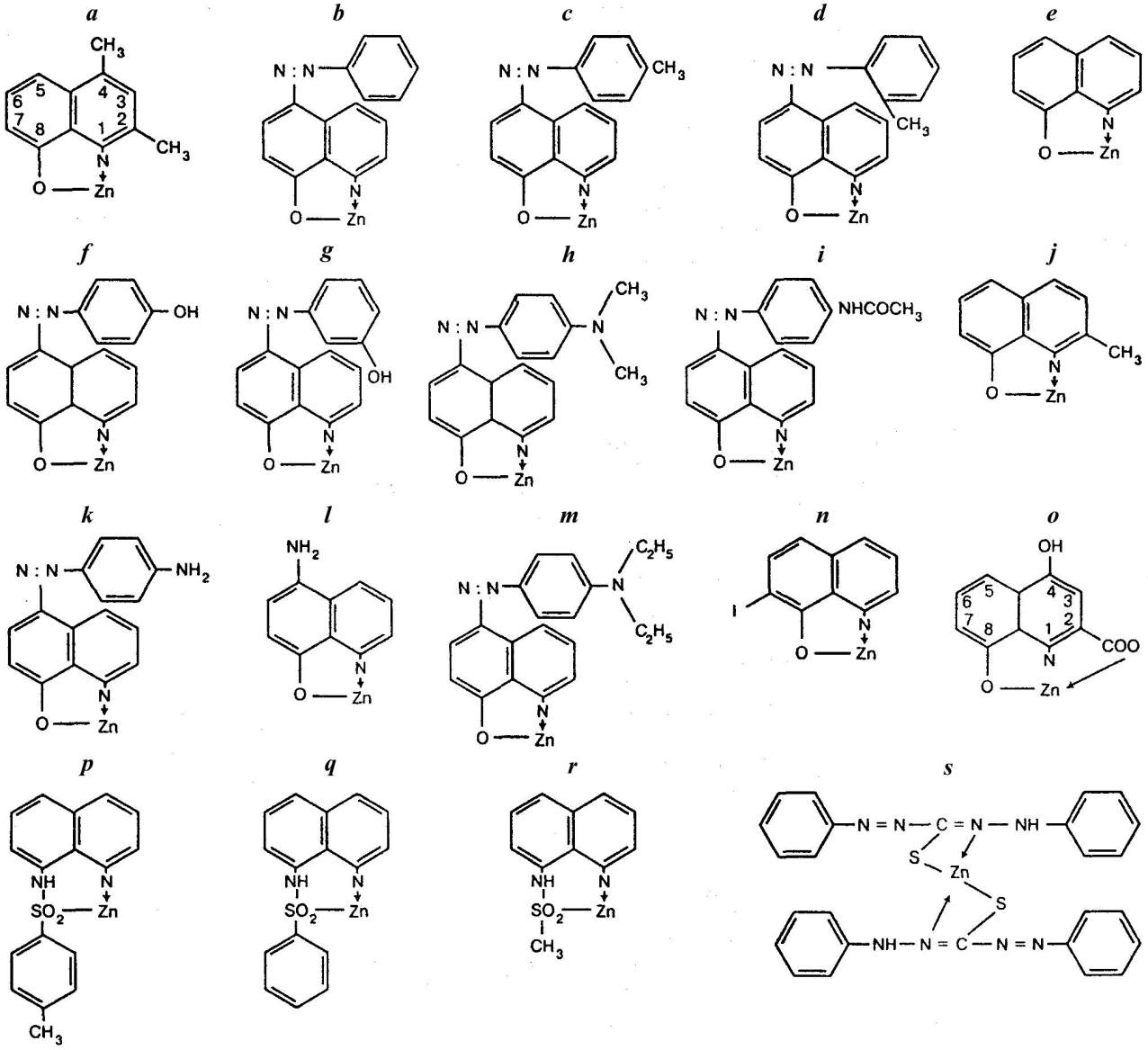
Meanwhile, T. Ueda and coll. [70] found that after dissociation of complex XA-insulin a new complex as XA-Zinc is formed. However attention to this fact was not given and this ability was not investigated. In experiences of in vitro it was shown that Xanthurenic acid interact with Zinc in B-cells that accompanied by damage of cells [57, 71, 72].

Deficiency vit. B6 stimulate metabolisation of Xanturenic acid for final product as 8-oxyquinaldinic acid whereas kynurenic acid metabolised into quinaldine acid. Both of these acids possess insulin releasing properties on model of isolated islets [50]. On the other hand, these metabolits slow down formation of B-granules as result of blocking of ions of Zinc in B-cells. 8-oxyquinaldine acid suppress proinsulin synthesis whereas kynurenic acid is in this regard less effective [69]. Besides, Xanthurenic acid slows down synthesis of insulin as a result of inhibition of binding of insulin with Zinc [28].

Disturbances of Tryptophan metabolism: as final product of metabolisation of Xanthurenic acid can be collected 8-oxyquinaldine which possess diabetogenic properties and caused hyperglycemia and developing of degenerative changes in islets [70]. Meanwhile, still nobody found this substance in blood, urine or in other biological liquids of animals. Nevertheless, it is impossible to exclude a possibility of its accumulation in an organism at disturbances of Tryptophan metabolism.

Diabetes caused by derivatives 8-oxyquinoline can be prevented by preliminary binding of Zinc by not diabetogenic chelat active chemicals or by elimination of Zinc from B-cells before action of diabetogenic ligands that protect B-cells in 90–95 % of animals of destruction for 12–24h. Meanwhile such method have not perspectives for practical application as well as method based on elimination of Zinc from B-cells: it is

almost impossible to keep Zinc ions in B-cells permanently in complex with not dia- betogenic ligands as well as to eliminate Zinc from B-cells for immeasurable period. Meanwhile, it is known that endogene synthesis of Xanthurenic acid principally may be supressed by compensation of deficiency of Pyridoxine in organism which is one of main causes of endogene synthesis of Xanthurenic acid.



a) 2,4-dimethyl-8-oxyquinoline, 35 mg/kg; *b*) 5-phenylazo-8-oxyquinoline, 20 mg/kg; *c*) 5-para (toluene)-8-oxyquinoline, 20 mg/kg; *d*) 5-orto(toluene)-8-oxyquinoline, 40 mg/kg; *e*) 8-oxyquinoline, 50–60 mg/kg; *f*) 5-para(diethylaminophenylazo)-8-oxyquinoline, 20 mg/kg; *g*) 5-meta(hydroxyphenylazo)-8-oxyquinoline, 30 mg/kg; *h*) 5-para(dimethylaminophenylazo)-8-oxyquinoline, 45 mg/kg; *i*) 5-para-(acetylaminophenylazo)-8-oxyquinoline, 50 mg/kg; *j*) 8-oxyquinaldin, 10 mg/kg; *k*) 5-para(aminophenylazo)-8-oxyquinoline, 10 mg/kg; *l*) 5-amino-8-oxyquinoline, 30 mg/kg; *m*) 5-para(diethylaminophenylazo)-8-oxyquinoline, 40 mg/kg; *n*) 9-oxy-7-iodoquinoline, 50–60 mg/kg; *o*) 4,8-dihydroxyquinolin-2 carboxylic acid (Xanturenic acid); *p*) 8-para(toluenesulphonylamino)quinoline, 30–50 mg/kg; *q*) 8-para(benzolsulphonylamino)quinoline, 30–100 mg/kg; *r*) 8-para(metansulphonylamino)quinoline, 40–81 mg/kg; *s*) diphenylthiocarbazone (dithizon), 45–50 mg/kg

Figure 2. Complex salts of Diabetogenic zincbinding chelat active chemicals with Zn-ions and its diabetogenic doses

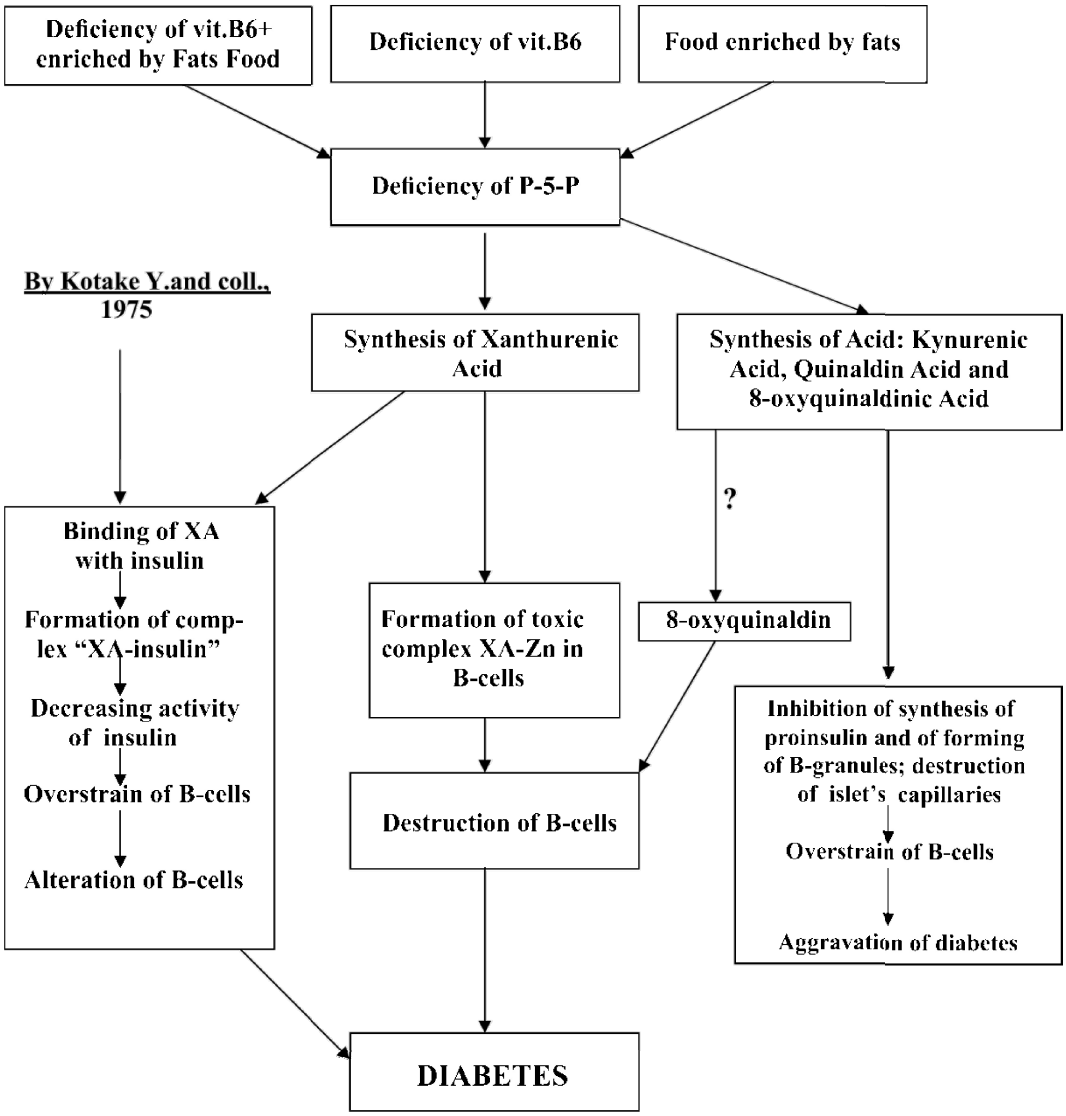


Figure 3. Mechanisms of Diabetogenic Activity of Xanthurenic Acid

As result of disturbances of Tryptophan metabolism the 8-oxyquinaldine may be accumulated in organism. Meanwhile 8-oxyquinaldine, a derivative of 8-oxyquinoline, is diabetogenic chemical which are able to induce hyperglycemia and degenerative changes in B-cells. However XA is eliminated from the organism with urine and now there are not reported facts that XA is transformed in 8-oxyquinaldine in organism. Nevertheless, we cannot to exclude this possibility.

These methods protection of B-cells which we have used in our investigations of mechanisms of developing of diabetes induced by chelat active chemicals, not have perspective for practical using because it is not possible and not expediently to keep Zn-ions in B-cells permanently connected with not diabetogenic substances or to eliminate permanently Zn-ions from the cytoplasm of B-cells or to keep cells free of Zn-ions permanently.

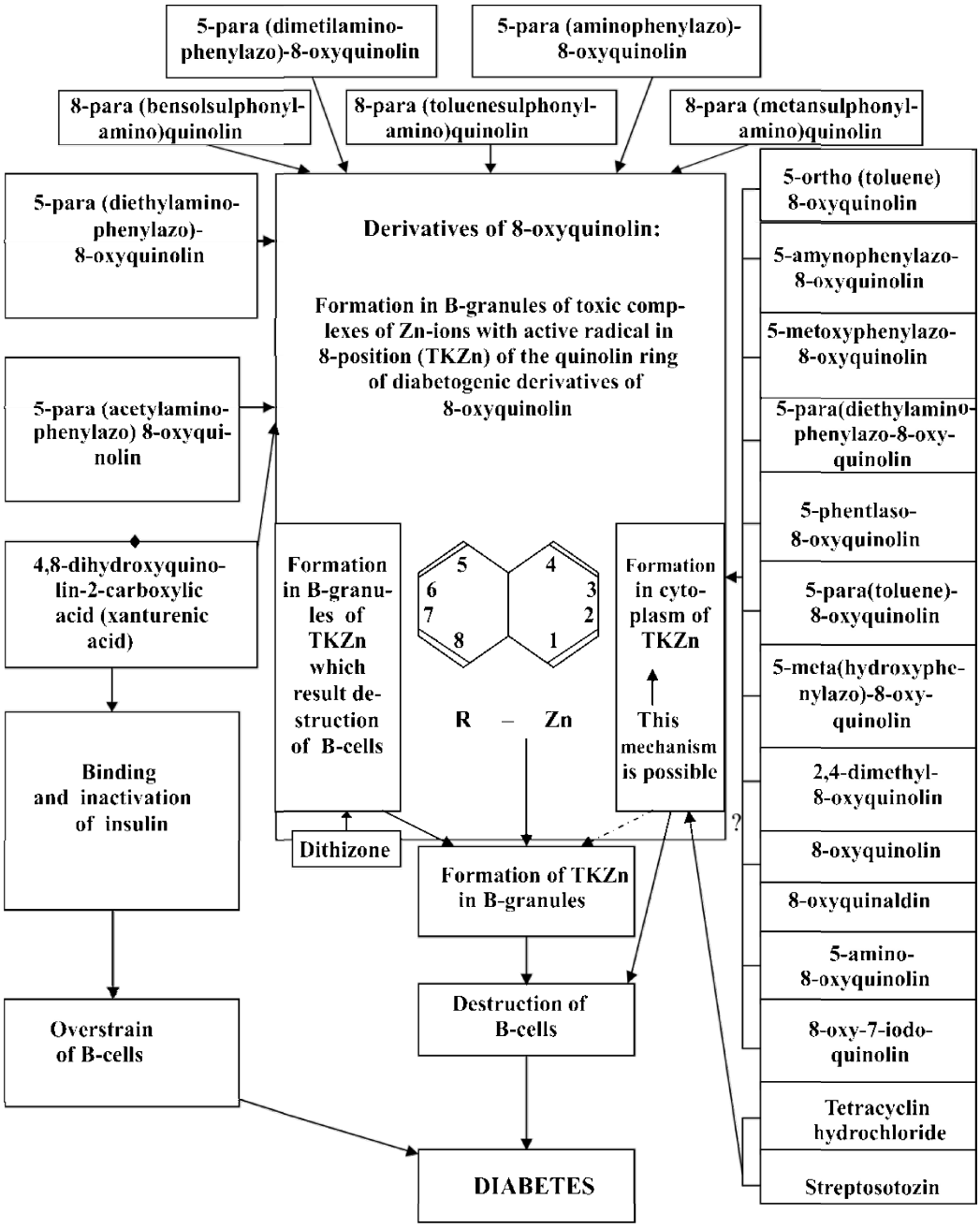
Thus, despite of fact that by aid of both methods is possible to prevent developing of experimental diabetes in 95–100 %, these methods are not suitable for protect of B-cells of XA-diabetes in human.

Now it is possible to suppose that among all metabolits of abnormal Tryptophan metabolism the main role is belong to XA. Other metabolits of tryptophan are able to aggravate diabetes induced by XA.

However it is known that synthesis of XA in organism may be prevented by administration of vitamin B6. This way for prevention developing of XA induced diabetes is, as we think, more perspective. Besides this method not need additional researches regarding practical using of vitamin B6.

Injection of other diabetogenic derivatives of 8-oxyquinolin (Fig. 2) result a few days later developing of heavy 1 type diabetes due to ability to form into cytoplasm of B-cells of toxic chelat complexes that result destruction of cells within 15–30 min. and developing of diabetes (Fig. 4, 5). Diabetes induced by XA in the

contrary developed like diabetes of 2 type. It is explained by a followed circumstances. Other diabetogenic derivatives of 8-oxyquinolin were used as one injection of diabetogenic doses of substance. In the contrary, more less amount of XA is formed in human more slowly, day by day permanently as changes of Tryptophan metabolism especially in old organism.



♦ — synthesized in human

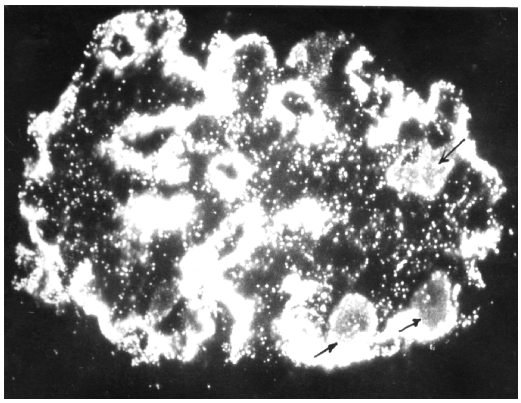
Figure 4. Mechanisms of damage of B-cells caused by diabetogenic chelat active chemicals

Interest to diabetes induced by XA is increased due to followed factors:

1) XA in the contrary to other diabetogenic derivatives of 8-oxyquinolin is formed in human organism as result of disturbances of diet in deficiency of vit. B6;

2) a large amount of XA is discovered in the urine not only of diabetic patients in middle or old age, but in the urine of persons in same age without diagnosis of diabetes;

3) deficiency of vitamin B6 is discovered in organism of old persons with registrated diagnosis of diabetes or without it.



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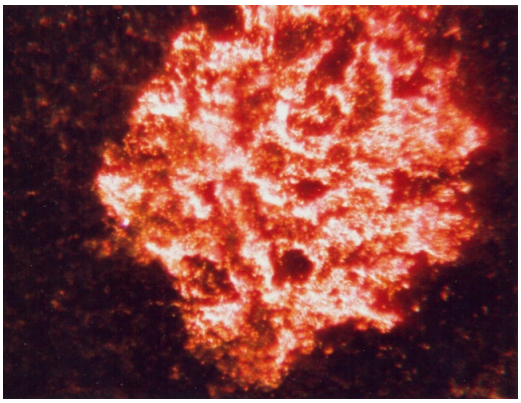

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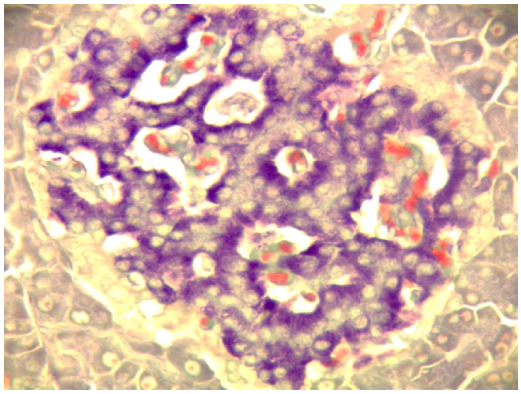

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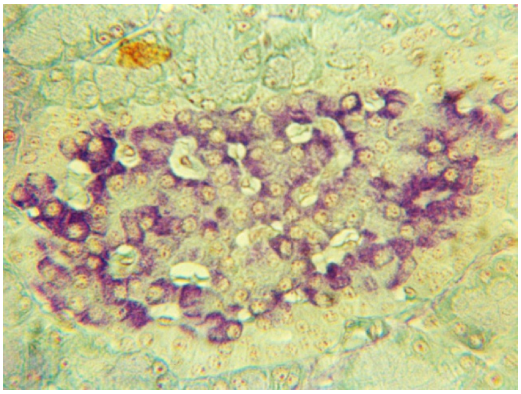

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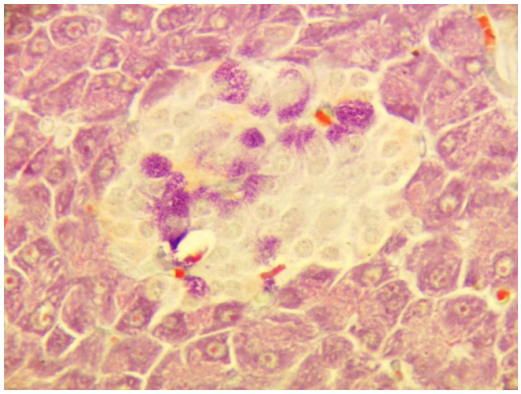

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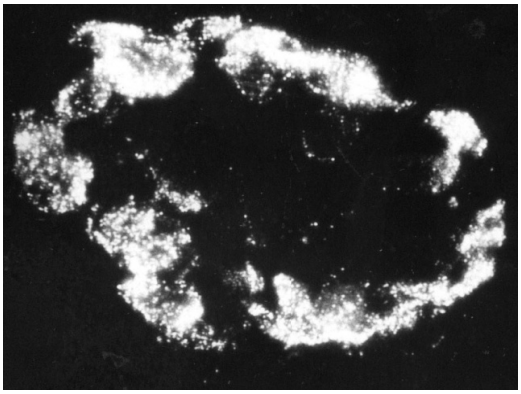

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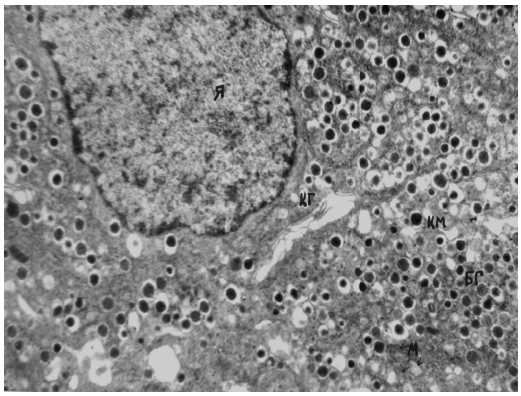
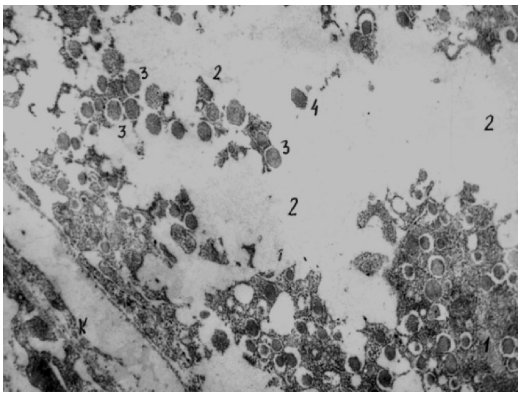


7



8

1 — Intact Rabbit. Injection of Ditizon (DZ), 31 mg/kg. Granules of complex Zn-DZ concentrated around capillaries; frozen section, 4 mcm; darc condensor; ×280; preparat and photo — by Meyramov G.G., 1964;

2 — Intact Rabbit. Injection of Ditizon (DZ), 50.6 mg/kg. Large amount of granules of complex Zn-DZ in cytoplasm of B-cells; frozen section, 5 mcm; darc condensor; ×280; preparat and photo — by Meyramov G.G., 2012;

3 — Intact Rat. Aldehydefucshin. Maximal concentration of violet granules of zinc-insulin depot form of insulin in B-cells around capillaries; ×280; preparat and photo — by Meyramov G.G., 2008;

4 — Rat with diabetes induced by endogen synthesized of XA. Aldehydefucshin. Destruction and degranulation of B-cells in central part of islet; ×280; preparat and photo — by Meyramov G.G., 2001;

5 — Rat with diabetes induced by streptosotozin, 34 mg/kg. Aldehydefucshin. Destruction and degranulation of B-cells; ×280; preparat and photo — by Meyramov G.G., 1998;

6 — Rabbit. Diabetes induced by Dithizon, 50.2 mg/kg; frozen section; darc condensor; ×280; complete destruction of B-cells in islet 30h past injection of DZ; preparat and photo — by Meyramov G.G., 1972;

7 — Intact B-cell of Rabbit. Transmission electron microscopy. Cell matrix without changes; a large amount of B-granules in cytoplasm; ×4450; preparat and photo — by Meyramov G.G., 1973;

8 — B-cells of Rabbit 2h past injection of Dithizon, 49.6 mg/kg. Transmission electron microscopy; 1 — destruction of cell matrix on 85–90 % of cell's surface; 2 — zones of cytoplasm free of matrix; 3, 4 — destroyed B-granules in zones free of matrix; ×5650; preparat and photo — by Meyramov G.G., 1973

Figure 5. Histostructure and ultrastructure of pancreatic islets in animals with diabetes caused by zincbinding chemicals (ditizon and xanthurenic acid)

Previous our investigations of mechanismes of diabetogenic action of derivatives of 8-oxyquinolin, which cannot be synthezed in organism or to come into organism outside, have theoretical significance only. However data obtained during these experiences let us to understand more profoundly mechanisms of diabetogenic action of XA. XA due to noted above data make us to keep our attention on this substance which may to have significance in pathogenesis of human diabetes.

On the base of data obtained by other investigators and by us is proposed a followed point of view on the mechanisms of diabetes induced by XA **(**Fig. 3**)**.

Thus, noted above data show a potential role of diabetogenic metabolits of tryptophan in the pathogenesis of human diabetes. From presented data it is possible to conclude that main role among a few metabolits as XA, kynurenic acid, oxyquinaldic acid, 8-oxyquinaldinic acid and 8-oxyquinaldin — are belong to XA. Kynurenic acid and oxyquinaldic acid not contain, in the contrary to XA, in position 8 of quinoline ring of active chemical group and not induced diabetes. But both these chemicals activate releasing of insulin from B-cells.

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Триптофанның диабетогендік метаболиттері

Мақалада бүгінгі таңда 30-дан астам заттардың ішінде диабетогендік химиялық заттың бірі болып табылатын, басқалардан ерекшелігі — ересек жастағы ағзада ғана түзілуге қабілетті, триптофан аминқышқылдарының алмасу өнімдерінің диабетогендік әсер ету механизмі және зерттеу әсеріне қатысты әдеби деректерге сараптама, өзіндік зерттеулер нәтижесі келтірілген. Авторлар ксантурен қышқылының гистоқұрылым күйін және В-жасушалардағы инсулин құрамын бұзу механизмдерін жан-жақты зерттеген. Осы заттар арқылы туындайтын диабетті болдырмаудың мүмкін жолдары, сонымен қатар ағзада эндогенді синтезделуді неғұрлым нақтырақ бәсеңдету жолдары жан-жақты қарастырылған.

Г.Г. Мейрамов, К.-Д. Конерт, А.Ж. Шайбек, О.-Н. Дюпонт, А.Г. Абдраимова

Диабетогенные метаболиты триптофана

В статье даны обзор и анализ литературных данных, а также результаты собственных исследований, касающихся изучения характера и механизмов диабетогенного действия продуктов нарушенного обмена аминокислоты триптофана. Она является единственным диабетогенным химическим веществом из более чем 30 известных на сегодня, которое способно, в отличие от всех других, синтезироваться в организме, особенно лиц старшего возраста. Авторами исследованы механизмы повреждающего действия основного из них — ксантуреновой кислоты, характер ее действия на состояние гистоструктуры и содержание инсулина в В-клетках. Исследованы возможные пути предотвращения развития диабета, вызываемого этим веществом, на основе чего обоснован наиболее реальный способ подавления эндогенного синтеза в организме данного вещества.

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Insulin pump in people with type 2 diabetes mellitus

Article summarizes results of important clinical studies targeting on potential benefits of continuous subcutaneous insulin infusion (CSII) by means of an insulin pump in people with type 2 diabetes. The problems are comprised into four chapters: (1) Historical introduction; (2) Effectiveness of CSII in type 1 diabetes; (3) Influence of CSII on HbA1c and global metabolic indices in type 2 diabetes; (4) Influence of temporary CSII on beta-cell recovery in recent type 2 diabetes. Conclusion: CSII appears to be an effective part of type 2 diabetes treatment aiming to early recovery of beta cell function (if introduced without delay in a recent diabetes) and to long-lasting improvement of metabolic indices (if introduced any time of diabetes development). Adequate education of pump treated persons and their family members is necessary.

Key words: diabetes mellitus, ominous octet, insulin pumps, HbA1c, Total daily insulin dose, body mass, incretins, gliflozins, metformin, therapeutic education, meta analysis.

Abbreviations:

AUC — area under the curve;
CIT — conventional insulin therapy;
CGMS — continuous glucose monitoring;
CSII — continuous subcutaneous insulin infusion;
MDI — multiple daily injections;
OHA — oral hypoglycaemic agents;
PWD1 — person with type 1 diabetes;
PWD2 — person with type 2 diabetes.

(1) Historical introduction

In the year 1921 *Paulesco* in Bucharest discovered the hypoglycaemic effect of pancreatic extract (pancrein) injected to a diabetic dog [1, 2]. Independetly, in January 1922, *Banting, Best and Collip* in Toronto first successfully used purified extract (isletin/insulin) to save life of a boy with diabetes [3, 4]. In the course of the following 50 years various insulin preparations were produced and injected by means of reusable glass syringes and needles.

In the year 1978 *Pickup* in London described a new method of insulin administration, namely, the continuous subcutanous insulin infusion (CSII) using Mill Hill Infusor [5] as the first small external personal insulin pump. Next, technical evolution together with motivating approach of physicians, nurses, health care givers, researchers and educators made insulin pumps available for more or less limited number of people with diabetes [6].

As late as five years after the first experience with a portable insulin pump, the era of manual insulin injectors (pens) started. The pens were developed since 1983 at Palacky University Olomouc and Institute of Diabetes «G. Katsch», Karlsburg (MADI, MD2) [7–9] as well as by companies Novo (Novopen) [10] and Nordisk (Insuject) followed by many others [11]. Some of the pens could be alternatively used as manually directed pumps called «catheter pens» [12–14]. Additional details have already been published elsewhere [15].

(2) Effectiveness of CSII in type 1 diabetes

Since the year 1978 several papers demonstrated the advantages of insulin pump in persons with type 1 diabetes mellitus.

Yki-Yarvinen [16] studied in 1984 the influence of CSII for 6 weeks on sensitivity to insulin (euglycemic clamp technique) and hepatic glucose production in 10 type 1 diabetic patients whose mean du-

ration of diabetes was 8 yr. The improved metabolic control resulting from pump therapy was associated with enhancement in sensitivity to insulin, and reduction in basal hepatic glucose production.

Chantelau [17] in Düsseldorf performed in 1989 a follow-up study of 116 Type 1 diabetic patients on long-term continuous subcutaneous insulin infusion and concluded that CSII has proved to be beneficial to a large proportion of experienced adult Type 1 diabetic patients, who voluntarily had opted for, and continued with, this particular mode of insulin treatment.

Chlup [18] in the year 2000 summarized experience with CSII at Olomouc Teaching Hospital Diabetes centre, including the start schedule for substitution of basal rates during the day (Fig. 1).

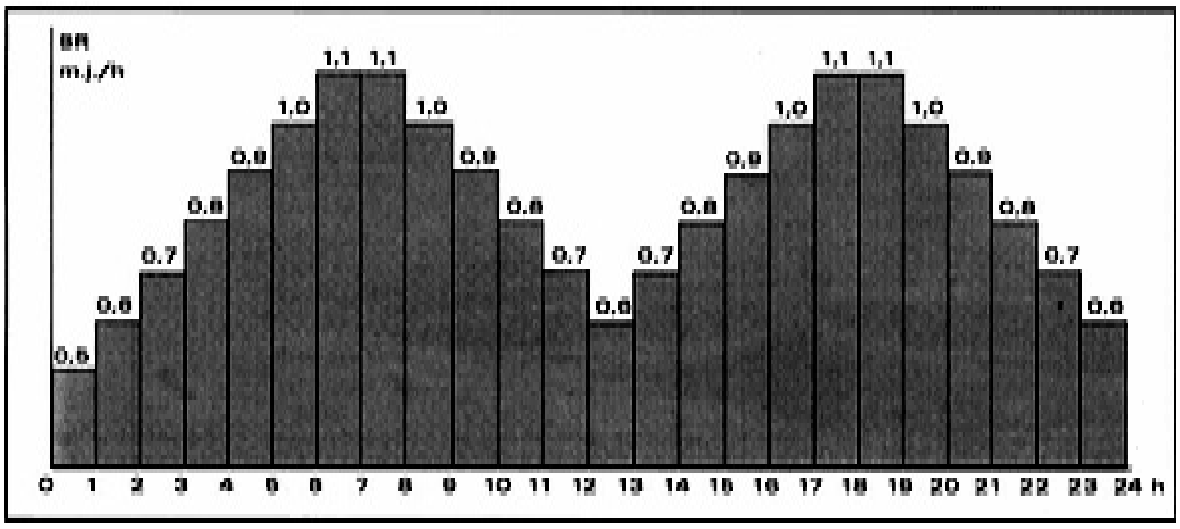

Figure 1. Basal rates in Continuous Subcutaneous Insulin Infusion (CSII) in persons with type 1 and type 2 diabetes mellitus — basal rates schedule at CSII start to be individually adopted according to plasma glucose evolution in the course of next weeks [18]

Pickup [19] performed in the year 2002 a meta-analysis of 12 randomised controlled trials to compare glycaemic control and insulin dosage in people with type 1 diabetes treated by CSII or optimised insulin injections. There were 301 people with type 1 diabetes allocated to insulin infusion and 299 allocated to insulin injections for between 2.5 and 24 months. Mean blood glucose concentration was lower in people receiving CSII compared with those receiving insulin injections (standardised mean difference 0.56, 95 % confidence interval 0.35 to 0.77), equivalent to a difference of 1.0 mmol/l. The percentage of glycated haemoglobin was also lower in people receiving insulin infusion (0.44, 0.20 to 0.69), equivalent to a difference of 0.51 %. Blood glucose concentrations were less variable during insulin infusion. This improved control during CSII was achieved with an average reduction of 14 % in insulin dose. So, glycaemic control was better during CSII compared with optimised injection therapy, and less insulin was needed to achieve this level of strict control. The difference in control between the two methods was small but should reduce the risk of microvascular complications.

Doyle [20] in the year 2004 studied the efficacy of the insulin analogs available for multiple daily injection (MDI) and CSII therapy in type 1 diabetes in pediatric patients. Lower HbA1c and premeal glucose concentrations were more achievable in this short-term study with CSII than with glargine-based MDI treatment. CSII appeared to be an efficacious treatment to improve metabolic control in youth with type 1 diabetes.

Retnakaran [21] performed in the year 2004 a pooled analysis of the randomized controlled trials that compared CSII and optimized MDI therapy using rapid-acting analogs in adults with type 1 diabetes. The three studies that met inclusion criteria provided data on 139 patients, representing 596 patient-months for CSII and 529 patient-months for MDI. Mean age was 38.5 years, with duration of diabetes of 18.0 years. When using rapid-acting insulin analogs in CSII and MDII regimens in adult patients with type 1 diabetes, insulin pump therapy was associated with better glycemic control, particularly in those individuals with higher baseline A1c. Thus, CSII emerges as an important modality for implementing intensive therapy and may be uniquely advantageous in patients with poor glycemic control.

Bruttomesso [22] in the year 2009 concluded that when compared with traditional NPH-based multiple daily injections (MDI), CSII provides a small but clinically important reduction of HbA1c concentrations,

diminishes blood glucose variability, decreases severe hypoglycaemic episodes and offers a better way to cope with the dawn phenomenon. Insulin analogues have improved the treatment of diabetes, eroding part of the place previously occupied by CSII, but CSII still remains the first option for patients experiencing severe hypoglycaemic episodes, high HbA1c values or marked glucose variability while being treated with optimized MDI. Furthermore CSII is better than MDI considering the effects on quality of life and the possibility to adjust insulin administration according to physical activity or food intake. CSII may be limited by cost. The estimates suggest that CSII may be cost-effective just for patients experiencing a marked improvement in HbA1c or a decrease in severe hypoglycaemic episodes, but the effects on quality of life are difficult to measure. CSII does not merely imply wearing an external device; it requires a multidisciplinary team, intensive patient education and continuous follow up.

In the Czech Republic, *Jankovec* [23] in the year 2010 collected patient data from the Czech National Register of patients treated with CSII to evaluate treatment indication, efficacy and safety with specific regard to the type of diabetes. Evaluation was done on complete data sets of at least 3 years from either DM 1 ($n = 730$, 93.1 %) or DM2 ($n = 54$, 6.9 %) between 1995 and 2006. HbA1c decreased from 9.65 (+/–0.07) and 9.66 (+/–0.05) for DM1 and DM2 respectively to 8.24 (+/–0.07) for DM1 and 8.52 (+/–0.27) for DM2 after 1 year of treatment, 8.34 (+/–0.07) and 8.54 (+/–0.26) after 2 years and 8.44 (+/–0.07) and 8.71 (+/–0.25) after 3 years (adjusted mean values, +/–SEM). This reduction is significant for both diabetes types. Results gathered from the safety analysis revealed almost comparable results for both patient groups (rates of adverse events of 42.5 and 34.8 for DM1 and DM2, per 100 patients and year). Both patient groups achieved substantial reduction of HbA1c. Safety evaluation showed that fewer patients with DM2 were affected by adverse events. Hence, CSII treatment DM2 is similarly effective with a slightly better safety profile.

(3) Influence of CSII on HbA1c and global metabolic indices in type 2 diabetes

Clinical evidence on CSII effectiveness for DM2 were sought for in many studies. When compared to MDI, CSII has resulted in both equivalent and lower HbA1c values. However, the studies are heterogeneous in design and subject population. Some persons with diabetes have indicated a preference for the CSII. Two questions of paramount importace need to be answered: (i) whether CSII provides incremental clinical benefits after MDI has failed in treating DM2 and (ii) whether undelayed CSII start at the time of diagnosis of DM2 may support and prolong the potential recovery of beta cell. In this chapter, attempts are made to answer the first (i) question.

Jennings [24], *1991*, compared the effects of CSII and conventional insulin therapy (CIT) in patients with poorly controlled sulfonylurea-treated diabetes mellitus. Outpatient treatment consisted of CIT (twice-daily injections of regular and NPH insulin) or CSII (basal infusion and prandial boluses of regular insulin).Glycemic control improved with both methods. Insulin treated patients achieved satisfactory control (HbA1 < 50 mmol hydroxymethylfurfural/mol Hb), whereas only 3 of 10 CIT-treated patients achieved the values of CSII. Patients' satisfaction with treatment improved during insulin therapy.

Pouwels [25], *2003*, investigated whether a period of euglycaemia using i.v. insulin, followed by CSII, would ameliorate the deleterious effects of hyperglycaemia on insulin sensitivity and result in sustained, improved metabolic kontrol in DM2 who are poorly controlled despite high-dose s.c. insulin treatment. A period of 2 weeks of euglycaemia achieved by i.v. insulin reverses hyperglycaemia-induced insulin resistance and substantially improves metabolic control. Subsequent CSII treatment, using insulin analogues, appears to maintain improved metabolic control for at least 1 year.

Raskin [26], *2003*, compared the efficacy, safety, and patient satisfaction of CSII with MDI therapy for patients with type 2 diabetes. A total of 132 CSII-naive MD2 were randomly assigned (1:1) to CSII (using insulin aspart) or MDI therapy (bolus insulin aspart and basal NPH insulin) in a multicenter, open-label, randomized, parallel-group, 24-week study. Efficacy was assessed with HbA1c and eight-point blood glucose (BG) profiles. Treatment satisfaction was determined with a self-administered questionnaire. Safety assessments included adverse events, hypoglycemic episodes, laboratory values, and physical examination findings. A total of 93 % of CSII-treated subjects preferred the pump to their previous injectable insulin regimen for reasons of convenience, flexibility, ease of use, and overall preference. Safety assessments were comparable for both treatment groups. Insulin aspart in CSII provided efficacy and safety comparable to MDI therapy. Patients with type 2 diabetes can be trained as outpatients to use CSII and prefer CSII to injections, indicating that pump therapy should be considered when initiating intensive insulin therapy for type 2 diabetes.

Herman [27], *2005*, compared the efficacy and safety of CSII and MDI in older adults with insulin-treated type 2 diabetes and assessed treatment satisfaction and quality of life in 107 adults. Forty-eight CSII subjects (91 %) and 50 MDI subjects (93 %) completed the study. Mean A1C fell by 1.7 ± 1.0 % in the CSII group to 6.6 % and by 1.6 ± 1.2 % in the MDI group to 6.4 %. The difference in A1C between treatment groups was not statistically significant (P=0.20). Eighty-one percent of CSII subjects and 90 % of MDI subjects experienced at least one episode of minor (self-treated) hypoglycemia (P=0.17), and three CSII and six MDI subjects experienced severe hypoglycemia (P=0.49). Rates of severe hypoglycemia were similarly low in the two groups (CSII 0.08 and MDI 0.23 events per person-year, P=0.61). body mass gain did not differ between groups (P=0.70). Treatment satisfaction improved significantly with both CSII and MDI (P=0.0001), and the difference between groups was not statistically significant (P=0.58). Hence, in older subjects with insulin-treated type 2 diabetes, both CSII and MDI achieved excellent glycemic control with good safety and patient satisfaction.

Wainstein [28], *2005*, compared the efficacy of insulin pump treatment with multiple daily injections in the treatment of poorly controlled obese PWD2 already receiving two or more daily injections of insulin plus metformin. Forty obese PWD2 using insulin were randomized to CSII or MDI. At the end of the first 18-week treatment period, patients underwent a 12-week washout period during which they were treated with MDI plus metformin. Then they were crossed-over to the other treatment for an 18-week follow-up period. Patients performed 4-point daily self blood-glucose monitoring (SBGM) on a regular basis and 7-point monitoring prior to visits 2, 8, 10 and 16. A subset of patients underwent continuous glucose monitoring (CGMS, Minimed) at visits 2, 8, 10 and 16. A standard meal test was performed in which serum glucose was tested at fasting and once each hour for 6 h following a test meal. Glucose levels were plotted against time and the area under the curve (AUC) was calculated. HbA1c, body mass, daily insulin dose and hypoglycaemic episodes were recorded. Treatment with CSII significantly reduced HbA1c levels compared with treatment with MDI. An additional CSII benefit was demonstrated by reduced meal-test glucose AUC. Initial reduction of daily insulin requirement observed in CSII-treated subjects during the first treatment period was attributable to a period effect and did not persist over time. So, in the intent-to-treat analysis, CSII appeared to be superior to MDI in reducing HbA1c and glucose AUC values without significant change in body mass or insulin dose in obese, uncontrolled, insulin-treated Type 2 diabetic subjects.

Lane [29], *2006*, determined the safety and efficacy of U-500 regular insulin delivered by CSII as treatment for PWD2 (n = 9) and severe insulin resistance (mean 24-hour insulin requirement, 1.46 U/kg daily) who had failure of previous insulin therapy with either MDI or CSII using U-100 insulin analogues. After 3 months, treatment with U-500 regular insulin by CSII resulted in mean decrease in HbA1c (P = 0.026) of 1.14 %, a marginal mean increase in body mass of 4.1 lb (P = 0.078), no significant change in total daily insulin dose (P = 0.622), and no clinically significant hypoglycemic episodes. Moreover, all study patients preferred the new treatment option over their previous regimens. So, U-500 regular insulin by CSII is a safe and effective therapeutic intervention for patients with type 2 diabetes who have had treatment failure with MDI insulin regimens or CSII with use of U-100 insulin or insulin analogues.

Berthe [30], *2007*, compared the effectiveness of two intensified insulin regimens, i.e., pump delivery versus multiple daily injections in PWD2 (n = 17) not optimally controlled with CIT by two daily injections of regular plus NPH; they were randomly assigned in a cross-over fashion to either three daily injections of lispro plus NPH or pump device delivering lispro. HbA1c, 6 points capillary blood glucose, 24-hour CGMS and global satisfaction score were evaluated at the end of each 12-week treatment period. Pump therapy provides a better metabolic control than injection regimens, and seems to be safe and convenient in PWD2 who fail to respond to CIT.

Labrousse-Lhermine [31], *2007*, compared over 3 years the efficacy of two treatment regimens combining CSII and oral hypoglycaemic agents (OHA) in PWD2 with HbA1cs>8 % despite OHA+/–insulin. Fifty-nine patients were randomized. During the 3 years follow-up, overall mean HbA1c values decreased similarly for both groups from baseline (9.45+/–0.83 %) to 1, 2, 3 years (7.76+/–0.85 %; 8.06+/–1.10 %; 8.27+/–1.06 % $P < 0.0001$). The mean frequency of minor hypoglycaemia was 1.3+/–2.3 events per month per patient and 14 severe hypoglycaemic events occurred with no difference between the two groups. In both groups we observed a significant and similar body mass gain and improvement in quality of life. Hence, long-term combination therapy with OHA and CSII with only basic manipulation and optimization of insulin doses exerted on basal rate or on boluses is feasible, effective and well accepted in PWD2.

Jeitler [32], *2008*, compared the effects of CSII with MDI on glycaemic control, risk of hypoglycaemic episodes, insulin requirements and adverse events in type 1 and type 2 diabetes mellitus. The electronic data-

bases MEDLINE, EMBASE and CENTRAL were systematically searched for randomised controlled trials up to March 2007. A systematic review and meta-analysis were performed. Overall, 22 studies were included (17 with PWD1, 2 with PWD2, 3 with children). In PWD1, our meta-analysis found a between-treatment difference of −0.4 % HbA1c (six studies) in favour of CSII therapy. Available median rates of mild or overall hypoglycaemic events were comparable between the different interventions (1.9 [0.9–3.1] [CSII] vs 1.7 [1.1–3.3] [MDI] events per patient per week). Total daily insulin requirements were lower with CSII than with MDI therapy. In PWD2, CSII and MDI treatment showed no significant difference for HbA1c. In adolescents with type 1 diabetes mellitus, glycated haemoglobin and insulin requirements were significantly lower in the CSII groups; no data were available on hypoglycaemic events. So, CSII in adults and adolescents with type 1 diabetesmellitus resulted in a greater reduction of HbA1c. No beneficial effect of CSII therapy could be detected for PWD2.

Chlup [33], *2009*, demonstrated that CSII in PWD2 may in comparison to MDI improve the metabolic control with less insulin and was from all investigated PWD2 well accepted.

Health Quality Ontario [34], *2009*. In June 2008, the Medical Advisory Secretariat began work on the Diabetes Strategy Evidence Project, an evidence-based review of the literature surrounding strategies for successful management and treatment of diabetes. The objective of this analysis is to review the efficacy of CSII pumps as compared to MDI for the type 1 and type 2 adult diabetics. The database search identified 519 relevant citations published between 1996 and March 24, 2009. Of the 519 abstracts reviewed, four RCTs and one abstract met the inclusion criteria outlined above. While efficacy outcomes were reported in each of the trials, a meta-analysis was not possible due to missing data around standard deviations of change values as well as missing data for the first period of the crossover arm of the trial. Meta-analysis was not possible on other outcomes (quality of life, insulin requirements, frequency of hypoglycemia) due to differences in reporting. HBA1C: In studies where no baseline data was reported, the final values were used. Two studies (Hanaire-Broutin et al. 2000, Hoogma et al. 2005) reported a slight reduction in HbA1c of 0.35 % and 0.22 % respectively for CSII pumps in comparison to MDI. A slightly larger reduction in HbA1c of 0.84 % was reported by DeVries et al.; however, this study was the only study to include patients with poor glycemic control marked by higher baseline HbA1c levels. One study (Bruttomesso et al. 2008) showed no difference between CSII pumps and MDI on Hba1c levels and was the only study using insulin glargine (consistent with results of parallel RCT in abstract by Bolli 2004). While there is statistically significant reduction in HbA1c in three of four trials, there is no evidence to suggest these results are clinically significant. Three of four studies reported a statistically significant reduction in the mean daily blood glucose for patients using CSII, though these results were not clinically significant. One study (DeVries et al. 2002) did not report study data on mean blood glucose but noted that the differences were not statistically significant. There is difficulty with interpreting study findings as blood glucose was measured differently across studies. Three of four studies used a glucose diary, while one study used a memory meter. In addition, frequency of self monitoring of blood glucose (SMBG) varied from four to nine times per day. Measurements used to determine differences in mean daily blood glucose between the CSII pump group and MDI group at clinic visits were collected at varying time points. Two studies use measurements from the last day prior to the final visit (Hoogma et al. 2005, DeVries et al. 2002), while one study used measurements taken during the last 30 days and another study used measurements taken during the 14 days prior to the final visit of each treatment period. All four studies showed a statistically significant reduction in glucose variability for patients using CSII pumps compared to those using MDI, though one, Bruttomesso et al. 2008, only showed a significant reduction at the morning time point.

Parkner [35], *2008*, compared insulin and glucose profiles during basal CSII of a rapid-acting insulin analogue and once daily subcutaneous injection of a long-acting insulin analogue in PWD2. Twenty-one PWD2 diabetes treated with oral glucose-lowering agents were randomized in this two-period crossover study to an equivalent 24-h dose of CSII of insulin aspart and subsequently once-daily bedtime subcutaneous injection of insulin glargine, or vice versa, for eight consecutive days. Plasma profiles of insulin and glucose were recorded. Basal CSII of a rapid-acting insulin analogue improved plasma insulin (more flat insulin profile with a lower variability) and glucose (lower AUC) profiles compared with once-daily subcutaneous injection of a long-acting insulin analogue in PWD2.

Edelman [36], *2010*, demonstrated that CSII using a simple dosing regimen significantly improved glycemic control in PWD2. Patients experienced limited body mass gain, there was no severe hypoglycemia, and overall treatment preference improved significantly.

Monami [37], *2009*, compared CSII and MDI for at least 12 weeks in PWD2 assessing between-group differences in HbA1c and insulin daily dose at endpoint, and incidence of hypoglycemia. However data do not justify the use of CSII for basal-bolus insulin therapy in type 2 diabetes.

Chlup [38], *2010*, in an open prospective uncontrolled study compared develop- ment of HbA1c concentration, daily insulin dose, BMI and well-being in PWD2 using IP. Data are presented as medians with minimum and maximum values. A total of 44 poorly controlled PWD2 previously on intensive plasma glucose selfmonitoring (up to 10 measurements/d) and supplementary insulin therapy, aged 58.5 (27–75) y, diabetes duration 13 (0–36) y, C-peptide 534.5 (101–4038) nmol/l, 33 men, were put on IP (various models; short-acting insulins or insulin aspart were used) and checked in 1- to 3-month intervals as before. Well-being incl. satisfaction with the IP therapy was assessed according to the routine questionnaire and interviews. Wilcoxon Signed Ranks Test was applied to compare the results (Table 1).

Table 1

Comparison of investigated parameters before IP (at start) and at the last check-up of the period on IP (*n* = 44)

Parameter	Before IP median (min – max)	Last check-up on IP median (min – max)	Difference	P (Wilcoxon)
HbA_{1c} (IFCC[a]) [%]	7.3 (3.9–14.1)	6.8 (2.9–12.0)	0.4 (–3.9–9.6)	0.560
Insulin aspart [IU/d]	48.0 (16–138)	37.9 (1.2–87)	11.0 (–45–101)	0.0003
BMI [kg/m^2]	30.9 (21.2–42.5)	30.7 (24.5–41.8)	0.3 (–5.3–6.7)	0.763
Well-being (satisfaction with therapy)	unsatisfactory	satisfactory	improved (in 43/44PWD2)	N/A

[a] Conversion of HbA1c values: NGSP = (0.915 * IFCC) + 2.15 [%].

The treatment period on IP lasted 3.0 (0.1–8) y. One PWD2 gave up using the pump 2 y after the start due to discomfort. Eight PWD2 died (coronary heart disease 3, stroke 2, Alzheimer disease 2, renal failure 1) at the age of 68 (66–78) y and diabetes duration of 23.5 (15–34) y having used the pump for 4 (2–6) y. In this trial, IP therapy contributed to a significant reduction of insulin dose/d, and, in approximately 50 % of PWD 2 to a better metabolic control in comparison to conventional therapy. There was no change in BMI. IP was well accepted in the majority of educated PWD2.

Rubin [39], *2010*, found out that insulin pump therapy improved qualitz of life and treatment preference in PWD2.

Bode [40], *2010*, performed a metaanalysis of CSII treatments for PWD2 and foud out that large randomized controlled trials have concluded that CSII was equivalent to MDI, whereas smaller trials have concluded that CSII was superior. The presently available evidence demonstrates that CSII improves glucose control, even with a simple insulin regimen. CSII also improves measures of quality of life and treatment satisfaction. As such, CSII may be a suitable option for PWD2 who have not reached their glycemic goals.

Reznik [41], *2010*, evaluated the long-term efficacy of CSII for treating PWD2 uncontrolled by MDI and concluded that the use of CSII in PWD2 is safe and effective for improving glycemic control, particularly in those patients with baseline HbA1c above 8 %. Such beneficial effect of CSII may persist until 6-year follow-up, suggesting the durability of CSII efficacy in our study population

Peyrot [42], *2011*, assessed the relationship between changes in glucose control and changes in patient-reported outcomes (PRO)—health-related quality of life (HR-QoL) and treatment satisfaction (TxSat) — in PWD2 initiating insulin pump therapy. Findings suggest that A1C, representing an «average» of both high and low blood glucose values throughout the day, may not capture aspects of glucose control with the greatest impact on HR-QoL. Although TxSat was more strongly associated with A1C and mean glucose readings than with glycemic variability, HR-QoL was more strongly associated with glycemic variability.

King [43], *2012*. It has been reported that most pump-treated PWD2 require only two or fewer basal rates. Using daily continuous glucose monitoring (CGM)-directed titration, this premise was re-evaluated at near-normal glycemic control. This study confirms that one basal rate is adequate for the majority of subjects with type 2 diabetes. The mathematical proportionality between dosing factors closely agrees with those obtained in CGM-titrated pump-treated type 1 diabetes but differs from those derived from clinical studies in

which insulin titration was based on infrequent self-monitored plasma glucose testing and while on an unstructured diet.

Aronson [44, 45], *2014*, reported on the ongoing project: OpT2mise study is a multicenter, randomized, trial comparing CSII with MDI in a large cohort of subjects with evidence of persistent hyperglycemia despite previous MDI therapy.

Reznik [44, 45], *2014*, reported on first outcomes of study OpT2mise: 495 of 590 screened patients entered the run-in phase and 331 were randomised (168 to pump treatment, 163 to MDI). Mean glycated haemoglobin at baseline was 9 % (75 mmol/mol) in both groups. At 6 months, mean glycated haemoglobin had decreased by 1,1 % (SD 1,2; 12 mmol/mol, SD 13) in the pump treatment group and 0,4 % (SD 1,1; 4 mmol/mol, SD 12) in the MDI group, resulting in a between-group treatment difference of −0,7 % (95 % CI −0,9 to −0,4; −8 mmol/mol, 95 % CI −10 to −4, p<0,0001). At the end of the study, the mean total daily insulin dose was 97 units (SD 56) with pump treatment versus 122 units (SD 68) for MDI (p<0,0001), with no significant difference in body mass change between the two groups (1,5 kg [SD 3,5] vs 1,1 kg [3,6], p = 0,322). Two diabetes-related serious adverse events (hyperglycaemia or ketosis without acidosis) resulting in hospital admission occurred in the pump treatment group compared with one in the MDI group. No ketoacidosis occurred in either group and one episode of severe hypoglycaemia occurred in the MDI group. Hence, in patients with poorly controlled type 2 diabetes despite using MDI of insulin, pump treatment can be considered as a safe and valuable treatment option.

Reznik [46], *2014*. Insulin pump therapy may be offered to PWD2 not controlled by MDI. PWD2 may suffer from unrecognized cognitive disabilities, which may compromise the use of a pump device.A total of 39 PWD2 from our database (n = 143) after CSII initiation using (1) an autonomy questionnaire evaluating the patient's cognitive and operative capacities for CSII utilization, (2) the Montreal Cognitive Assessment (MOCA) for the detection of mild cognitive disabilities, (3) the Hospital Anxiety and Depression Scale (HADS) for the detection of anxiety and depression, and (4) the Diabetes Treatment Satisfaction Questionnaire (DTSQ) were evaluated. Patients were selected to constitute 3 groups matched for age, with different degrees of autonomy at discharge after the initial training program: complete (n = 13), partial (n = 13), or no autonomy (n = 13). The satisfaction level with the pump device was high. At the last follow-up visit, only 23 % of patients did not reach complete autonomy. The autonomy score correlated fairly with the MOCA score (R = 0.771, P <.001). A receiver operating characteristic (ROC) analysis showed that at a cut-off score of 24, the MOCA identified autonomous versus dependent patients at long-term follow-up (area under the ROC curve [AUC], 0.893; sensitivity, 81 %; specificity, 81 %). The HADS correlated negatively with the autonomy score, and the sociocultural level also influenced autonomy with pump utilization. Hence. PWD2 with partial autonomy at discharge may progress to complete autonomy. The MOCA and HADS may help predict a patient's ability to manage with a pump device.

Chlup [47], *2015*, reported on a prospective single-center study which recruited insulin-resistant CSII-naive PWD2, uncontrolled, using insulin analogues-based MDI therapy (+ metformin). Insulin dosing was optimized over an 8-week run-in period and subjects with persistent HbA1c ≥8 % were randomly assigned to the CSII arm or to MDI continuation arm to explore global metabolic improvement: glucose control, body mass loss, reduction of insulin and insulin resistance. After 6 months, the MDI arm crossed over to CSII therapy as well. A total of 23 PWD2 (16 men) were randomized (mean±SD, age 57.6±7.94 y, BMI 35.4±6.54 kg/m^2, diabetes duration 14.3±5.93 y, HbA1c 10.0±1.05 %). At 6 months, subjects, assigned to the CSII arm, achieved a significant mean HbA1c reduction of –0.9 % (95 % CI = –1.6, –0.1) while reducing their total daily insulin dose (TDD) by –29.8±28.41 U/d (33 % of baseline 92.1±20.35U/d) and achieving body mass reduction of –0.8±5.61 kg (0.98 % of baseline 104.8±16.15 kg). PWD2 on MDI demonstrated a non-significant HbA1c reduction of –0.3 % (95 % CI = –0.8, 0.1) with TDD reduction of 5 % from baseline 99.0±25.25 U/d to 94.3±21.25 U/d, and body mass reduction of –1.0±2.03 kg (0.99 % of baseline 108.9±20.55 kg). At 12 months, patients continuing on CSII demonstrated an additional mean 0.7 % HbA1c reduction with 54.6 % achieving HbA1c<8 %. TDD and body mass increased during the perusing 6 months, the final reduction achieved in TDD was –9.7 U/d in comparison to baseline; body mass increased by 1.1 kg from baseline. MDI patients crossed to CSII showed a HbA1c reduction of –0.5±1.04 %, HbA1c response rate 27.3 %, TDD reduction of –17.4±21.06 U/d and body mass reduction of –0.3±3.39 kg. No ketoacidosis or severe hypoglycemia occurred in either group. Hence, in insulin resistant PWD2, CSII significatively and safely improved meta- bolic control with less insulin and with no sustainable reduction of body mass.

Thrasher [48], *2015*, provided clinical information regarding the use of insulin lispro versus insulin aspart in CSII in adult PWD2. Insulin lispro and insulin aspart performed similarly after 16 weeks of treat-

ment, with noninferiority for HbA1c and no significant difference in parameters measured. These findings indicate that insulin lispro and insulin aspart can both be used safely and effectively in PWD2 using CSII.

Conget [44, 45, 49, 50], *2016*, reported on the OpT2mise randomized trial designed to compare the effects of CSII and MDI on glucose profiles in PWD2. Changes in glucose profiles were evaluated using continuous glucose monitoring data collected over 6-day periods before and 6 months after randomization. After 6 months, reductions in HbA1c were significantly greater with CSII (–1.1 – 1.2 % [–12.0 –13.1 mmol/mol]) than with MDI (–0.4 – 1.1 % [–4.4 – 12.0 mmol/mol]) ($P < 0.001$). Similarly, compared with patients receiving MDI, those receiving CSII showed significantly greater reductions in 24-h mean sensor glucose (SG) (treatment difference, –17.1 mg/dL; $P = 0.0023$), less exposure to SG > 180mg/dL (–12.4 %; $P = 0.0004$) and SG > 250mg/dL (–5.5 %; $P = 0.0153$), and more time in the SG range of 70–180 mg/dL (12.3 %; $P = 0.0002$), with no differences in exposure to SG < 70 mg/dL or in glucose variability. Changes in postprandial (4-h) glucose area under the curve 180 mg/dL were significantly greater with CSII than with MDI after breakfast (–775.9 – 1,441.2 mg/dL/min vs. –160.7 – 1,074.1 mg/dL/min; $P = 0.0015$) and after dinner (–731.4 – 1,580.7 mg/dL/min vs. –71.1 – 1,083.5 mg/dL/min; $P = 0.0014$). Hence, compared with MDI, CSII treatment in suboptimally controlled PWD2 provides a significant improvement in glucose profile, with increased time spent within target ranges and less exposure to hyperglycemia, without increasing time spent in hypoglycemia.

Aronson [44, 45, 49, 50], *2016 (Randomized multicentric study Opt2mise 2011–2014).* This overview deals with the first outcomes of the 4-year study (Opt2mise) to compare insulin pump therapy and (MDI) (Table 2) in PWD2 diabetes receiving basal and prandial insulin analogues. After a 2-month dose-optimization period, 331 patients with glycated haemoglobin (HbA1c) levels ≥8.0 % and ≤12 % were randomized to pump therapy or continued MDI for 6 months [randomization phase (RP)]. The MDI group was subsequently switched to pump therapy during a 6-month continuation phase (CP). The primary endpoint was the between-group dif- ference in change in mean HbA1c from baseline to the end of the RP. The mean HbA1c at baseline was 9 % in both groups. At the end of the RP, the reduction in HbA1c was significantly greater with pump therapy than with MDI (–1.1±1.2 % vs –0.4±1.1 %; $p < 0.001$). The pump therapy group maintained this improvement to 12 months while the MDI group, which was switched to pump therapy, showed a 0.8 % reduction: the final HbA1c level was identical in both arms. In the RP, total daily insulin dose (TDD) was 20.4 % lower with pump therapy than with MDI and remained stable in the CP. The MDI-pump group showed a 19 % decline in TDD, such that by 12 months TDD was equivalent in both groups. There were no dif- ferences in body mass gain or ketoacidosis between groups. In the CP, one patient in each group experienced severe hypoglycaemia. Hence, pump therapy has a sustained durable effect on glycaemic control in uncontrolled type 2 diabetes (see Fig. 2 and Fig. 3).

In addition, several studies demonstrated further improvement of metabolit indices in PWD 1 and in PWD 2 treated by means of an insulin pump when continuous glucose monitoring have been used (so called sensor augmented CSII). We have participated in the following studies.

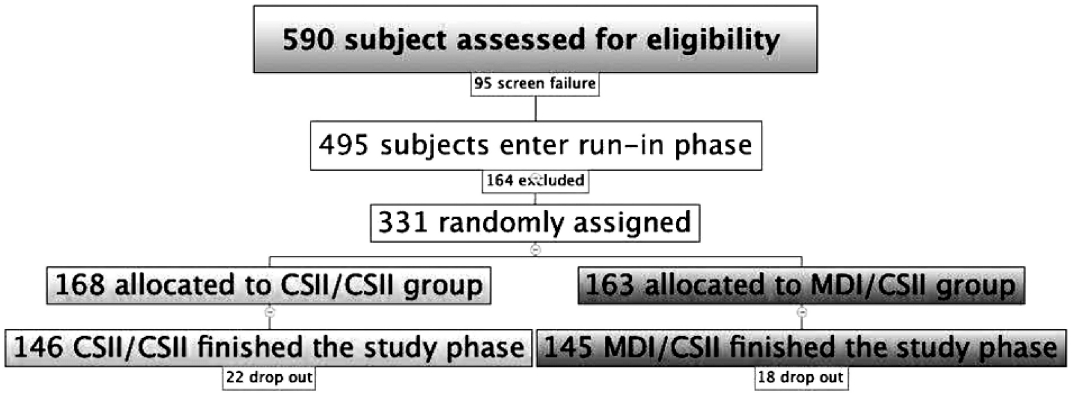

Figure 2. Study OpT2mise: Randomization of PWD2 at the end of run-in period [44, 45, 49, 50]

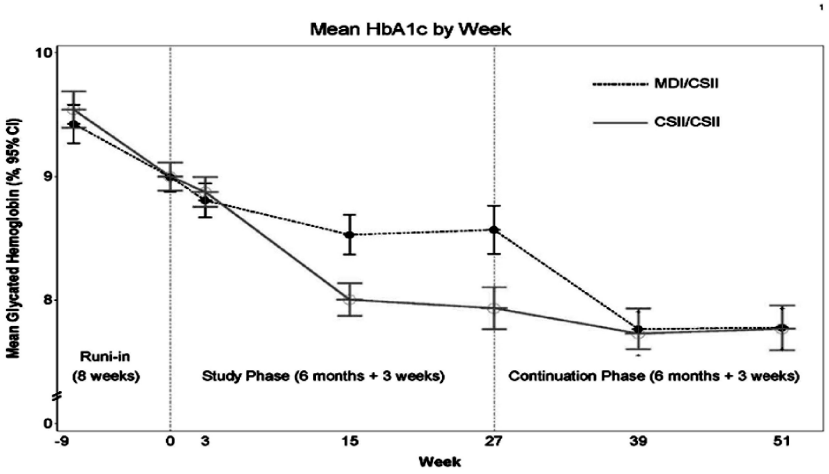

Figure 3. Devolpement of HbA1c in the course of run-in period and throughout the study and continuation phase in MDI/CSII arm and CSII/CSII arm [50]

Table 2

Selected studies comparing CSII and MDI in PWD2

Author	Year	Ref.	Type	*n*	Observ. time	Assessed parameters						
						A1c	Ins./D.	BM	Hypo.	Keto.	Satisf.	Satisfaction Results
Raskin	2003	26	Parallel randomized	132	6 m	+	+	+	+	–	+	Posit. for CSII
Herman	2005	27	Parallel	107	1 y	+	–	–	+	–	+	Posit. for CSII
Wainstein	2005	28	Crossover randomized	40	18 w	+	+	+	+	–	+	Posit. for CSII
Labrousse..	2007	31	Parallel	51	3 y	+	–	+	+	–	+	Posit. in both groups
Chlup	2010	38	Prospective observational	44	0,1–8 y	+	+	+	–	–	+	43 % use CGSM after the study
Reznik	2010	41	Retrospective observational	102	0–13 y	+	+	+	–	–	–	–
Aronson Reznik Conget Aronson	2014 2014 2015 2016	44 45 49 50	Multicenter crossover randomized	331	1 y	+	+	+	+	+	–	–
Chlup	2015	48	Prospective single center	23	1 y	+	+	+	+	+	–	–

Note. Ref. — refference number of citation in resources; *n* — number of patients in the study; Observ. Time — observation time; w — week; m — month; y — year; A1c — HbA1c; Ins/D. — dosage of insulin per day; BM — body-mass; Hypo. — hypoglycemia; Keto. — ketoacidosis; Satisf. — satisfaction with the treatment; Labrousse.. — Labrousse-Lhermine.

Mlčák [51], *2004*. This pilot study deals with the possibilities of a CGMS (Minimed-Medtronic) to optimize insulin substitution. Ten persons with type 1 diabetes mellitus treated by means of an insulin pump entered the study and eight of them completed the protocol. CGMS was introduced for a period of 5 days. The standard dinner (60 g of carbohydrates) and overnight fasting were designed to ensure standard night conditions in all persons in the study while maintaining their usual daily eating routine, physical exercise and assessment of prandial insulin boluses. The only adaptation of basal rates of insulin pump was performed on day 3. Comparison of the mean plasma glucose concentration (0:00–24:00 hrs) between day 2 (before adaptation) and day 4 (following adaptation) was made. An independent comparison of the mean plasma glucose concentration between the night from day 2 till day 3 (22:00–6:00 hrs) and the night from day 4 till day 5

(22:00–6:00 hrs) was performed. The mean plasma glucose investigated by means of CGMS improved in the 24-hour period in 5 out of 8 persons and in the night fasting period (22:00 to 6 hrs) in 6 out of 8 persons. The CGMS is a useful means for assessment of the effectiveness of basal rate and prandial insulin doses in persons with type 1 diabetes treated by means of an insulin pump.

Chlup [52], *2008*. The aim of this prospective study was to asses the demands for long-lasting use of sensors in persons with diabetes (PWD) on insulin pumps. Forty PWD aged 19 to 83 years, duration of diabetes 1 to 44 years, using insulin pump Paradigm X22 were given a concise 30-min lecture on CGM and offered transcutaneous sensors for a 3-month period free of charge. The education of PWD was performed individually or in small groups by an experienced educator. Several months later the same offer was repeated. The diabetes control at start and end of the study was compared. Twenty two of 40 PWD (55 %) accepted the suggestion and entered the 3-month sensor study. The reasons for a primary sensor refusal ($n = 18$, 45 %) were insufficient educational capacity of the center ($n = 9$), lack of time due to occupation ($n = 5$) or family ($n = 2$) and blindness ($n = 1$), nevertheless, 13 of them (33 % of 40) would be interested in a short use of sensor (up to one week) without being involved in the study. In the course of 3 study-weeks, 5 persons (12 %) interrupted CGM due to technical problems with the transmitter ($n = 1$) or due to personal reasons ($n = 4$); To date, 17 PWD (43 %) are using the sensor continuously, all of them are showing interest in long-lasting use in the future. Hence, the sensors (free of charge) are demanded for long-lasting use by about 43 % of PWDs on insulin pumps Paradigm X22. The main reason for the CGM denial was the insufficient educational capacity of the diabetes center.

Peterson [53], *2009*. The Paradigm 722 insulin pump, Medtronic MiniMed, USA, enables daily reading of 288 interstitial fluid glucose concentrations determined by a sensor inserted into subcutaneous tissue; the sensor signals are transmitted into the insulin pump, enabling the patient to see real-time glucose concentration on the display and adapt further treatment. The purpose of this study was to assess the evolution of HbA1c over the course of a 3-month period in two cohorts of PWD1 ($n = 39$) or PWD2 ($n = 3$) diabetes (PWD): 1) PWD on Paradigm 722 using sensors for continuous glucose monitoring (CGM group), 2) PWD on other types of insulin pumps performing intensive self-monitoring as before (3 to 6 times/d) on glucometer Linus, Wellion, Agamatrix (control group). Compliant PWDs using insulin pump with insulin aspart for several previous months were included in the study. Seventeen were put on Paradigm 722 with CGM and 25 were included in the control group. Paired t-test and the statistical program SPSS v.15.0 were used to analyze the data. There was no significant difference in age between the two groups ($P = 0.996$), in diabetes duration ($P = 0.482$) or in daily insulin dose ($P = 0.469$). In the CGM group (but not in the control group) HbA1c/IFCC dropped from 6.98±0.43 % to 5.98±0.36 % ($P = 0.006$) within 1 month and remained reduced. Hence the use of the Paradigm 722 insulin pump with CGM resulted in significant improvement in HbA1c which appeared within one month and remained throughout the whole 3-month study period. No significant improvement in HbA1c was seen in the control group.

Cohen [54], *2009*. This study was conducted by highly experienced investigators with abundant time and resources, phase III studies of continuous glucose sensing (CGS) may lack generalizability to everyday clinical practice. Method: Community or academic practices in six Central and Eastern European or Mediterranean countries prospectively established an anonymized registry of consecutive PWD1-dependent diabetes mellitus starting CGS-augmented insulin pump therapy with the Paradigm® X22 (Medtronic MiniMed, Northridge, CA) under everyday conditions, without prior CGS with another device. We compared glycosylated hemoglobin (GHb) values before and after 3 months of CGS and assessed relationships between insulin therapy variables and glycemia-related variables at weeks 1, 4, and 12 of CGS. Of 102 enrolled patients, 85 (83 %) with complete weeks 1, 4, and 12 sensor data and baseline/3-month GHb data were evaluable. Evaluable patients were ~54 % male and ~75 % adult (mean age, 33.2 ± 16.9 years) with longstanding diabetes and high personal/family education levels. Mean GHb declined significantly after 3 months of CGS (7.55 ± 1.33 % at baseline to 6.81 ± 1.08 % after 12 weeks, 0.74 %.

Valensi [55], *1996*, studied the effect of a CSII associated with a low-calorie diet and metformin 1,700 mg/day on glycaemic control and basal and stimulated insulin secretion in a series of 82 overweight NIDD before (T1), during CSII (T2), and after CSII withdrawal (T3). Patients were treated for 8 to 23 days with a mean amount of 0.50 +/– 0.02 IU/kg/day. Glycaemic control was very good after 3–5 days of CSII and remained good at T3. At T2, fasting and postprandial plasma C peptide levels decreased significantly. At T3, fasting C peptide was very similar to T1, and postprandial C peptide was significantly higher than at T1.

(4) Influence of temporary CSII on beta-cell recovery in recent type 2 diabetes

The molar fasting and postprandial plasma C peptide/glycaemia ratios increased significantly at T3. After glucagon injection, the molar delta C peptide/glycaemia ratio was significantly increased at T2 and even higher at T3. At T2, as at T1 and T3, there were significant correlations between fasting and postprandial C peptide levels and between the glucagon-induced C peptide peak and fasting and postprandial C peptide levels. Between T1 and T3 body mass changes correlated significantly with the molar fasting C peptide/glycaemia ratio at T1. Twenty-nine of the 30 patients for whom this ratio was > 6.6×10(–8) lost body mass. The length of CSII treatment did not correlate with body mass changes or other biological parameters. Hence, CSII with moderate amounts of insulin associated with a low-calorie diet and metformin provided rapid glycaemic control, led to body mass loss, maintained regulation of insulin secretion and seemed to improve insulin secretion and sensitivity. These results were obtained in only 8 to 10 days.

Ilkova [56], *1997*, (Table 3) studied whether the induction of euglycemia, using intensive insulin therapy at the time of clinical diagnosis, could lead to a significant improvement in insulin secretion and action and thus alter the clinical course of the disease. Thirteen newly diagnosed diet-unresponsive PWD2 were treated with CSII for 2 weeks and followed longitudinally while being treated with diet alone. Four patients were considered therapeutic failures since CSII failed to induce euglycemia (n = 1) or glucose control deteriorated within 6 months after CSII (n = 3). The remaining nine patients were maintained on diet alone with adequate control from 9 to > 50 months (median ± SE, 26 ± 4.8 months). In five patients, glycemic control deteriorated after 9–36 months, but a repeat 2-week CSII treatment reestablished control in four patients. One of these patients underwent a third CSII treatment 13 months later. At the time this article was written, six patients of the initial group were still controlled without medication 16–59 months (median ± SE, 45.5 ± 6.6 months) after the initiation of treatment. Body body mass remained unchanged in all patients. Hence, in a significant proportion of PWD2 who fail to respond to dietary measures, short-term intensive insulin treatment can effectively establish responsiveness, allowing long-term glycemic control without medication. Further studies are required to establish whether simpler treatment regimens could be equally effective. If the hypothesis offered here finds support, present approaches to the management of newly diagnosed type 2 diabetes may need to be revised.

Table 3

Months of CGS (7.5±1.33 % at baseline to 6.81±1.08 % after 12 weeks, 0.74 %)

Author	Year	Ref.	n	Treating	CSII	MDI	Other	Insulin/day	OHA/d	Duration of remission
Valensi	1997	55	82	8–23 d	–	–	CSII+met.	0.50±0.02 IU/kg	met: 1,7 g	FCP, PCP — After treatment the remission was reached, but the lenght was not observed.
Ilkova	1997	56	13	9–50 m	+	–	–	–	–	9–59 months, in some still continued
Li	2004	57	126	2 w	+	–	–	max. 0.7 units/kg	–	Remission rates third, sixth, twelfth, and twenty-fourth months were 72.6 %, 67.0 %, 47.1 %, and 42.3 %
Weng	2008	58	261	2 w	+	+	SU, met.	0,4–0,5 IU/kg	SU: 160 mg, met.: 2g	Remission after 1 year: CSII 51,1 %, MDI 44,9 %, PAD 26,7 %
Wan	2016	60	60	2 w	+	–	CSII+Sig.	4.14±8.59 CSII, 2.12±7.50 CSII+Sig.	Sig: 100 mg	CPI, SUIT — after treatment the remission was reached, but the lenght was not observed.

Note. Ref. — Ref. — reference number of citation in resources; n — number of patients in the study; Treatment — duration of treatment; PAD/D./day — dosage of PAD per day; d- day; w — week; m — month; met. — metformin; Sig — sitagliptin; FCP — Fasting C-peptide; PCP — Postprandial C-peptide; CPI — C-peptide reactivity index; SUIT — Secretory unit of islet in transplantation index.

Li [57], *2004*, (Table 3) investigated whether long-term optimal glycemic control can be achieved without medication by transient CSII and the possible mechanisms responsible for this remission. Newly diagnosed PWD2 (n = 138, fasting glucose > 11.1 mmol/l) were hospitalized and treated with CSII for 2 weeks. Intravenous glucose tolerance tests (IVGTTs) were performed, and blood glucose, HbA1c, lipid profiles, proinsulin, insulin, and C-peptide were measured before and after CSII. Patients were followed longitudinally on diet alone after withdrawal of insulin. Optimal glycaemic control was achieved within 6.3 ± 3.9 days by CSII in 126 patients. The remission rates (percentages maintaining near euglycemia) at the third, sixth, twelfth, and twenty-fourth month were 72.6, 67.0, 47.1, and 42.3 %, respectively. Patients who maintained glycemic control >12 months (remission group) had greater recovery of beta-cell function than those who did not (non-remission group) when assessed immediately after CSII. Homeostasis model assessment of beta-cell function (HOMA-B) and the area under the curve (AUC) of insulin during IVGTT were higher in the remission group (145.4 ± 89.6 vs. 78.5 ± 68.5, P = 0.002, and 1,423.4 ± 523.2 vs. 1,159.5 ± 476.8 pmol.× $\times l^{-1} \times min^{-1}$, P = 0.044). Change in acute insulin response was also greater in the remission group than that in the nonremission group (621.8 ± 430.4 vs. 387.3 ± 428.8 pmol.$\cdot l^{-1} \cdot min^{-1}$, P = 0.033). Hence, short-term intensive insulin therapy can induce long-term glycemic control in newly diagnosed PWD2 patients with severe hyperglycemia. The improvement of beta-cell function, especially the restoration of first-phase insulin secretion, could be responsible for the remission.

Weng [58], *2008*, (Table 3) hypothesized that early intensive insulin therapy in newly diagnosed PWD2 might improve beta-cell function and result in extended glycaemic remissions. Multicentre, randomised trial to compare the effects of transient intensive insulin therapy (CSII or MDI) with oral hypoglycaemic agents on beta-cell function and diabetes remission rate was performed. a total of 382 patients, aged 25–70 years, were enrolled from nine centres in China between September, 2004, and October, 2006. The patients, with fasting plasma glucose of 7.0–16.7 mmol/L, were randomly assigned to therapy with insulin (CSII or MDI) or oral hypoglycaemic agents for initial rapid correction of hyperglycaemia. Treatment was stopped after normoglycaemia was maintained for 2 weeks. Patients were then followed-up on diet and exercise alone. Intravenous glucose tolerance tests were done and blood glucose, insulin, and proinsulin were measured before and after therapy withdrawal and at 1-year follow-up. Primary endpoint was time of glycaemic remission and remission rate at 1 year after short-term intensive therapy. Analysis was per protocol. More patients achieved target glycaemic control in the insulin groups (97.1 % [133 of 137] in CSII and 95.2 % [118 of 124] in MDI) in less time (4.0 days [SD 2.5] in CSII and 5.6 days [SD 3.8] in MDI) than those treated with oral hypoglycaemic agents (83.5 % [101 of 121] and 9.3 days [SD 5.3]). Remission rates after 1 year were significantly higher in the insulin groups (51.1 % in CSII and 44.9 % in MDI) than in the oral hypoglycaemic agents group (26.7 %; p = 0.0012). beta-cell function represented by HOMA B and acute insulin response improved significantly after intensive interventions. The increase in acute insulin response was sustained in the insulin groups but significantly declined in the oral hypoglycaemic agents group at 1 year in all patients in the remission group. INTERPRETATION: Early intensive insulin therapy in PWD2 has favourable outcomes on recovery and maintenance of beta-cell function and protracted glycaemic remission compared with treatment with oral hypoglycaemic agents.

Kohnert [59], *2015*. Type 2 diabetes mellitus is a complex metabolic disorder characterized by a relative deficiency of insulin in the presence of hepatic, adipose tissue, and skeletal muscle insulin resistance. The pathological process underlying the ß-cell dysfunction occurs already prior to the disease onset. While at the initial stage, ß-cell mass and insulin secretory function are sufficiently well maintained in the majority of individuals with type 2 diabetes, the later stages are characterized by aggravating insulin deficiency. The clinical course of the disease requires escalating therapy with oral drugs over time and eventually consistent application of insulin at the late stage for control of glycemia. Oral therapies are quite effective in improving the short-term insulin secretory capacity, but are incapable of preventing the inexorable decline in ß-cell function during diabetes progression. On the other hand, long-term use of antidiabetic agents is not without various side effects. Since a series of clinical trials have recently shown that implementation of short-term intensive insulin therapy in individuals with newly diagnosed type 2 diabetes can drastically improve and preserve ß-cell function and induce glycemic remission, this treatment strategy has gained considerable interest. However, whether early intensive treatment with insulin can really provide longer-term protection of the pancreatic ß-cells and may be preferable to other therapy modalities is a question that is not yet clearly established and requires appropriate clinical studies.

Wan [60], *2016*, (Table 3) tried to identify a new regimen to optimize treatment for patients with newly diagnosed type 2 diabetes (PWD2) by short-term CSII alone. Sixty newly diagnosed PWD2 were random-

ized into two groups (n = 30 each) and treated for 2 weeks with CSII alone (CSII group) or with CSII plus sitagliptin (CSII + Sig group). The glycemic variability of the patients was measured using a CGMS for the last 72 hours. A standard meal test was performed before and after the interventions, and the levels of glycated albumin, fasting glucose, fasting C-peptide, postprandial 2 h blood glucose, and postprandial 2 h C-peptide were examined. Compared with the CSII group, the indicators of glycemic variability, such as the mean amplitude of glycemic excursion (MAGE) and the standard deviation of blood glucose (SDBG), were decreased significantly in the CSII + Sig group. The changes before and after treatment in the C-peptide reactivity index (ΔCPI) and the secretory unit of islet in transplantation index (ΔSUIT) indicated a significant improvement in the CSII + Sig group. So, add-on therapy with sitagliptin may be an optimized treatment for patients with newly diagnosed T2DM compared with short-term CSII alone.

Cohen [61], *2016*. The goal is to assess the usability and satisfaction of implementing the Getting2Goal(SM) protocol by physicians transitioning PWD2 from MDI to CSII. PWD2 from three diabetes clinics were switched from MDI to CSII. Physicians used the Getting2Goal type 2 pumping protocol to prescribe and manage insulin pump therapy for T2DM. Surveys were conducted in which the physicians rated their feedback related to acceptability of the Getting2Goal on a 5-point Likert scale. The data indicate Getting2Goal materials as a standard approach that is simple and efficient to initiate pump therapy for T2DM. At the same time, it is safe and a useful tool for physicians that are starting to prescribe pump therapy for T2DM.

Conclusion

Insulin pump (CSII) appears to be an effective part of both type 1 and type 2 diabetes complex treatment aiming to early recovery of beta cell function and/or to longlasting improvement of metabolic indices.

CSII may be considered either as a tool for potential recovery of beta-cells and also as a part of combined therapeutic approach for general recovery of metabolit state in longlasting (neglected) diabetes.

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Р. Хлуп

2-Типті қант диабетіне шалдыққан науқастарды емдеу барысында инсулинді сорғышты пайдалану

Мақалада автор жүргізген 1- және 2-типті диабетпен ауыратын науқастарға инсулинді сорғышты тұрақты инсулин инфузиясын қолдануда аса маңызды және ұзақ уақыт бойы жүргізілген клиникалық зерттеулер нәтижесі берілген және ол 4 бөлімнен тұрады: 1) тарихи экскурс; 2) инсулинді (инсулинді насос) үздіксіз енгізуді қолдану тиімділігі; 3) инсулинді үздіксіз енгізуді қолдану қандағы гликолизденген гемоглобин деңгейі және 2-типті диабеттің глобалды метаболитті индексі тиімділігі; 4) инсулинді үздіксіз енгізуді қолдану 2-типті диабеттің В-жасушалары функциясын қалпына келтіру. Мақалада инсулинді насостарды ұзақ уақыт бойы қолдану емдеу тиімділігін жоғарылату ғана емес, сонымен қатар ұйқы безінің В-жасушаларын қалпына келтіруде аса маңыздылығы көрсетілді.

Р. Хлуп

Использование инсулиновых насосов при лечении диабета 2 типа

В работе обобщен значительный объем результатов серьезных и длительных клинических исследований, проведенных автором и посвященных изучению применения инсулиновых насосов для постоянной инфузии инсулина в процессе лечения больных диабетом 1 и 2 типа. Исследование состоит из 4 разделов: 1) исторический экскурс; 2) эффективность применения непрерывного введения инсулина (инсулиновые насосы) при лечении диабета 1 типа; 3) эффективность применения непрерывного введения инсулина на уровень гликозилированного гемоглобина в крови и глобальные метаболические индексы при диабете 2 типа; 4) влияние непрерывного введения инсулина на восстановление функции В-клеток при диабете 2 типа. Показано, что длительное применение инсулиновых насосов не только весьма эффективно в плане повышения эффективности лечения, но и, что особенно важно, способствует восстановлению функции В-клеток поджелудочной железы.

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Lifestyle Interventions for the Prevention of Type 2 Diabetes Mellitus

Prevention of diabetes requires using of the achievements of basic science in clinical practice. For the last many years it was established that lifestyle factors in preventing type 2 diabetes in people at risk. Subsequent studies have provided important information on the actual implementation of diabetes prevention programs. In some countries efforts for diabetes prevention were realized but it is difficult to extrapolate on work according a large regional or national programs, specific items which must be scheduled for execution. For trained professionals in the field of health care, medical profile economists, health professionals and representatives of public organizations, capable of interacting with influential politicians. Political support is a very important component of this work. The article presents the results of a study that could help in the successful implementation of diabetes prevention programs in the «Practice of the real world.

Key words: prevention of type 2 diabetes; diabetes mellitus; lifestyle interventions; health care.

Preface

In recent decades the world has experienced a significant increase in the number of patients with diabetes mellitus [1]. This is primarily type-2-diabetes. Parallel to this, the increase is mostly attributable to a significantly higher frequency of diabetes diagnosis in the age group below 60, but also below 35 years of age. The growing economic burden in complex socioeconomic structures becomes obvious. The development of the diabetes epidemic is predicted to have a significant impact on the global economic growth [2]. The situation requires fundamentally different approaches from national health care systems depending on national health care structures and their medical, environmental, social and economic means. In order to respond rapidly in a coordinated fashion to the health threat diabetes and its associated co-morbidities, it is necessary to plan and prioritize the quality and structures of diabetes prevention and care in a standardized way presenting the goals, processes, responsibilities, availability and accessibility of diabetes care as part of the implementation of a Chronic Care Management [3] as part of a National Diabetes Program (NDP) [4].

At the United Nations High Level Meeting for Non Communicable Diseases (NCD) in September 2011 inNew York, Ministers of Health requested an international cooperation and policy decisions on diabetes according to the present context of globalization of health issues [5, 6]. There was a consensus across countries that national programs for prevention and control of chronic diseases have to be developed and implemented and that strategies to monitor progress on implementation needed to be established. In April 2012 the European Diabetes Leadership Forum [7] was held, to discuss developing strategies on political, medical and patient centered level for improving diabetes prevention, early detection and management. Kofi Annan said at the meeting «There is no other option than to act — we do not have enough money not to act.» In November 2012 a major breakthrough at the World Health Organization (WHO), governments agreed an aspirational set of targets to drive progress on diabetes and non-communicable diseases (NCDs), including the first ever global target to halt the rise of diabetes. The governments agreed a Global Monitoring Framework including 9 global targets and 25 indicators on diabetes and NCDs. The diabetes related target include a 25 % relative reduction in overall mortality from NCDs by 2025, a halt the rise in diabetes and obesity and a 10 % relative reduction in prevalence of physical inactivity. Furthermore a goal was set that 50 % of eligible people receive drug therapy and counseling (including glycaemic control) to prevent heart attacks and strokes [8].

The burgeoning health care costs associated with the treatment of type 2 diabetes and the consistent and high quality of evidence for the effectiveness and cost-effectiveness have been central elements in necessitating a major realignment in national health care priorities away from models based solely on treatment, to those that incorporate structures around primary prevention. This has been supported by high level international advocacy. The cooperation between the United Nations and World Health Organization is a major footstep on non-communicable disease prevention and control. This marks only the second time in the history of the United Nations that its General Assembly has been convened to tackle an emerging health issue.

This has necessitated a parallel shift in the focus to successful implementation of diabetes prevention research, to include the translation of effective prevention strategies into routine clinical practice. This work has been focused on addressing the major challenges to prevention, particularly around identifying resource-efficient risk identification and intervention strategies.

The global epidemic panorama

Currently, we are experiencing an epidemic growth in the number of people with diabetes worldwide [1]. An estimated 366 million people, corresponding to 8.3 % of the world's adult population has diabetes today but the prevalence is expected to grow to 552 million by 2030, corresponding to 9.9 % of the adult population. It goes hand in hand with «westernization» of lifestyle, with consuming more energy-dense food as well as with decreasing physical activity. Driven by this development, diabetes affects more and more young people.

These changes have driven a huge increase in type 2 diabetes — the most common form of diabetes mellitus, particularly in young people, especially in their working age [9]. The medical burden is rising as patients with diabetes mellitus are developing a growing number of metabolic and cardiovascular comorbidities. The growing economic burden in complex socioeconomic structures becomes obvious. The development of the diabetes epidemic is predicted and the World Economic Forum foresees the development of the diabetes epidemic as a disaster likely to occur in the near future with an significant impact on the global economic growth at least similar in scale to the recent banking crisis [2]. The number of people affected by chronic diseases globally necessitates better chronic care management. The central programs including early detection and treatment strategies as well as investment into the development and implementation of prevention programmes [4] prominence of lifestyle in the causal pathway of progression to diabetes represents an opportunity to utilize lifestyle promotion as a preventive strategy and key line of defense against the rising tide of T2DM.

Evidence for sustainable diabetes prevention

There is now consistent evidence from randomized controlled trials across diverse countries and populations that lifestyle interventions, aimed at promoting physical activity, a healthy diet and weight loss can successfully reduce the risk of progressing to T2DM by between 30 to 60 % in those with impaired glucose tolerance (IGT) [10]. IGT is an intermediary condition between normal glucose regulation and T2DM and is associated with a substantially elevated risk of progression to Type 2 diabetes [11]. In 2001 the Finnish Diabetes Prevention Study and in 2002 the US Diabetes Prevention Program as well as the Da Qing IGT and Diabetes Study [12–14] demonstrated that lifestyle modifications focused on losing weight, increasing physical activity and improving diet could reduce the risk of progression to diabetes by nearly 60 % [15–17]. Similar findings were also seen in India [18] Japan [19] and China [12]. There is a strong dose-response effect for people who adopted four or five lifestyle changes, the progression rate after seven years was reduced by 80 % compared to those making no changes [20]. There is consistent evidence that some pharmaceutical agents, such as Metformin, a drug that is effective for glucose-lowering in people with type 2 diabetes, can prevent the onset of diabetes in high risk populations by 31 % in people with IGT [15, 18] and also other agents have been proven to be effective [21, 22], but the evidence consistently suggests that lifestyle interventions are more effective than pharmacological interventions in preventing the onset of T2DM [23].

Economic evaluation has demonstrated the cost-effectiveness of primary prevention of T2D [24]. However despite the evidence, it remains questionable whether these programs are feasible at a population level. The challenge, therefore, is to establish a scientifically-based structural framework for efficiently managing nationwide prevention programs.

Currently the evidence about short-term reduction of diabetes risk and conversation to type-2-diabetes in people with IGT is very good. The major question is however, how sustainable this effect may be. A current report has summarized the long-term effect of type 2 diabetes prevention pointing out a significant sustainability of the effect if the initial intervention was able to achieve lifestyle change [25]. The first study suggesting a sustainable effect was the Malmö Feasibility Study [26]. Here the effect of exercise and diet was tested on incidence of type 2 diabetes among 161 men with impaired glucose tolerance. After a 5 year study period 11 % of the men in the intervention group developed diabetes compared to 29 % of the men in the reference group who did not want to join in lifestyle intervention. After the 12 years follow-up the all-cause mortality was significant lower in the former intervention group (6.5 versus 14.0 per 1000 person years, p=0,009) and was similar to healthy individual without any glucose disturbance [27].

The Da Qing study [28] undertaken in China included 577 men and women with impaired glucose tolerance who were randomized into an intervention and control group. The interventions included either diet alone, exercise alone and a combination of diet and exercise. The lifestyle intervention was for a period of 6 years and resulted in lower cumulative type 2 diabetes incidences in all 3 intervention groups (41–46 %) compared to the control group (68 %). Interestingly the participants in the study were relatively lean so that the weight reduction was relatively small. In the participating clinics assigned to the dietary intervention the recommendation included a high carbohydrate (55–65 E %) and moderate fat (25–30 E %) diet. This study indicated that it is not only bodyweight reduction alone that is important for the prevention of type 2 diabetes. Also other lifestyle issues are important and bodyweight may be a summary indicator for several dietary and activity factors[28, 29]. The 20 year follow-up of the study showed a sustained and persisting reduction in the incidence of type 2 diabetes (43 %) in the intervention group compared to the control participants [25]. Surprisingly there was no significant effect in the reduction of cardiovascular disease or mortality, but a sustained effect in reducing the prevalence of micro vascular disease in diabetes patients [30]. The Da Qing study is the study with the longest follow up. The quintessence of the study is — lifestyle intervention enables an significant delay in the conversion to diabetes mellitus in those at risk and, at least for a period of 20 years, significantly prevents diabetes mellitus. For persons who develop diabetes the intervention significantly reduces the development of microvascular complications [28, 30].

The Finish Diabetes Prevention Study (DPS) was a multi-centered trial carried out between 1993 and 2001 in Finland in 5 clinics [31]. The main objective of the study was to test the effect of a 3 years lifestyle intervention on the reduction and incidence of type 2 diabetes compared to a control group. 522 men and women were recruited into the study and randomly allocated into a control and intervention group. The reduction in incidence of type 2 diabetes was 58 % associated with a weight reduction of, on average, 4.5 kg in the intervention group versus 1.0 kg in the control group ($p < 0.001$) after one year, and similar results maintained after 3 years. Overall, visceral obesity, dietary habits and exercise habits improved significantly and were independently associated with diabetes risk reduction [32, 33]. The cumulative incidence of diabetes was 11 % (95 % CI 6 to 15 %) in the intervention group and 23 % (95 % CI 17 to 29 %) in the control group after four years, and thus the risk of diabetes was reduced by 58 % ($p<0.001$) in the intervention group compared with the control group [17]. The following analysis utilising data collected during the extended follow up of the study showed that after a follow-up time of 7 years, a marked reduction of the cumulative incidence of diabetes was sustained, reaching a risk reduction of 43 % [34]. The corresponding incidence rates were 4.6 and 7.2 per 100 person years between the intervention group and control group. The 10 year follow-up results of the effect of the lifestyle intervention in the diabetes prevention study included total mortality and cardiovascular risk and showed a significant reduction in total mortality, but similar to the Da Qing study no effect on reducing cardiovascular morbidity [35]. Interestingly, when the DPS intervention and control groups together were compared with a population-based cohort including people with IGT, adjusted hazard ratios were 0.21 (95 % CI 0.09–0.52) and 0.39 (95 % CI 0.20–0.79) for total mortality and 0.89 (95 % CI 0.62–1.27) and 0.87 (95 % CI 0.60–1.27) for cardiovascular morbidity. Thus the risk of death among the DPS participants was markedly lower than in a population based IGT cohort [25].

The Diabetes Prevention Program (DPP) was a United States multicenter randomized clinical trial [36]. It compared the efficacy and safety of three interventions — an intensive lifestyle intervention, standard lifestyle recommendations combined with metformin, or placebo [25]. The goals of the dietary intervention were to achieve and maintain a 7 % weight reduction by consuming a healthy low-calorie, low-fat diet and to engage in physical activities of moderate intensity (such as brisk walking) 150 minutes per week or more. The intensive lifestyle intervention reduced type 2 diabetes risk after 2.8 mean follow-up by 58 % compared with the placebo control group. Lifestyle intervention was also shown to be superior to metformin treatment which resulted in a 31 % type 2 diabetes risk reduction compared with placebo. At the one-year visit the mean weight loss was 7 kg (about 7 %) [25]. After the publication of the main results in 2002 the randomized trial was stopped and the participants were invited to join the Diabetes Prevention Program Outcomes Study (DPPOS) [37]. During the follow-up, all participants regardless of their original treatment group were offered lifestyle counseling. During the overall follow-up of 10 years (calculating from the randomization to the DPP) diabetes incidence in the original lifestyle intervention group was reduced by 34 % compared with the control group. However during the post-intervention follow-up diabetes incidence was similar in all treatment groups (5.9 per 100 person-years in the former intervention group and 5.6 % in the placebo control group, confirming that lifestyle intervention that was initiated in the former placebo control group was successful even after several years of follow-up without any active intervention [25].

The elements for prevention: Identifying people at risk

The question of who should be targeted for diabetes risk reduction is not easy to answer because the effect of an intervention program to prevent type 2 diabetes in adulthood depends on the setting where the intervention is performed, the effectiveness of the intervention in addressing the high risk individual, accessibility and affordability and a variety of additional variables [38]. However, the main considerations when deciding who should be targeted for diabetes prevention are the effectiveness and affordability of the interventions available after the high risk person has been identified. Screening for diabetes risk makes no sense without availability of a successful and sustainable intervention program [39]. Interventions can have various approaches, strategies and concepts. Furthermore, strategies for targeting people at high risk will vary significantly between different settings and different population groups. The risk factors for T2DM are well recognized and T2DM is often preceded by a period of impaired glucose tolerance which is characterized by increasing insulin resistance and Beta cell dysfunction [40]. Visceral obesity plays a key role in triggering the development of insulin resistance and increasing diabetes risk [23]. It is also recognized that many people with T2DM remain undiagnosed and that patients with long diagnostic delays often have significant complications at diagnosis [41]. This suggests that combined screening for both impaired glucose tolerance and undiagnosed prevalent T2DM could be a pragmatic option. Indeed, data shows that screening for both conditions together is cost effective, particularly when lifestyle and pharmacological based interventions are then used to delay the onset of T2DM in high risk individuals [10, 42] Screening for T2DM and impaired glucose tolerance in high risk populations is now recommended by a number of international Diabetes Associations [43–46] and there is a plethora of tools available to identify people at increased risk of T2DM and there is little evidence of detrimental, long term, physical or psychological harm from such screening [47, 48].

The consensus (based on screening approaches used in practice in the US, Germany, Australia, Finland, UK and other countries) [4, 46, 49, 50] seems to favor a targeted, staged approach with the first step being to identify those at high risk and a second step to confirm glycaemic status [51] (whether T2DM, impaired glucose tolerance or normoglycaemia). Preliminary data about these broad approaches suggest that it is more cost-effective to use a non-invasive screening tool as the first stage in screening rather than a blood test [52]. Risk scores tend to be based around risk factors such as age, gender, BMI, ethnicity, family history of diabetes and taking anti-hypertensive medication. Risk scores have been shown to have good sensitivity and specificity for identifying diabetes risk [51]. For example the FINDRISC, the Danish Risk Questionnaire, the Cambridge Risk Score, the Leicester Diabetes Risk Score and the Indian Score have all been associated with a sensitivity of between 76–77 % and specificity between 55–72 % with a positive predictive value varying between 7–11 % [53–58]. The most common approach used is the FINDRISC questionnaire which individuals use to self-assess their risk based on seven questions and which has been shown to have good validity at predicting future diabetes over a ten year period [59]. Importantly, FINDRISC has been validated for use in various countries [60]; but given the varying profile and prevalence of risk factors in different settings[40], the score performance cannot be generalized from one country to another. It is therefore important that risk scores are validated in the population in which they will be applied. The other approach is to use data which is routinely available to the general practitioner (for example, the Cambridge Risk Score, QD Score or the Leicester Practice Risk Score [51, 61–64].

The second stage involves diagnostic testing. In practice, this usually consists of either a fasting glucose or HbA1c, although oral glucose tolerance testing can also be used. A recent statement by the International Expert Committee of the WHO, has advocated that HbA1c of >6.5 % define T2DM [65]. Meanwhile there is an ongoing debate about the use of HbA1c<6.5 % in defining impaired glucose tolerance, although this may be a pragmatic option for identifying people at high risk for T2DM [66]. A consensus approach by WHO recently included the use of HbA1c > 6.5 % as a diagnostic threshold for T2DM. However, there is no clear consensus on how or whether HbA1c should be used to classify diabetes risk below this level. The ADA tentatively suggested that an HbA1c value of between 5.7–6.4 % indicates a high risk of T2DM whereas an international expert committee suggested a range of 6.0–6.4 % [44, 67]. The latter range was also recently endorsed by NICE in the UK, which now recommends that HbA1c can be (48 mmol/L/mol) can now be used to of type 2 diabetes and that those with a value of between 6.0–6.4 % should be referred into a diabetes prevention programme [68]. This is supported by prospective data which found that those with an HbA1c of between 6.0–6.4 % had twice the risk of developing type 2 diabetes compared to those with a value of between 5.5–5.9 %. Prospective data from the United Kingdom supports the use of 6.0–6.4 % as those in this group were found to have a risk of future T2DM that was twice that in the range of 5.5–5.9 % [23]. Howev-

er, other data from Germany suggest 5.7 % is likely to have the best sensitivity and specificity at detecting future diabetes risk [66] but demonstrate that the combination of HbA1c and the 1-hour plasma glucose concentration in predicting future diabetes risk was significantly better in a multivariate model than either one of them alone. The 1-hour PG concentration has previously been shown to be a strong predictor of T2DM risk [69–71] and also other chronic disease [72, 73] but has major logistical issues. Further, the optimal HbA1c cut point for identifying subjects at increased diabetes risk is 5.65 % [66, 74] and not 6.0 % as originally suggested by the ADA expert committee [67]. If a HbA1c >6 % was used to identify subjects at increased risk for future T2DM, only about one third of subjects who developed T2DM would have been identified. Thus, use of a HbA1c cut point of 5.65 % together with the 1-hour PG concentration [75] would identify many additional high risk individuals who could benefit from an intervention program [66, 76, 77].

The most cost-efficient way to balance resources against risk has yet to be determined. In the meantime, the balance that is struck may depend to a large extent on pragmatic considerations, particularly financial constraints [49]. It is acknowledged that, along with strategies for identifying and intervening in those with a high risk of a widely prevalent condition such as type 2 diabetes, it is also fundamentally important to employ initiatives that are aimed at shifting the distribution of known risk factors, such as BMI in adults or BMI percentiles in childhood as well as waist circumference within the population as a whole [78]. Strategies for primary prevention on public health level and high risk strategies need to work in parallel [50].

Waist circumference

Waist circumference is a powerful indictor of metabolic dysfunction as it represents a surrogate indicator for the accumulation of visceral fat [79, 80]. It is well established that visceral fat does not only play a role in the human energy metabolism, but that it also actively secrets hormones and peptides (adipocytokines), such as MCP-1, Retinol binding protein 4 as well as a variety of interleukins together with TNF-α, which enhance the development and/or the progression of chronic diseases, including insulin resistance and chronic inflammation. There is a strong risk association between an increase in visceral fat mass and risk of developing T2DM [81].

From a public health point of view, waist circumference presents a clinically valuable measure because of accessibility [82], as no lab investigation is needed and no invasive procedure is necessary. In addition, direct patient feedback during an intervention program is possible. As it is known that the metabolic activity of visceral fat is higher than that of subcutaneous fat, alterations in baseline metabolic turnover from an individual patient during an intervention associated with increased physical activity would predominantly reduce the visceral fat depot [83]. It might be concluded that any reduction in the visceral fat depot is accompanied by a reduction in most of the visceral adipocyte-secreted hormones and therefore has beneficial effects for prevention of chronic diseases. Waist circumference provides a valid measure to predict diabetes risk in the adult population and has been included in the criteria to define the metabolic syndrome [84]. For consistency with the criteria for adults, the measurement of waist circumference has meanwhile also been included in the definition of the metabolic syndrome in children and adolescents [85].

The elements for prevention: Physical activity

Epidemiological, experimental, and randomized controlled clinical studies trial level evidence have all consistently demonstrated that levels of physical activity are centrally involved in the regulation of glucose homeostasis, independent of other factors including adiposity [10, 86–88]. A modest increase in walking activity, towards levels that are consistent with the minimum recommendations, significantly improved 2-hour glucose levels by 1.3 mmol/l over 12 months in high-risk overweight and obese individuals, despite no change was obvious in body weight or waist circumference [89]. This may correspond to a > 60 % risk reduction of developing T2DM within 24 months [90] and was consistent with findings from other studies [33] but an replication of the results is needed and is underway. Therefore, physical activity promotion should be the corner-stone of any diabetes prevention program. However, the role of physical inactivity in helping identify diabetes risk is less clear and more problematic for several reasons. First, physical inactivity is a nearly universal condition: it has consistently been shown that 50–80 % of the population in both developed and developing countries fail to meet the minimum recommendations for health [90–93]. Indeed, when physical activity levels are objectively measured, rather than by subjective self-report, a substantial fraction of the population are considered inactive [93, 94]. Therefore commonly used definitions of physical inactivity do not provide a clear mechanism for stratifying diabetes risk. Secondly, methods that rely on individuals self-reporting their activity levels are highly inaccurate and unreliable. For example, an internationally used and

validated self-reported measure of physical activity described as little as 10 % of the variation in objectively measured levels through accelerometry [95, 96]; being in contrast to simple measures of adiposity, such as BMI or waist circumference, which are reasonably accurate on a population level. For these reasons, self-recording levels of physical (in)activity has not been shown to add to the predictive power of diabetes risk scores or to be usefully incorporated into other methods of quantifying diabetes risk [97, 98]. However, it is important that physical inactivity, as with other lifestyle variables, is considered for the individual assessments of diabetes risk [23].

The spectrum of evidence underpinning the link between physical activity and health is particularly compelling in relation to metabolic health and the development of T2DM. Prospective observational research has consistently demonstrated that undertaking levels of physical activity that are consistent with current physical recommendations are associated with a 30–50 % reduction in the relative risk of developing T2DM [87]. Mechanistic studies have identified multiple pathways linking physical activity to improved glucose transport [96–98]. For example, acute and long-term changes in insulin action and fuel utilisation occur through mitochondrial biogenesis, increased fatty acid oxidation, and increased expression and translocation of key signalling proteins involved in the insulin mediated glucose uptake pathway, particularly GLUT-4. Furthermore, muscular contractions are known to induce glucose uptake through insulin independent pathways, which is likely to involve the up-regulation of AMP-activated kinase [96]. Finally, randomized controlled trials have demonstrated that physical activity interventions result in improved glucose tolerance and a reduced risk of diabetes in those with a high risk of the disease [10, 89]. Importantly, physical activity has also consistently been shown to reduce the risk of diabetes regardless of body weight status[33, 88], confirming that physical activity should be promoted for its own sake rather than simply to help achieve weight loss [23, 99–101].

National and international recommendations are based on achieving 30 minutes of moderate- to vigorous-intensity physical activity on at least 5 days or 150 minutes per week, accumulated through multiple bouts of at least 10 minutes [102–104]. However, particularly in relation to the prevention of type 2 diabetes and metabolic health, it should be emphasized that this is a minimum recommendation and that greater health benefits will be achieved through higher doses of physical activity.

In order to be successful, lifestyle intervention programmes should focus on types of physical activity that are acceptable to the majority of the population. Walking has consistently been shown to be the most popular choice of physical activity; including those with a high risk of T2DM [33]. Indeed, walking for 150 minutes per week during leisure time is associated with a 60 % reduction in the relative risk of type 2 diabetes compared with walking for less than 60 minutes per week [33]. Importantly, walking is associated with fewer barriers than other forms of physical activity in black and minority ethnic populations dwelling in developed countries, such as South Asians [23, 105].

Wearing a pedometer and keeping a daily step log have been widely advocated as effective self-regulatory strategies in the promotion of increased ambulatory activity and their use has consistently been shown to successfully promote increased physical activity [106]. The success of pedometer interventions is centered on the pedometer's ability to raise awareness of current activity levels, provide objective feedback to the individual and facilitate clear and simple goal setting. In order to be effective, it is essential that realistic and personalised step-per-day goals are used; goals that are too ambitious can often be de-motivating and lead to failure.

Sedentary individuals (let than 5000 steps per day) should initially aim for an average increase in ambulatory activity of around 2000 steps per day conducted at a moderate to vigorous-intensity, which is roughly equivalent to an additional 150 minutes of walking activity per week [107]. Alternatively, the categories of ambulatory activity shown in Table 1 can be used to guide lifestyle interventions. For example, those in the sedentary or inactive categories could initially aim to increase their ambulatory activity by at least 2000 steps per day. Those in the moderate category could be encouraged to try and enter the high category, whereas those achieving the high or very high categories should be helped to at least maintain their activity levels. For people who have significant barriers to walking, such as joint problems, alternative forms of physical activity, such as cycling, or swimming should be encouraged.

Exercise is well known to be the potential lifestyle intervention to treat and prevent type 2 diabetes. The evidence has been firmly established by several clinical trials. The challenge we have is to address the implementation of the evidence into clinical and public health practice — and here the question about the key items for changing lifestyle becomes relevant. Support for behavior change is the predominant issue. Physical activity such as step counts on a pedometer is a good sign of behavior change but maintaining physical activity requires sustained behavioral support.

Table 1

Physical activity categories based on steps per day

Category	Steps per day
Sedentary	<5000
Low (Typical of daily activity excluding volitional activity)	5000–7499
Moderate (likely to incorporate the equivalent of around 30 minutes per day of moderate intensity physical activity)	7500–9999
High (likely to incorporate the equivalent of around 45 minutes of moderate intensity physical activity)	10,000–12499
Very High (likely to incorporate the equivalent of over 45 minutes of moderate intensity physical activity)	>12500

Adapted from Tudor Locke and Bassett, 2004 [107].

The more intuitive the behavioral strategy, the more success it will have in increasing physical activity. «Walking» is natural from an evolutionary point of view and may have the potential to reach a wide audience with the right behavioral support program and incentives. «Exercise therapy» is a therapy associated with a disease which can be highly successful but needs an individualized strategy and by this is only applicable for a fraction of our patients. In order that «Physical activity» becomes a core therapeutic element for diabetes prevention and most patients with type 2 diabetes mellitus» we have to improve our understanding of the behavioral and physiological as well as contextual mechanisms of the development of diabetes and the disease itself. To reach every patient we need an individual proposal which can become part of daily life. Nothing is more natural than «walking» and to 'walk our diabetes away' is effectively achievable.

Smart Health and Physical Activity

The recent very fast development of smart health technology enables a wide variation of new tools to target patients as customers and uses smart health tools to encourage a healthy lifestyle [108]. A recent evaluation identified a large number of smartphone apps as pedometer app or fitness and physical activity apps to encourage people for a healthier and more active lifestyle [109, 110]. Some of these apps are linked with clinical studies that show a very good success rate in encouraging daily physical activity [111]. One of the examples is the AnkerSteps App — www.ankersteps.com — which uses a gamification approach to sustainably encourage people to walk 10,000 steps a day. The AnkerSteps model was tested and shows a sustainable increase of daily physical activity of people reaching 10,000 steps a day at about 65 % of the days. AnkerSteps is an example, in which cost free smart technology helps to anchor motivation of people to reach a health goal sustainably, based on a sustainable social business model [112].

The elements for prevention: Nutritional aspects

Obesity is one of the most important risk factors for T2DM and population trends in obesity and diabetes run in parallel [113]. The pathophysiology of adiposity regarding the development of T2DM is not fully understood; however, several mechanisms that may interplay have been identified. Adipose tissue, especially the tissue surrounding internal organs (visceral fat) is today regarded as an active endocrine organ that secretes a variety of pro-inflammatory adipokines, which act at both the local and systemic level [114]. Increasing adipose tissue mass leads to changes in the secretion of these adipokines as well as increased turnover of free fatty acids which bring on insulin resistance, the harbinger of metabolic disturbances leading to T2DM, as reviewed by Cornier et al. [115].

Waist circumference is a powerful indictor of metabolic dysfunction as it represents a surrogate indicator for the accumulation of visceral fat [80, 116]. It is well established that visceral fat does not only play a role in the human energy metabolism, but that it also actively secretes hormones and peptides (adipocytokines), such as MCP-1, Retinol binding protein 4 as well as a variety of interleukins together with TNF-, which enhance the development and/or the progression of chronic diseases, including insulin resistance and chronic inflammation, providing evidence that there is a strong risk association between an increase in visceral fat mass and risk of developing T2DM [81]. On the other hand adiponectin, an additional adipocytokine secreted from (visceral) fat cells, has been shown to have beneficial effects on the development of insulin resistance and arteriosclerosis. From a public health point of view, waist circumference presents a clinically valu-

able measure because of accessibility [117], as no laboratory investigation is needed and no invasive procedure is necessary. In addition, direct patient feedback during an intervention program is possible.

Further evidence supporting the causative role of obesity in the development of T2DM comes from lifestyle intervention studies which have consistently shown that moderate weight reduction (5–7 %) prevents type 2 diabetes [17, 118]. In the DPP study weight loss was identified as the main driver of changes in diabetes incidence, with each kilogram of weight loss being associated with a relative reduction of 16 % in the risk of progression to T2DM [118].

Weight reduction seems to be beneficial, at least in the short term, regardless of the mechanism of weight loss (e.g. diet or physical activity or both) [119] Interestingly, beneficial changes in glucose metabolism seem to appear soon after the initiation of energy-restricted diet, even before any significant reduction in body fat which suggests that there are several different simultaneous mechanisms in play [120]. Another important point is that weight reduction of only 5 to 10 % seems to have a large effect on diabetes risk [121].

Even though the basic cause of excess body fat accumulation is an imbalance between energy intake (=dietary intake) and expenditure, the factors predisposing to the development of overweight and obesity are multifactorial and poorly understood. Nevertheless, regular physical activity, high dietary intake of fibre and reduced intake of energy-dense micronutrient-poor foods were identified by the World Health Organization as lifestyle factors for obesity [122]. In the DPS energy density of diet was found to be associated with achieved weight reduction [20] which supports the intuitive recommendation to increase foods with low energy density such as vegetables and fruits to increase satiety while reducing total energy intake. An increased understanding of these mechanisms will be helpful in providing prioritization of behavioural targets for future prevention programs.

Nutritional recommendations

For the majority of people, weight reduction is difficult to sustain. Fortunately, diabetes prevention studies have shown that changing lifestyle is effective without significant weight reduction [12, 18, 89] (Tables 2, 3). An important contributor is physical activity; however the composition of diet seems to be important as well. Epidemiological studies have suggested that several dietary factors may either increase diabetes risk (e.g. intake of refined grains, red and processed meat, sugar-sweetened beverages, heavy alcohol consumption) or decrease it (e.g. intake of whole-grain cereal, vegetables, legumes, nuts, dairy, coffee, moderate alcohol consumption), independently of body weight change [23]. The suggested mechanisms behind these observations include improvement of insulin secretion and/or insulin resistance as a result of reduced glycaemia and lipidemia, reduced ectopic fat, reduced low-grade inflammation, changes in cell membrane phospholipids and improvement of intestinal peptide secretion [23].

T a b l e 2

Nutrition and dietary guidance for sustained diabetes prevention

Goals for food intake	Goals for long-term nutrient intake
• Consuming fruit, vegetables, and legumes inabundance (≥ 500 g or five portions per day) • Choosing whole grain in all cereal products • Limit sugar to ≤ 50 g/day, including sugar in food and beverages • Consuming vegetable oil and/or soft margarines and/or nuts as the primary source of fat • Limiting butter, other saturated fat and partially hydrogenated fats • Choosing low-fat milk and meat products • Consuming fish regularly (≥2 per week) • Consuming alcoholic beverages in moderation (≤2 drink/day for men and ≤1 drink/day for women) if at all • Other goals according to individual needs (e.g. body weight, diseases, medications, age)	• Energy intake balanced with physical activity levels to achieve or maintain healthy body weight • Total fat 25–35 E%* (60–80 g/day with 2000 kcal daily intake level), of which saturated or trans fat ≤ 10 E% • Dietary fibre 25–35 g/day • Salt (NaCl) ≤ 6 g/day • Alcohol ≤ 5 E%* *E% = proportion of total energy

Table 3

The EAT CLEVER principle provides brief practical advice for counsellors to be applied within the framework of national dietary recommendations

EAT CLEVER	
Estimation of the dietary pattern compared to the recommendations	Use the food diary, or interview to help your client to become aware of his/her dietary pattern and food consumption. Compare dietary intake to the recommendations. Consider special needs, resources and readiness to change food habits.
Aims in the long and short term	Discuss both short and long term goals: what is your client willing and able to do at the moment? Help to set practical, achievable targets and proceed with small steps. Make a plan with your client.
Tools, guidance and support	Which kind of tools, guidance, support or skills are needed and available? Involving the family and friends and group counseling are all worth considering.
Composition of the diet	A diet with high sugar and other refined carbohydrates and low fibre content, or high saturated and trans fat content may increase the risk for diabetes and other related disorders. Whole grains and moderate amounts of coffee and alcohol may decrease the risk. Encourage the use of herbs and spices to reduce salt. Refer to your national nutrition recommendations but consider the special requirements of people with high diabetes risk, such as the improvement of the components of the metabolic syndrome. Take into account any additional disease your client may have.
Lifestyle for the whole life	Diet is influenced by culture, religion, ethical, physiological, psychological, social and economical aspects, availability, and individual likes and dislikes. Help your client to find his/her own healthy way of life. Lifestyle change is a process and relapses are part of it. Help your client to learn from these experiences to develop successful strategies over time.
Energy	Excessive energy intake causes weight gain. If the client is overweight, make a plan with her / him to support gradual weight loss (step by step). Focus on substituting foods with high saturated fat and/or refined carbohydrate content with lower-energy items. How many meals and snacks, beverages and alcohol included, does he/she have during a day and night? Some regularity in the daily meal plan helps to control over-eating.
Variety	Emphasise variety instead of restriction. A health-promoting diet provides satiety and pleasure as well as protective nutrients. Encourage clients to try new foods. Give advice on how to read food labels. This can help your client to feel more confident and expand their healthy food choices.
Evaluation	Evaluation and self-monitoring help in achieving and maintaining new food habits. Body weight and /or waist circumference should be measured regularly. Encourage your client to use a food diary (see Appendix) or some other methods to monitor eating habits: the number of meals and snacks, the amounts of certain food stuffs, such as vegetables, whole grains, sugar, alcoholic beverages, vegetable oil and/or fat etc.
Risks management	Dietary guidance must be based on evidence from nutrition and behavioural sciences. Focus on the big picture: changing one aspect in the diet affects many others. Strict restrictions and 'crash dieting' may lead to an unhealthy diet, and can cause damage in the long term as well as psychological and social harm. A multi-disciplinary team, including a registered dietician and a psychologist, can give essential support to avoid these risks.

The Finnish DPS aimed, in addition to weight reduction and increased physical activity, at reduced total and saturated fat intake and increased fiber density of diet [123]. The post hoc analyses showed that diabetes risk reduction was clearly associated with the achievement of these lifestyle goals. In the DPP study from the USA, dietary goals were reduced energy intake (to achieve weight reduction) and reduced total fat [124]. The diabetes prevention studies from China, India and Japan aimed at reduced fat, energy, alcohol and refined carbohydrates and increased fiber [12, 18, 19]. A recent study from Spain showed that adopting a Mediterranean diet, characterized by high intake of vegetables, fruit, legumes, extra virgin olive oil, nuts, fish, whole grains and red wine, also decreases diabetes incidence remarkably [125], without body weight reduction.

A pragmatic way to prevent diabetes therefore would be to focus on diet composition and physical activity. A strict diet emphasising dietary restriction and avoidance of certain food groups (e.g. sources of fat or carbohydrates) and aiming solely at weight reduction may be more efficient for achieving weight loss in the

short term, but may not be sustainable in the long run [126]. Diet may well vary according to food culture, food availability and personal preferences, and yet follow the same general principles:

– High intake of vegetables and fruits should be encouraged.

– Grain products should mainly be unrefined, with high natural fibre content.

– The vegetable sources of fat with low saturated fat content (such as olive oil) should be preferred.

– As a source of protein nuts, legumes, dairy and fish should be favoured and red meat limited.

The intake of highly processed foods (e.g. processed meat, sweetened beverages, confectionery) should be limited.

The elements for prevention: The right intervention to the person at risk. Supporting behavior change

As described above, there seem to be several possible routes to non-pharmacological diabetes prevention, but a common factor is the need to support sustained changes in lifestyle behaviors. However, achieving the required changes reliably is challenging. Both clinical intervention programs [127–129] and 'real world' diabetes prevention programs demonstrate wide variation in their ability to deliver weight loss or changes in physical activity [23]. It is therefore of importance to be able to characterise the components of lifestyle interventions that are reliably associated with increased effectiveness. Only by understanding what makes interventions effective, can we design diabetes prevention programs that will a) deliver the expected benefits and b) optimize cost-effectiveness in scalable, real world prevention programs [39].

A recent 'review of reviews' systematically examined a wide range of evidence from existing high quality reviews of RCTs of interventions to support changes in diet and /or physical activity in people at high risk of developing T2DM [118]. Based on the grading of 129 analyses that related intervention characteristics to effectiveness, evidence-based recommendations were developed and these are shown in Table 4. These recommendations are broadly consistent with other recent international guidelines on supporting lifestyle change in people with high cardiovascular risk [130], with type 2 diabetes [131] and obesity [132].

Table 4

The F.I.T.T. recommendations: general guidelines for individuals of moderate fitness

F.I.T.T. principle		Aerobic Endurance Training	Resistance Training
Frequency	How often	3x / week (minimum) Max. 2 days gap between training sessions	2–3x / week
Intensity	How hard	(a) light to moderate (40–60 % VO_2 max. / 50–70 % HRmax) (e.g. brisk walking — 5–6 km/h) slightly increased breathing rate; (b) vigorous (e.g. jogging — 8–10 km/h) increased breathing rate and sweating	light to moderate (slight muscular fatigue)
Time	How long	(a) light to moderate 45–60 min (in total > 150 min/week) (b) vigorous 30–40 min (in total > 90 min/week)	1–3 sets of 8–15 repetitions for each exercise
Type	What kind	walking, jogging, cycling, swimming, hiking, skiing	about 8 different strength exercises using the major muscles of the body (e.g. with fitness machines, resistance-bands or just with your own body weight)

Applying these recommendations may help to guide the selection of intervention components in a way that maximises the likely effectiveness of diabetes prevention programs. However, it is worth noting that the evidence base on «the best strategies for supporting behavior change» is far from complete. Individuals with high diabetes risk from different backgrounds and cultures may be responsive to a number of different strategies that modify the cognitive, social, and emotional processes that underpin their lifestyle behaviors. There are also a number of possible modes of intervention beyond persuasive face-to-face interaction, including modifying the physical environment and changes in food-pricing or regulatory /taxation regimes. Hence, there may be considerable opportunities to further increase the efficiency and cost-effectiveness of programs to support lifestyle behavior change.

Considerable attention is also needed to address the issue of maintenance of lifestyle changes. Long term follow-up of weight loss interventions shows a clear pattern of weight regain over 5 to 10 years, even in the successful diabetes prevention research studies [37, 126]. It is likely that when weight loss is achieved through changes in diet or physical activity that are challenging for people to adhere to or that they do not enjoy, these changes will not be sustainable in the long term. Recent data from a meta-analysis of multiple long-term cohort studies indicates that a habitual energy imbalance of about 50 to 100 kcal per day seems sufficient to cause the gradual weight gain observed in most adults [133]. Consequently, «modest, sustained changes in lifestyle could mitigate or reverse such an energy imbalance». Hence, promoting a series of small changes that people can easily live with, rather than dramatic changes in diet or activity may be a strategy worth further investigation.

Recommendation for diabetes prevention practice

The European Union supported the IMAGE project (Development and Implementation of a European Guideline and Training Standards for Diabetes Prevention), a multi-professional initiative to develop practice recommendations for diabetes prevention practice [134]. More than 100 experts in this field worked for 2.5 years to prepare an evidence-based guideline on T2DM prevention [46], a Toolkit for diabetes prevention practice [49], a guideline for evaluation and quality management in T2DM prevention [135] and an European training curriculum for prevention managers [136]. The major output of the IMAGE project — relevant for prevention practice — is the practical diabetes prevention guideline called «Toolkit for the prevention of type 2 diabetes». This toolkit is developed for all professionals involved in diabetes prevention: those working in primary healthcare services, physicians, physical activity experts, dieticians, nurses, teachers, but also stakeholders and politicians. The Toolkit condenses the essence what is necessary to build up the management of a diabetes prevention program, financial, intervention and quality assurance aspects and refers to the latest evidence in diabetes prevention. The core of the Toolkit describes elements of an effective lifestyle intervention program and gives the core goals of lifestyles (behavior, physical activity and diet) and finishes with an overview on how to evaluate intervention programs and how to establish quality assurance. It provides several recommendations that may help in planning and implementing a type 2 diabetes prevention programs worldwide [4, 25, 137].

Intervention cost/scarce resources: There is clearly a tension between the evidence-based recommendation for maximizing intervention intensity (number or frequency of contacts) and the practical availability of resources (suitably trained staff and funding) for diabetes prevention. However, this tension might be reduced in several ways. These include:

- Using group-based interventions. There are several good examples of group-based interventions that produce levels of weight loss similar to those in the large diabetes prevention studies, at least in the short term (Table 1). Group-based intervention also costs less than individual intervention [138, 139].
- Reducing staff costs: Lifestyle interventions can be delivered successfully by a range of staff, including doctors, nurses, dieticians /nutritionists, exercise specialists and lay people [118]. More research is needed to define the range of personal skills and type of training required to maintain program effectiveness [136].
- Self-delivered and internet based approaches. This type of intervention could potentially provide a low cost solution for a considerable sub-group of the population and may be a useful supplement for face-to-face programs. Given the success of such approaches to support smoking cessation [140] and recovery from depression [141], it should, in theory, be possible to use them to support changes in diet and physical activity. Although a number of programs are under evaluation, more robust evidence on effectiveness is still needed before this approach can be endorsed.
- Developing standardized recommendation for diabetes prevention practice [46, 49]: Applying the recommendations on supporting behavior change (Table 4) should enhance the efficiency of lifestyle intervention programs.
- Disclosing the economic benefits of diabetes prevention [142]. Economic modelling indicates that group-based diabetes prevention interventions in the US would provide a return on investment within a 3 year timeframe. This has resulted in the release of significant resources in the US from government and Health Maintenance Organisations.
- Expertise: In order to deliver prevention programs on a large scale, we need to identify a sufficient number of people with the expertise and experience to design and deliver them. Investing in high quality training would seem to be essential for the implementation of successful programs [136].

• Maximising the uptake of both screening and intervention: Further research is needed in this area, but this may require multi-media approaches, involvement of multiple sectors (public health, voluntary sector, commercial /workplace programs, healthcare and social care) and the use of social marketing techniques to target messages to appropriate population sub-groups.

• Ensuring sustainability of funding and support within both healthcare and political arenas: This will require a sustained focus and willingness to invest in preventive healthcare. The forthcoming UN Summit on Non-Communicable Diseases presents an opportunity to more firmly and sustainably establish diabetes prevention on the global health agenda [143].

• Developing quality management systems: Quality management systems are needed to provide continuous bench marking and monitoring of the effectiveness of prevention programs [135].

• Further improving the technology to support behavior change: This could be achieved by establishing «networks of practice» so that we can learn how to improve the efficiency of interventions from practice /real world experience as well as from developments in theory /research. The Global Network «Active in diabetes prevention» — www.activeindiabetesprevention — provides a forum for exchanging knowledge and intervention materials as well as educational standards and recommendations for prevention practice.

Improving effectiveness in diabetes prevention practice

One of the challenges in developing intervention programs for diabetes prevention is to find the right intervention which has the highest probability to be successful in the individual with high diabetes risk. This strongly varies between different individuals. In today's practice we should aim to be using standardized and structured intervention programs that we apply to all the people at risk which we have identified in a prevention plan. By this approach, we accept that sometimes only 20 % of the people achieve the highest effect and that in 80 % of the people the programme may be less efficient [144]. It is possible to increase the probability of success by developing intervention programs that follow a behavior change model. Such a model was developed as part of the IMAGE project whereas the patient is seen as being in 3 stages [145, 146]:

– the stage of motivation;

– the stage of action;

– the stage of maintenance.

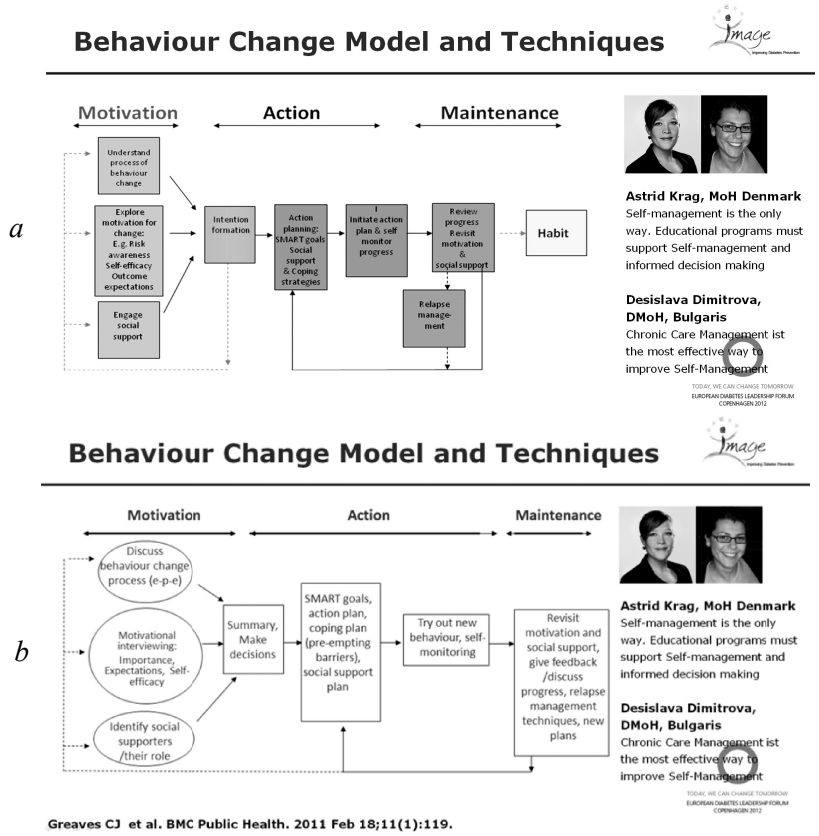

Figure. Behaviors Change Model and behavior change techniques based on [146]

The development of intervention programs following this behavior change model may generate a higher efficacy due to an increase in flexibility in the program execution. The key point in the IMAGE project was that the behavior change model (BCM) was accompanied by a collection of behavioral techniques for supporting the lifestyle changes (Figure). Specific tools and techniques for each stage of the BCM were elicited from more than 300 studies [146] and shown to be effective. The prevention manager can choose the techniques needed for the intervention in several stages. The use of the techniques allows a much more widespread implementation of an intervention plan and may be one step away from only focusing on structured and standardized intervention concepts by allowing a higher degree of flexibility of the intervention manager and focusing more on individual needs and preferences.

This behavior change model then was further developed by a working group derived from the IMAGE project [23, 146]. Daily practice in performing intervention shows that even the intervention planning by focusing on the BCM misses an effect in a large number of people receiving the intervention. One of the difficulties is associated with the use of standardized programs which follow a standardized curriculum. Furthermore, difficulties also arise by the effect that most of the intervention programs do not include different preferences and interests of the people receiving the intervention. This is followed by different stages of morbidity [39] which also define different preferences and interests which can be a barrier to an effect of a program if someone with the very low risk expression is sitting together in an intervention group with someone having a very high risk and different preferences and interests. Based on this background the further development of intervention programs have to take into account to develop an assessment to identify the most suitable intervention characteristics for a person at risk.

The elements for prevention: Moving Diabetes Prevention into practice

A challenging step is to translate the research findings into nationwide or regional diabetes prevention programmes that translated the research findings to the real-life health care settings. Finland has led the way with FIN-D2D, a large-scale implementation covering a quarter of the Finnish population [147]. Another landmark was the profusion of published implementation trials including GOAL and the Saxon DPP in Europe [148], the Greater Green Triangle DPP in Australia, the Walking Away from Type 2 Diabetes programme in the United Kindom (UK) [39, 149] and programs in Indianapolis Pittsburgh and Montana in the United States [150, 151]. A great challenge will be the scaling up from these implementation trials to sizeable regional and national programs.

Political support is needed and this requires the development of a national or international action plan for diabetes prevention, which needs involvement of a number of stakeholders at a governmental and non-governmental level. Furthermore, the presentation of the evidence in the field for diabetes prevention on the scientific and practical level as well as the training of people to deliver preventive intervention is required.

The European experience

The two European funded Projects DE-PLAN [152] and IMAGE [153] have been addressing the implementation process. Especially the IMAGE project was able to collate this information in a systematic manner, including an evidence-based guideline on T2D prevention [46], a toolkit for the prevention [154] and a paper on quality indicators in T2D prevention [155]. Furthermore, IMAGE developed a curriculum for the training of prevention managers. This training includes a seven day curriculum for educators and to learn necessary skills to deliver preventive intervention, and acquire accreditation.

Toolkit for the prevention of type 2 diabetes

One major output of the IMAGE project is the practical guideline called «Toolkit for the prevention of type 2 diabetes». This toolkit is aimed at all people involved with diabetes prevention: those working in primary and specialised healthcare services, physicians, physical activity experts, dieticians, nurses, teachers, but also stakeholders and politicians. The IMAGE Toolkit contains useful information for local and national politicians and health policy makersinterested in creating an environment which facilitates healthy ageing and the implementation of the WHO recommendation that «we must make the healthy choice the easy choice.»

The Toolkit [156] includes the essence of what is necessary to build up a diabetes prevention program covering management, financial, intervention and quality assurance aspects and refers to the latest evidence in the science of diabetes prevention and allows translating this knowledge into practice. The Toolkit addresses issues such as how to finance a prevention program and how to identify people at risk. The core of

the toolkit describes elements of an effective lifestyle intervention program. A process model for supporting lifestyle behaviour change is presented and described in its phases (motivation, action and maintenance). The Toolkit gives the core goals of lifestyles (physical activity and diet) and gives practical instructions about how to address these with the individual. Other behaviours to consider in diabetes prevention are, e.g., smoking, stress/depression and sleeping patterns. The Toolkit finishes with an overview on how to evaluate intervention programs and how to establish a quality assurance programme.

The toolkit provides a good balance between clear, accurate information and practical guidance, it is not however intended to be a comprehensive source of information. Specifically, detailed instructions about how to achieve and maintain weight reduction, which is one of the main issues in diabetes prevention are not given because local and national guidelines as well as other information are available elsewhere. Furthermore, intervention delivery staff are assumed to have basic knowledge about e.g. diet and physical activity and their health effects and about supporting behaviour change. Finally, the toolkit is not designed to be used to provide intervention materials to be delivered directly to those participating in prevention interventions, although it does contain some examples of information sheets and materials which might be used with participants.

Content of the toolkit

The toolkit starts with an executive summary including the rationale for diabetes prevention [49]. It is followed by a chapters representing the background (type 2 diabetes prevalence, risk factors, consequences, evidence of successful prevention), and giving instructions about the planning and development of prevention programmes and the identification, and recruitment of participants at high risk for T2DM. One of the core items of the toolkit is the description of what to do and how to do it. Behaviour change is a process which requires individual attention, and effective communication to achieve motivation, self-monitoring, sustained support and other intervention to prevent and manage relapses. This section includes a model of intervention including empowerment and patient-centred messages. It is followed by key messages on behaviour (physical activity and diet) that are important in prevention of diabetes, and practical advice for patient-centred counseling. The focus is on long-term, sustainable lifestyle changes.

Finally, a brief guide for evaluation and quality assurance in reference to the «Quality and outcome indicators» is included. This section is followed by a consideration of possible risks and adverse effects. The IMAGE Toolkit main text ends with a positive mission statement, emphasizing what can be achieved if we work together. The appendices give the reader a set of easy-to-use tools including a checklist for prevention programme development, templates for goal-setting and for food and physical activity diaries, an example of a risk screening questionnaire (the FINDRISC questionnaire) and a template for evaluation and quality assurance data collection [49].

Prevention manager

As part of the IMAGE project, a curriculum for the training of prevention managers was also developed [157]. The purpose was to develop common European learning goals, teaching methods and contents as well as teaching material for the training of health care professionals who want to carry out lifestyle interventions for diabetes prevention (Prevention managers^{T2Dm}). With this curriculum, for the first time a standardised state of the art training for health care professionals interested in offering preventive intervention can be performed Europe-wide in a comparable and consistent way. This is particularly useful because a standardised method to train the trainers for diabetes prevention can also pilot the same strategies for the prevention of other chronic diseases. All materials needed to train a prevention manager will be freely available at www.virtualpreventioncenter.com. National institutions, such as universities or associations interested in the training of eligible health care professionals are encouraged to download the specific teaching material and follow the curriculum for the training of prevention managers.

The idea behind the curriculum for the training of diabetes prevention managers was to develop a standardised training curriculum for people coming from different professional disciplines, but who, together want to deliver coordinated interventions for the prevention of type-2-diabetes. Currently 11 European countries and more than 20 extra European countries have started to train prevention managers following the IMAGE curriculum.

National Initiatives

Along with European level support, National governments and health care organisations are increasingly developing tailored national policies and guidance aimed at the prevention of chronic disease. For example, Finland has adopted a regional systematic whole system approach across all sectors of the health care community, including primary care, pharmacy and community settings, to the prevention of type 2 diabetes [147]. In the United Kingdom, the National Health Service Health Checks Programme has been rolled out nationally and aims to screen all individual between 45 and 70 years for the risk of chronic disease and treat high risk individuals accordingly (http://www.healthcheck.nhs.uk/) [158]. In addition, new NICE guidance has been published which provides a blueprint for the prevention of type 2 diabetes in the community and primary care [68]. A similar program is underway in Germany. A health check were all persons between 35 and 65 years are eligible will be established including FINDRISC, parameters of the metabolic syndrome, HbA1c and creatinine. A standardized management of persons screened at risk into primary and secondary prevention programmes will be established or inclusion into disease management programmes for newly identified diabetes patients.

In November 2011 Denmark has introduced a tax on saturated fatty acids. 1 kg saturated fatty acids increased taxes by 2,50 €. This has successfully reduced the sales of products with a high content of fat significantly. Unfortunately after 11 months Denmark has postponed the tax due to disruption of national business, because Danish people tended to cross boarder shopping in Germany. Both examples show that standardized guidelines and summarized evidence alone does not foster itself the implementation of diabetes prevention programs. National initiatives are the key targeting people at high risk which can be a success model on regional, local or national arena. Population based strategies for example including taxes for unhealthy food require pan national policies and activities, but can be very efficient on overall public health on a population.

The US experience

Reduction in the incidence of type 2 diabetes on a population level requires collaboration among community-based organizations, insurance payers, health care and public health professionals, academia, and others. In 2010, the U.S. Congress authorized the Centers for Disease Control and Prevention (CDC) to establish the National Diabetes Prevention Program (National DPP) to translate and systematically scale the U.S. DPP for individuals at high risk. The National DPP brings together the groups listed above and unifies delivery of proven lifestyle change programs in communities throughout the country. The National DPP consists of four components:

Training

CDC established the Diabetes Training and Technical Assistance Center (DTTAC) at Emory University to help increase the work force by providing training to lifestyle coaches and those who train lifestyle coaches. There are other organizations, such as the YMCA, that provide training so DTTAC also serves to coordinate training functions (http://dttac.org).

Program Recognition

The CDC Diabetes Prevention Recognition Program (DPRP) (www.cdc.gov/diabetes/prevention) assures program quality, consistency, provides a registry of re- cognized programs, and implements standardized reporting on performance of recognized programs.

Intervention Sites

The YMCA (Y) and United Health Group (UHG) are the first to participate in the National DPP and are collaborating on instituting community-based prevention programs in which the Y delivers the lifestyle change program while the UHG provides third-party reimbursement for its beneficiaries. This is a new payment model in which an insurer reimburses a community-based organization based on performance. With implementation of the DPRP, more organizations are involved in program delivery and reimbursement.

Health Marketing

Participant engagement and health care provider referrals are important for program success. CDC and others, such as the Diabetes Prevention and Control Alliance, are testing various marketing strategies to enhance program participation. The public health sector can play an important role in continuous evaluation and monitoring to ensure successful implementation of diabetes prevention programs. Furthermore, this is

vital for quality assurance and benchmarking of standardized procedures. Scientific outcome evaluation indicators and measurement recommendations (e.g., body weight, waist circumference, HbA1c, total energy intake, etc.) have been developed to monitor the effectiveness and efficiency of programs [135]. Recent experience demonstrates that monitoring alone, as function of quality management, is a driver for increasing the quality of intervention programs [159]. The CDC DPRP, as part of the National DPP, serves this monitoring function for diabetes prevention programs in the U.S.

The elements for prevention: steps to develop a prevention program.
Basic science in diabetes prevention

Exploration of the molecular physiology of the prevention of type 2 diabetes is key in both understanding the pathomechanisms of diabetes prevention and also in developing targeted intervention programs with improved outcome. Growing evidence suggests that insulin resistance, in a normoglycaemic person, is the key processor of the development of diabetes risk [40]. The role of visceral fat mass and visceral obesity seems to be a key trigger for the development of insulin resistance [160]. The visceral fat secreted adipokine profile directly influences inflammatory processes and insulin resistance development which then altogether directly influences diabetes risk [161]. Furthermore, together with an increasing level of circulating insulin, also proinsulin seems to become a major factor in triggering diabetes development and, subsequent cardiovascular disease and cardiovascular morbidity. Understanding these pathophysiological mechanism will make it necessary to explore the genetic basis of the regulation of insulin resistance and to understand visceral obesity and the combined pathophysiology behind it. Current evidence from genome-wide association studies explains a small proportion of diabetes pathophysiology [162, 163]. However, current investigations suggest that there is a link between genetic susceptibility and the outcome in preventive interventions [164, 165]. Furthermore, basic prevention studies show there is a substantial proportion of people at risk for diabetes, who do not respond to an intervention or do not benefit from an intervention, even without diabetes development. A significant challenge in the future is the development of pathophysiology-targeted prevention programs, as well as the identification of non-responders for preventive interventions.

Efficacy in diabetes prevention

To test intervention concepts and to generate evidence about intervention structures, diabetes prevention programs have to be tested in ideal randomized control trial (RCT) settings. In recent years considerable evidence showing that sustained lifestyle change enables a significant ability to prevent or delay type 2 diabetes has developed [15, 166], A number of large randomized clinical trials have shown that interventions, focussing on improved physical activity and nutritional intake along with strategies and supports for behaviour change, enabled up to 58 % prevention of type 2 diabetes. Furthermore, using traditionally known diabetes drugs, enables prevention of type 2 diabetes [15, 17]. Lifestyle interventions and drug treatment do not show an additive effect; unfortunately, there is conflicting evidence about the combination. Lifestyle intervention was more effective in older adults and less in obese people than the drug metformin. Metformin was more effective in younger, heavier people and women with a history of GDM in the United States Diabetes Prevention Program (U.S. DPP) [15]. By summarizing the efficacy in diabetes prevention, we have learned that the prevention of diabetes is effective and feasible, but we have also identified barriers and the challenging task of how to implement this knowledge. [167].

The efficacy of diabetes prevention programs may be strongly influenced by pathophysiological differences. There is a huge variation for the conversion from impaired glucose tolerance to diabetes mellitus and the trigger mechanisms are not completely understood. The efficacy will increase as higher the conversion rate is, as well as higher the prevalence of impaired glucose metabolism in the population is. Due to the fact, that the prevalence of impaired glucose tolerance increases in nearly all populations, the efficacy of diabetes prevention programs may increase in the future [23].

Effectiveness in diabetes prevention

After obtaining the evidence derived from RCTs, it is necessary to translate this knowledge into real-world settings. This generates a number of new challenges and makes it necessary to start a critical discussion about necessity and practicability of what was done in the RCTs and what is applicable to real-world settings. A number of translation studies have tried to do this and have found ways to reduce costs and achieve the same or similar weight loss as the RCTs. There are challenges in moving from RCTs to real-world implementation in diabetes prevention. One issue is screening to identify those at high- risk. It is unre-

alistic to believe that performing two OGTTs for screening, which is done in some countries, can be appropriate for prevention programs in real-world settings, except for a very high risk individuals in the medical environment. A number of translational trials have been performed in several parts of the world, with different experiences. The implementation design often depends on limited financial resources and is driven by the circumstances in the environment to enable screening and intervention. Therefore, the translational trials are often driven by the practical need for diabetes prevention and the dimension of the clinical and public health problem in the environment. They adjust screening procedures and interventions to the existing environments, driven by the hypothesis to test the feasibility and applicability of an intervention program to the real-world setting [51]. The subsequent translation studies of the U.S. DPP have shown that by delivering the program in a group setting (instead of one-on-one) and utilizing lower-cost trained health educators and community organization staff, the program can be delivered effectively and cost-effectively [168].

Efficiency of diabetes prevention

After having learned from the implementation trials and having put together practical evidence from effectiveness studies, the next challenge is to modify the programs or their implementation to achieve the biggest impact for the most people who need the intervention. The efficacy research studies are often only applicable to a limited part of the population and studies often include a relatively small number of people. The effectiveness trials are more likely to use a more broadly defined high risk population, but the interventions that have been proven to be effective in real-world settings still may not address factors that will scale the intervention to reach the most people. At this stage, for the first time, policy perspectives and plans for cost-effective expansion of the intervention come into account. RCTs or effectiveness trials cannot tell us how to achieve the best effect for most of the people; this requires networking with a number of specialists and stakeholders from neighbouring fields in medicine and public health and expertise in fields such as management, economics and policy development.

To be efficient in the prevention of type 2 diabetes on a population-level, political support on local and national levels to build national diabetes prevention plans is needed. These plans help relevant players and stakeholders to network in order to agree on a concerted action involving different resources from societal and personal life to enable an efficient and wide reaching type 2 diabetes prevention program.

Availability of diabetes prevention

After addressing the efficiency of diabetes prevention through a practical framework of stakeholders, as well as, political support and necessary resources to enable a population impact, it is necessary to address program availability and accessibility and capacity. Availability includes an adequate number of programs in the com- munity within easy access, the existence of adequate personnel resources to train the prevention managers, as well as, an adequate number of prevention managers. The development of the European curriculum for the training of prevention mangers is a relevant achievement to standardise intervention procedures and to develop «train the trainer» strategies. As part of the National Diabetes Prevention Program, the United States has developed the Diabetes Training and Technical Assistance Center at Emory University to help train master trainers and lifestyle coaches and coordinate training efforts [168]. Policies that support adequate resources and coordination are important at this stage and support from scientists and medical experts in the field to drive the right political decisions and program availability is vital.

The industrialization of diabetes prevention programs becomes a relevant challenge. The Danish example with the tax on saturated fatty acids is an effective model for diabetes prevention on a national scale, but failed due to political reasons and the missing pan European policy. The industrialization can also be achieved by adequate and intensified training of medical professional and healthcare workers to perform diabetes prevention programs and to build a framework to implement business solutions for diabetes prevention. The extensive growth of new media and mobile health solutions may help to make healthy lifestyle information more available throughout the population, but also to enable mobile health intervention concepts. We have to except that not one solution will address the needs of a large population. We will need a number of solutions providing adequate care and attention for diabetes prevention, based on target population, individual prevalence, readiness to change lifestyle, environmental and regional aspects and many more [23].

Distribution of diabetes prevention

The best program, if it is not reachable for people with increased risk, will fail [148]. Any preventive action will have to be performed in the environment in which the people with increased risk live and work

[3, 169]. Structures and policies to identify high-risk individuals and manage intervention follow-up, and evaluation have to be established. Scientific evaluation standards based on the RCTs need to be translated into the public health care setting with careful management of considerably more limited resources. This has been achieved in Europe by the international IMAGE consortium with a quality management structure [135]. In the United States, the National Diabetes Prevention Program contains a recognition program that set standards that help assure program quality and consistency. CDC is responsible for conducting this program and reporting on the distribution and quality of the diabetes prevention program across the United States [169].

Fulfilling the development of a national diabetes prevention program

Within the European Union, only five of 27 countries have a national diabetes plan and only one has a national diabetes prevention program [170]. In Asia, the situation is similar with a progressive increase in the number of countries including diabetes prevention in their national policies [171]. The United States is at the forefront of governmental initiatives for developing a diabetes prevention program with the CDC being the driving force for coordinating the national effort [168]. The existence of a national policy for supporting diabetes prevention does not always equate with a positive outcome, but it is a mandatory first step for successful public health implementation. The European Coalition for Diabetes, together with the EU Diabetes Working Group, has installed working groups to address the need for delivering adequate care for diabetes in Europe. Those working groups have elaborated recommendations to the EU institutions and other governments to take urgent action to address the major public health challenge that diabetes represents. Currently in the UK and Germany National programmes undergoing development include the NICE and the UK Vascular Check Programme and the German Check-up 35+ programme.

To prevent type 2 diabetes, an adequate scientific basis provided by research, efficacy studies in highly controlled environments, and effectiveness studies in real-world environments performed by clinical researchers and public health experts are necessary. To scale up diabetes preventive actions to the population, the program strategies have to be adjusted to have the best effect for a relevant proportion of the population as well as the supply and diffusion of the intervention into the population. Policy development is a necessary part of the latter three steps. The development of national diabetes plans, which are supported by local prevention management and adequate networking and stakeholder involvement, are necessary to address this challenge and guide implementation of diabetes prevention [4].

Health Literacy: barrier or improvement measure?

In addition to political and financial challenges of health systems, we are witnessing, that it is not enough to plan, implement, monitor and evaluate prevention by just looking at medical needs of patients. Scientific evidence shows, that people with low health literacy have a higher risk for a poor health status [172], higher hospitalization rates [173] and higher mortality rates [174]. Looking especially at type-2-diabetes, patients with low health literacy tend to have a poorer glycemic control [175] and are less aware of symptoms related to hyperglycemia [176]. Those who have the lowest health literacy competences have a higher risk for developing chronic conditions. On top of that, it is less likely that these patients receive the care they actually need. Additionally, they are having substantially poorer preconditions to seek, find, understand, and use (online) health information, to take informed decisions [177].

The adherence to medical treatments and behavioral lifestyle change primarily works for those with a considerable level of health literacy and systematically causes inequalities in terms of access to care, support and information [178]. Recent studies indicate that some patients seem to be systematically excluded from these benefits due to low health literacy skills, potentially leading to an extension of health inequalities and a growing amount of people not participating in care [179, 180]. A recent review of Morony emphasizes that more than 90 % of educational materials written for kidney disease is higher than an average patient's literacy, limiting the understanding of key massages [181].

A recent report from the European Commission indicated that more than 80 % of the European population is using the internet for private purposes on a daily basis but more than 40 % of the total population and even 59 % of citizens with low health literacy have never searched for health related information online [182]. However, improved digital health literacy and literacy-adequate health information represent a great opportunity to gain positive impact on the citizens' personal level regarding knowledge, motivation, self-confidence, treatment adherence, feelings of control, social involvement, improved decision making and empowerment [111].

For the prevention and care of diabetes it is therefore of utmost importance to incorporate the ability of patients in understanding, translating and applying health-related information.

Diabetes risk in childhood and adolescence

The prevalence of childhood obesity has increased dramatically during the past decades although there is emerging evidence that prevalence rates seem to have stabilized at present, albeit at high levels, especially in the younger age groups [183, 184] Overweight and obesity now affects between 15–30 % of all children and adolescents in many industrialised countries. The rise in childhood overweight and obesity has dramatically altered the demographic profile of chronic disease in affected countries. For example, type 2 diabetes, once a clinical rarity in younger adults (< 40 years) and children, has now prevalence rates estimated to have increased by up to 10-fold in recent decades [185]. This shift in the profile of type 2 diabetes has a serious consequence as its emergence in younger age groups represents an extreme phenotype that magnifies the disease profile observed in adults. Risk factors for the development of T2DM in childhood and adolescents include [186, 187]:

– Type 2 diabetes of first- or second degree relatives;
– Morbid obesity (BMI > 99.5 percentile);
– Ethnical background (East Asians, African-American, Hispanics);
– Clinical signs of insulin resistance or associated features (syndrome of polycystic ovaries, acanthosis nigricans, dyslipidemia, elevated liver enzymes).

In addition to the development of T2DM, affected individuals are also at higher risk for the development of significant cardiovascular comorbidities early in life: Compared to age-matched healthy controls, incidence of myocardial infarct in younger people with type 2 diabetes has been shown to be fourfold higher than in late-onset type 2 diabetics and 14-fold higher than in people without diabetes[188]. Preliminary data from adolescents with type 2 diabetes in Canada, followed-up for 9 years, found that the mortality during this period was almost 10 %. Along with increasing the prevalence of chronic disease and mortality rates in younger age ranges, childhood obesity also significantly increases the risk of chronic disease into adulthood [189]. Thus the emergence of deleterious lifestyle practices and obesity in younger age ranges will have a devastating clinical and societal legacy that is only just beginning to emerge. The focus of health care policy and research, which has commonly targeted those over 40 years of age, has lagged behind this substantive shift in the demographic profile of obesity and chronic disease. However, if left unchecked, it is clear that this will become one of the primary clinical priorities within the next couple of decades. Therefore, high-quality research is urgently needed to investigate optimal methods of identifying and treating diabetes risk in children and adolescents. This includes the development of integrated risk scores that are lacking in this group. However, at present the World Health Organisation recommends that, starting at 10 years of age, an oral glucose tolerance test (OGTT) should be performed in overweight (BMI > 90. percentile) children or adolescents who present with at least 2 additional risk factors mentioned above or several clinical signs or associated sequalae of insulin resistance [186]. Once diagnosed, «conservative» approaches including lifestyle changes, promoting physical activity, and assessing and optimizing dietary habits should be the main focus of intervention at that age group. Metformin [190], a common first or second line therapy for adults, may also be appropriate for children and adolescents with diagnosed T2DM, and clinical studies for the use of metformin in impaired glucose tolerance in the pediatric population are underway. It is crucial that children and adolescents with type 2 diabetes are seen by a pediatric endocrinologist/diabetologist to receive comprehensive diabetes health education and long term clinical care within a specialized centre [187].

The clinical environment sets a number of limitations because only a selective clientele of adult patients is accessible — those who go to a physician due to disease burden, whereas the majority of the paediatric population is regularly seen by a paediatrician for routine medical checkups, vaccinations, or other reasons and might than be screened for relevant risk factors. On the other hand the clinical environment enables a more comprehensive and targeted approach due to the availability of diagnostic and treatment as well as intervention procedures. The public health environment offers a far more wide spread accessibility to target populations and to identify people at risk. The public health strategy is more related to address population embedded risk behaviour to be addressed by comprehensive health policy.

For a clinical applicable approach to target diabetes risk reduction we recommend

• screen the adult population by using the FINDRISK score or a comparable risk score as well as available clinical data by screening computer data bases;

• Where possible, those above a predefined high risk threshold level should have their risk status confirmed, and the presence of type 2 diabetes ruled out, by a simple measure of glycaemia, such as fasting glucose or HbA1c.

• In children > 10 years of age, an OGTT should be performed in overweight (BMI > 90. percentile) subjects who present with at least 2 additional risk factors (T2DM of first- or second degree relatives, morbid obesity (BMI > 99.5 percentile); ethnical background (East Asians, African-American, Hispanics), clinical signs of insulin resistance orassociated features (syndrome of polycystic ovaries, acanthosis nigricans, dyslipidemia, elevated liver enzymes).

• Those children/adolescents and adults confirmed to have a high risk status or even confirmed IGT/T2DM, are eligible for lifestyle intervention programs (all age groups) or pharmaco-preventive strategies (mainly adults).

Conclusions

It seems that diabetes prevention is a major opportunity for global health and some have even referred to it as «the future of diabetology». The evidence that diabetes is a preventable disease is excellent. A number of large randomized clinical trials have shown that more than 50 % of diabetes risk can be reduced and diabetes can be postponed and prevented sustainably over more than a decade. Translational studies that tried to translate scientific evidence into clinical practice have proven that similar results are reachable in clinical practice and that it's feasible to implement diabetes prevention programs in different care processes and structures. But those translational studies also have shown that it's the responsibility of healthcare policies to harness existing care structures and infrastructure to structure the prevention program and what is the outcome for the person at risk and the community. Over recent years we have learned a lot about non pharmacological interventions and that they are effective in preventing diabetes from developing and we have gained a lot of knowledge regarding policies that still need to be developed [23]. Effective strategies to identify people with increased diabetes risk are available. Changing physical activity and eating habit can be effective in prevention diabetes but most effective seems to be to «walk the diabetes away» approach. 10000 steps and more a day prevent diabetes significantly but already importantly 1000 additional steps to the normal daily amount of steps — even if much less than 10000 — are as effective as 1000 mg metformin.

Now we have to play the ball from the research arena into political field. Political support is needed to build up the framework for a successful implementation of diabetes prevention programs. But finally we together with all relevant stakeholders have to build effective and sustainable prevention programs. This should not be an excuse for researchers not to act — like Kofi Annan said: «We have not enough money to do nothing».

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П.Е.Х. Шварц, П. Тимпел

2-Типті диабеттің алдын алу мүмкіндігіне өмір сүру салтының ықпалы

Клиникалық тәжірибеде диабеттің алдын алу іргелі ғылымдар жетістігін қолдануды талап етеді. Соңғы он жыл ішінде клиникалық зерттеулер тәуекел тобының 2-типті диабет дамуын болдырмау мәселесінде өмір сүру факторларының маңыздылығы нақты тұжырымдалды. Қазіргі таңда диабеттің алдын алу бағдарламаларын нақты түрде ендіруде маңызды ақпараттарды соңғы зерттеулер беріп отыр. Жекелеген елдерде диабеттің алдын алу шаралары қабылданған, бірақ нақты тармақтар міндетті орындалу жоспарында ауқымды аймақтар немесе ұлттық бағдарламалары жұмыстарда қиындық тудырады. Жұмыс жүзеге асу үшін арнайы дайындықтан өткен медициналық қызмет көрсету, медицина саласындағы экономистер, денсаулық сақтау қызметкерлері және қоғамдық ұйымдар

өкілдері беделді саясаткерлермен өзара әрекеттесе қызмет жасауға бейім болулары қажет. Мақалада саяси қолдау өте маңызды құраушы болып табылады. «Қазіргі әлем тәжірибесінде» диабеттің алдын алу бағдарламасын жүзеге асыруда қажет зерттеулер нәтижелері көрсетілген.

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Влияние образа жизни на возможность предотвращения развития диабета 2 типа

Профилактика диабета требует использования достижений фундаментальной науки в клинической практике. В течение последних десятилетий клиническими исследованиями было твердо установлено значение факторов образа жизни в вопросах предотвращения развития диабета 2 типа среди лиц из группы риска. Последующие исследования предоставили важную информацию о реальном внедрении программ профилактики диабета. В отдельных странах предприняты усилия по профилактике диабета, однако при работе по большим региональным или национальным программам, конкретные пункты которых должны быть запланированы и выполнены, возникают определенные трудности: отсутствие подготовленных специалистов в области медицинского обслуживания, экономистов медицинского профиля, работников здравоохранения и представителей общественных организаций, способных взаимодействовать с влиятельными представителями политических кругов. Политическая поддержка является очень важным компонентом в работе по профилактике диабета. В статье представлены результаты исследования, которые могли бы помочь в успешном выполнении программы по профилактике диабета «Практика реального мира».

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Structure of risk factors developing of diabetes and cardiovascular diseases depending of the type of tobacco smoking

Smoking is a factor in increasing the risk of endothelial dysfunction and increase the risk of developing diabetes and cardiovascular diseases. The influence of active and passive smoking on the risk of developing diabetes and cardiovascular disease among population of industrial cities of Central Kazakhstan is analyzed. Smokers surveyed 766 people (609 women and 157 men) in Karaganda, Saran, Karaganda region. It is established that a high risk of developing diabetes was observed in 31 % persons with passive type of smoking with prevalence of women 92 % in comparison with 63 % active type of smoking. Physical work predominated, higher in the group with active type of Smoking — 71 % comparatively with 65 % in the group of passive smoking. A high cardiovascular risk among almost 80 % of persons with active type of smoking and high risk of diabetes in group with passive smoking.

Key words: active, passive smoking, the risk of diabetes, screening, Findrisk, Score.

Actuality

Among of the leading behavioral and physiological risk factors related to mortality, the second after high blood pressure (13 % mortality) followed factor of tobacco smoking (9 %) [1, 2]. Development of Endothelial dysfunction and cardiovascular diseases are a important factors in their development and in combination with diabetes mellitus, tobacco use exacerbates the development and further progression of diabetic macroangiopathy in the form of lesions of the coronary vessels of the brain. Combination of smoking and one of other risk factors such as hypercholesterolemia and blood hypertension result risk increasing exponentially in compared with persons without risk factors. Prevalence of tobacco use to date is an important prognostic indicator of the future burden of active smoking-related diseases, including important role in the risk of developing diabetes. The prevalence of active smoking among adults globally, according to WHO prevails among men: 36 % comparatively with 8 % in women. Recently, there is evidence held by the research on the effect of passive smoking on the risk of developing of lung disease and of diabetes. This type of smoking the most pre-dominant among females [3, 4, 7].

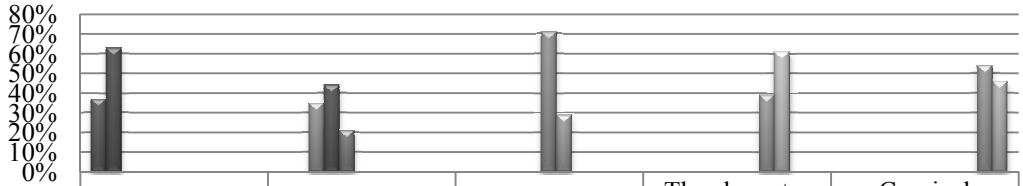
According to the WHO the number of people with registered diabetes had increased from 108 million in 1980 to 422 million in the year 2014. The global prevalence of diabetic patients among people older than 18 years increased from 4.7 % in 1980 to 8.5 % in 2014. WHO estimates that in 2012 year 1.5 million deaths were directly caused by diabetes and a 2.2 million deaths were due to the high level of blood glucose concentration. Almost half of all deaths caused by high concentration of glucose in the blood occurs before the age of 70 years. Mortality in European region accounted for 238 person and a maximum mortality rate — in the African region, South-East Asia: 322 and 382 person per 100000 population respectively [1]. According to the Ministry of health of Kazakhstan in 2013, the number of incidence of diabetes is 170 persons per 100 thousands of population and mortality from late complications of diabetes as a diabetic macroangiopaty (strokes, heart attacks) accounted for 141 to 100000 of the adult population with a tendency to increase compared with the year 2012 [6].

The aim of investigation: to evaluate the prevalence of active and passive tobacco smoking while carrying out a screening survey of the population of downtown Saran, Land Karaganda and to study their possible influence on the risk of developing diabetes.

Materials and methods

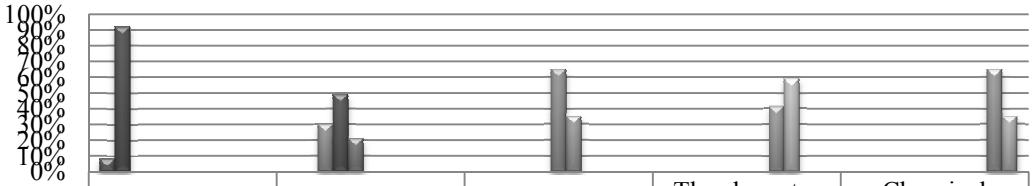
A cross-sectional investigation as form of screening among residents of the city of Saran was carried out. Human 766 patients aged 18 to 65 years have been examined: 609 women (79.5 %) and 157 men (20.5 %). Questionnaires included questions of active and passive smoking, duration of smoking, social and demographic indicators, history of chronic disease. Active smoking was assessed by the smoker index (IR): IR of more than 10 — high risk, passive smoking by means of a questionnaire, data on smoking spouse, partner. The risk of developing diabetes was estimated using of scale Findrisk, the criteria for a low risk:

<7–11 points, high risk of development of diabetes from 12 to 20 points and measuring of blood glucose concentration was used to determine the glucose level of capillary blood. Cardiovascular risk was estimated by the SCORE scale (Fig. 1, 2.)



	Gender	Education	Employment	The character of work	Cronical disease
Male	37%				
Female	63%				
Average		35%			
Specialized secondary		44%			
higher		21%			
Work			71%		
Not work			29%		
Mental				39%	
Physic				61%	
Yes					54%
No					46%

Figure 1. General characteristics of subjects in the contingent of active smoking group



	Gender	Education	Employment	The character of work	Chronical disease
Male	8%				
Female	92%				
Average		30%			
Specialised secondary		49%			
higher		21%			
Work			65%		
Not work			35%		
Mental				41%	
Physic				59%	
Yes					65%
No					35%

Figure 2. General characteristics of contingent subjects in the passive smoking group

Results

Results of comparative investigation of the characteristics in terms of social and demographic indicators showed the presence of prevalence among women in groups with active and passive smoking: 92 % and

63 % respectively regardless of the level of education of women (secondary education (average), specialized secondary education and highest education) — 35 %, 44 % and 21 % in group 1 comparatively with 30 %, 49 % and 21 % in group 2 (Fig.1,2). 71 % and 65 % of women have job and 29 % and 35 % without job respectively. Regarding type of work we showed prevalence of more active smoking in groups 1 and 2 of women-workers of physical work: in group 1 of active smoking — 61 % and 59 % in women of passive smoking group 2 in compared with 39 % and 41 % respectively in women of not physical work. Prevalence of chronic diseases were showed in a group with passive smoking type of chronic disease in 65 % of respondents comparatively with 54 % in group of active smoking (Fig. 1, 2).

Analysis of clinical investigation identified a groups of active and passive smoking as 25 % and 43 % respectively. In the Group of active smokers in compared with the Group passive smokers noted the predominance of high cardiovascular risk in 77 (41 %) respondents. In a group of passive smoking we have showed the prevalence of risk of developing diabetes comparatively with group of active smoking has reached 102 (31 %) and also high rates of cardiovascular risk was revealed in a group of passive smoking, which were increased until 124 (38 %) respondents.

Conclusions

1. A high risk of developing diabetes was associated with passive smoking and reached 102 (31 %).
2. High risk developing of cardiovascular diseases associated with active smoking and reached 77 (41 %) respondents.

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Е.М. Ларюшина, Ф.У. Нильдибаева, В.Ф. Парахина, Д.Т. Амирханова

Шылым шегу түріне байланысты қант диабеті және жүрек-қантамыр ауруларының тәуекел факторларының құрылымы

Шылым шегу салдарынан қант диабеті және жүрек-қантамырлары ауруларының дамуы және эндотелий дисфункциясының артуы дәлелденген қауіпті фактор болып табылады. Диабет және жүрек-қантамырлары ауруларының даму қауіпі бойынша белсенді және пассивті темекі шегудің әсері зерттелген. Қарағанды қаласы және Қарағанды облысының Саран қаласының шылым шегетін 766 адам (609 әйелдер мен 157 ерлер) зерттеуге қатысқаны анықталды. Нәтижесінде қант диабеті ауруының жоғары деңгейде қауіпті дамуы пассивті темекі шеккен тұлғаларда 102 (31 %) байқалды. Топта белсенді және пассивті темекі шегетін әйелдер саны жоғары болды, оның ішінде белсенді шылым шегу 63 %-бен салыстырғанда, пассивті шегетін (92 %) әйелдер басым түсті. Жұмыс түрінің сипатын ескере отырып, дене шынықтырумен айналысатын пассивті темекі тобында — 65 %, белсенді темекі шегу 71 % құрады. Созылмалы ауруларды зерттеу барысында, ол аурулардың негізгі түрі пассивті темекі шегудің тобындағы науқастардың 65 %-да табылған. Пассивті темекі шегетіндер тобымен салыстырғанда белсенді темекі шегетін топтарында 77 (41 %) респонденттердің кардиоваскулярлы қауіпі басым екені анықталды. Белсенді темекі шегудің тобымен салыстырғанда пассивті темекі шегу тобында қант диабетінің даму қауіпі 102 адамды (31 %) құрайтыны, сонымен қатар пассивті темекі шегу тобында жүрек-қантамырлар ауруларының даму қауіпінің жоғарғы көрсеткіші 124 (38 %) науқастарда байқалды.

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Структура факторов риска развития диабета и сердечно-сосудистых заболеваний в зависимости от типа курения

Курение является доказанным фактором в увеличении риска дисфункции эндотелия, и как следствие — повышение риска развития диабета и сердечно-сосудистых заболеваний. Изучено влияние активного и пассивного курения на риск развития диабета и сосудистых заболеваний. Обследованы 766 курящих человек (609 женщин и 157 мужчин) г. Караганды и г. Сарани Карагандинской области. Установлено, что высокий риск развития сахарного диабета наблюдался у 102 (31 %) лиц, подвергавшихся пассивному курению. Одинаково часто в группе с активным и пассивным типом курения преобладали женщины: в группе с пассивным типом курения — 92 %, среди активно курящих — 63 %. Занятые физическим трудом преобладали больше в группе с активным типом курения — 71 %, в группе пассивного курения — 65 %. При изучении хронических заболеваний их наличие выявлено в основном в группе с пассивным типом курения — у 65 % обследованных. В группе активно курящих в сравнении с группой пассивно курящих отмечено преобладание высокого кардиоваскулярного риска у 77 (41 %) респондентов. В группе пассивного курения установлено преобладание риска развития сахарного диабета в сравнении с группой активного курения — 102 человека (31 %). Также отмечены высокие показатели риска развития сосудистых заболеваний в группе пассивного курения — у 124 (38%) обследованных.

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The prevalence of risk factors of developing of cardio-vascular diseases and diabetes among the urban population of Karaganda region

Frequency of developing of diabetes mellitus in patients with risk factors developing of cardiovascular diseases was investigated. The prevalence of main modifiable factors that generate a high risk of diabetes and cardiovascular disease were investigated in 891 respondents of the city of Saran, Land Karaganda (population 56,000, city-satellite of Karaganda) using of international questionnaire FINDRISC and cardiovascular risk calculator-SCORE. It was showed that increasing of risk of cardiovascular diseases accompanied parallel by increasing of risk of diabetes. Among of urban population of Karaganda region it were established the role of risk factors like obesity, fasting glycemia, arterial hypertension, hypercholesterolemia, allowing realization of preventive activities in the target population.

Key words: risk factors, diabetes mellitus, cardio-vascular diseases, Karaganda region, obesity, arterial hypertension, hyperholesterolaemia, hyperglycemia.

Actuality

Last period it was reported a intensive increase number of incidence of diabetes mellitus (DM) in the world. It is expected that by the 2035g. the prevalence of DM be increase to 347 million. people and 145 millions in rural areas [1]. Kazakhstan DM is rankedas socially significant disease, requiring a system of decisions and actions of the State supporting. According to data from a large clinical trials of diabetes is an independent factor for development of cardiovascular diseases, which led to the emergence of the term of cardiometabolic syndrome [2]. Each every second man in the group very high cardiovascular risk: each second man has high and very high risk of developing diabetes mellitus [3].

According to the State Health Kazakhstan Program named «Densaulyk 2016–2020», as well as plan of WHO on prevention and control of not infectious diseases is one of the objectives of improving of state of health by prevention of risk factors at the global, regional and national levels [4, 5]. In this regard, effective measures reducing premature mortality from diseases of the circulatory system and DM, is prevention, which is possible as result of studying the prevalence of risk factors for these diseases. In this context we tried to investigate the risk of development of diabetes mellitus among respondents with varying degrees of cardiovascular risk, as well as to identify the prevalence of modifiable factors in investigated groups.

Research objective: to investigate the risk of development of diabetes mellitus in patients with various level of cardiovascular risk and also to study prevalence of the main modified factors forming high risk of a diabetes mellitus and of cardiovascular diseases

Materials and methods

This clinical investigation is based on the results using of questionnaire and clinical analysis of 891 respondents of the city of Saran, the Karaganda region, with existence of risk of cardiovascular diseases at the age of 18–65 years are the basis for a research, a male made 20,4 % of them, the woman of 79,5 %. The volume of selection was defined proceeding from necessary significance value. Screening included questioning, with use of the international questionnaires on establishment of risk factors of socially important diseases as SD, the cardiovascular diseases (CD); anthropometry, measurement of the ABP, definition of a glucose and cholesterin of a blood. Definition of a glucose of a blood was carried out by means of the Accu-Chek glucose meter (Roche Diagnostics, Germany), a blood cholesterol — Accutrend Plus (Roche Diagnostics, Germany).

In the first part was carried out calculation of total cardiovascular risk (CVR) on a scale SCORE, using a special risk calculator. To assess total CVR takes into account gender, age, level of systolic HELL, smoking, total cholesterol. In the second phase 850 complete answers were selected from 891which were grouped CVR: I — no risk, low-moderate risk (<5 %), high risk (5–10 %) and very high risk (10 %). 41 answers were not selected as not completed.

Respondents with different cardiovascular risk on a scale SCORE, conducted interviews using questionnaire FINDRISC. For measuring the risk of DMfollowing questions from the questionnaire were used:

age, body mass index, waist circumference, the presence of at least 30 minutes of physical activity, blood pressure, blood glucose level, facts of presence of diabetes at family or at relatives. According to results of a questionnaire FINDRISS installed: low risk (sum of points < 7), moderate risk (sum of points 7 ≤ 14), high and very high risk (over > 15). In the group of patients with high and very high risk of diabeteswith different cardiovascular the frequency of major modifiable risk factors: low physical activity, smoking, obesity, arterial hypertension, hyperglycemia, hypercholesterolemia were investigated using of FINDRISC scale. Statistical processing was done using Microsoft Excel.

Results and discussion

According to the results of analysis of 850 respondents at 126 (14.8 %) respondents did not identify the risk of cardiovascular disease. The cardiovascular risk was confirmed at 724 respondents (85.1 %). Among respondents with the presence of CVR on a scale SCORE from 629 (86.9 %) respondents set low/moderate risk, 65 (8.9 %) respondents have high and 30 (4.2 %) respondents — very high risk (Table). Among respondents with low/moderate risk, high and very high CVR on a scale SCORE risk gradation were studied using of SCORE scope. Among respondents with low and moderate CVR at 318 (50.6 %) the low risk of DM were found, 257 (40.9 %) respondents identified as patients with moderate risk and at 54 (8.5 %) respondents found the high and very high risk of DM. Among group with high risk of CVR the low risk of DM identified in 21 respondents (32.4 %), moderate risk of DM– in 37 persons (56.8 %) and high risk (10.8 %) have 7 respondents. In patients with very high CVR a low risk of DM is defined at 5 (16.7 %) respondents, moderate risk — in11 respondents (36.6 %) and the high at 14 (46.7 %) respondents.

Table

The prevalence of modifiable risk factors in varying degrees by SCORE of cardiovascular system respondents with high and very high risk of developing type 2 diabetes, %

Risk factors	Low/moderate cardiovascular risk FINDRISK high and very high	High cardiovascular risk FINDRISK high and very high	Very high cardiovascular risk FINDRISK high and very high
Lowphysicalactivity	3.9	20.1	40.1
Smoking	4.8	15.4	37.7
Obesity	19.2	33.6	100
BP >140/90 mmHg	40.3	85.1	88.9
Fastingglucose > 5.6	11.1	82.5	100
Hypercholesterolemia	11.5	26.1	45.1

Thus, a most number of respondents with very low risk of development of 2 type of DM are belong to patients with very low or moderate risk of CVR (50.6 %) while in groups with high and very high to CVR the real risk of development of 2 type of DM in the nearest 10 years were determined at 32.4 % and 16.7 % accordingly, at respondents with high risk of CVR — at 56.8 % respondents — a moderate risk of developing of DM andamong persons with very high risk of CVR more often there was a high risk of development of diabetes mellitus — at 46.7 %.

The analysis of the obtained results demonstrate that the risk of development of DM is increases as far as growth of cardiovascular risk, that confirm the presence of relation between risk of CVR and diabetes mellitus.

In a group with high and very high risk (1) and very high risk (2) of CVR we observed a for 1.9 and 10 times more low frequency of physical activity among persons with the very high risk of development of СД 2 types (Table 1) frequency of subzero physical activity in 1.9 and 10.2 time higher as compared with group low/moderate risk of developing of CVR.

Frequency of smoking was confirmed as higher among respondents with very high CVR risk and risk of DM in compared with groups with high and moderate / low risk of CVR (37.7 % against 4.8 % and 15.4 %).

Frequency of obesity revealed at 100 % respondents with very high risk of CVR and high/very high risk of development of diabetes mellitus, that in 2.9 and 5.2 time exceeds frequency in groups with high and low/moderate CVR risk accordingly.

A similar tendency is observed regarding frequency of high blood pressure in patients: most frequency was revealed in a group with high and very high risk of CVR: 88.9 % and 85.1 % accordingly that in 2 times higher than in a group with low/moderate SSR.

The high level of blood glucose level was determined at 100 % of respondents with very high cardiovascular risk in compared with 11.1 % at respondents with low/moderate risk of CVR.

We have found the prevalence ofhypercholesterolaemia for 2–3 times more high among persons with the high and very high risk of development of 2 type of DM types in groups with very high risk of CVR and is as 45.1 and 26.1 %.

Thus, it was showed that by the important modified factors among respondents with highrisk of CVR and DM there are obesity, hyperglycemia arterial hypertension, hyperchosterolaemia, a low physical activity and smoking were revealed at many respondents with high risk developing as DM among group with high risk of CVR.

Conclusions

1. The risk of development of cardiovascular diseases accompanied by increasing of risk of developing of diabetes mellitus. Among respondents with a low/moderate cardiovascular risk there are prevalence persons with low risk of diabetes mellitus (50.6 %), at persons with high to CVR–a low risk of DM (56.8 %), with very high of CVR- a high risk of development of DM (46.7 %).

2. Among persons with the high risk of cardiovascular diseases and of high risk of DM among the urban population of the Karaganda area the important modified risk of DM factors were established, as obesity — 100 %, hyperglycemia — 100 %, hypertension — 88.9 %, hypercholesterolaemia — 56.7 %.

3. Obtained results allow to allocate group of patients for realization of purposeful prophylaxis of cardiovascular diseases and of diabetes mellitus.

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Қарағанды облысының қала тұрғындары арасында жүрек-қантамырлар ауруларының және қант диабетінің қалыптасуында қауіптілік факторының таралуы

Қарағанды облысының Саран қаласындағы 891 респонденттерінде әр түрлі дәрежедегі жүрек-қантамыр аурулары бар адамдарда қант диабетінің даму қауіпі бағаланды, сонымен қатар жоғарғы дәрежелі және кардиоваскулярлы ауруларды тудыратын кең таралған негізгі модификацияланған факторлар зерттелді. Бұл зерттеу FINDRISC халықаралық сұрақнамасы мен SCORE жүрек-қантамыр қауіпін есептеуіш арқылы жүргізілді. Жүрек-қантамыр аурулары қауіпі өскен сайын қант диабетінің даму қауіпі де жоғарылайтындығы белгілі. Қарағанды облысының қала тұрғындарының арасында семіздік, ашқарын гликемиясы, артериалды гипертензия, гиперхолестеринемия сынды ҚД қауіпі бар маңызды модификацияланған факторлар анықталды. Бұл толық топта алдын алу шараларды жүргізуге мүмкіндік береді.

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Распространенность факторов риска в формировании сердечно-сосудистых заболеваний и сахарного диабета среди городского населения Карагандинской области

Авторами проведена оценка риска развития сахарного диабета у лиц с различной степенью риска развития сердечно-сосудистых заболеваний, а также изучена распространенность основных модифицируемых факторов, формирующих высокий риск сахарного диабета и кардиоваскулярных заболеваний, у 891 респондента г. Сарани Карагандинской области с использованием международного опросника FINDRISC и калькулятора сердечно-сосудистого риска — SCORE. Установлено, что по мере нарастания сердечно-сосудистого риска возрастает риск развития сахарного диабета. Среди городского населения Карагандинской области установлены значимые модифицируемые факторы риска СД: ожирение, гликемия натощак, артериальная гипертензия, гиперхолестеринемия, что позволит проводить профилактические мероприятия в целевой группе.

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Determination of trimethylamine N-oxide level and its metabolic precursors in biological material

The level of trimethylamine N-oxide, exceeding the threshold indices, is a precursor to a number of diseases, leading to disability and death. In this context the definition of titers and the normalization of its levels in the body is one of the stages of preventive medicine. This review presents the methods for determining the levels of TMAO and its metabolic precursors in the biological material. The world practice mainly use the high performance liquid chromatography for TMAO quantitative determination in biological material, the detection is performed using tandem MS/MS spectroscopy, and in some cases nuclear magnetic resonance spectroscopy. The time-consuming sample preparation and complex combinations of the composition of the mobile phase are applied for effective separation and receiving of reliable results. Nevertheless, the problem of the quantitative and qualitative determination of TMAO and his predecessors not only hasn't lost the relevance, but has acquired the new horizons to improve this analysis in view of recent events in the scientific world.

Key words: TMAO, choline and metabolites, atherosclerosis, trimethylaminuria, GC-MS/MS, NMR-spectroscopy, HPLC-MS/MS, ion chromatography, analysis technique.

Trimethylamine N-oxide (TMAO) is the end product of metabolism of phospha- tidyl- choline, entering the organism with food of animal origin (such as red meat, egg yolk, seafood), which under the influence of the intestinal microbiota is metabolized to trimethylamine (TMA), and it enters the liver with a current blood, where is oxidized to its final form TMAO with the help of an enzyme of flavinmonooxygenase (FMO3) genus (Fig. 1) [1, 2]. Initially, in clinical practice, the levels of TMA and TMAO in blood and urine were considered as a diagnostic character of genetically caused disease Trimethylaminuria (insufficient synthesizing of FMO3 enzyme in liver) as well as in the diagnosis of renal disease. From the perspective of environmental protection, the levels of TMAO and other methylamines are important as a component of organic nitrogen spray in the areas with increased levels of these substances that affect the climate and human health as a whole [3]. Also TMAO can be regarded as a new, relatively modifiable risk factor for cardiovascular [1, 2, 4], it is especially important that this group of diseases is the leader for morbidity and mortality worldwide on a global healthcare [5]. According to recent reports, the control of TMAO level allows to monitor the risk of atherosclerosis development and its complications, as well as to evaluate the effectiveness of treatment and prevention, which can be one of the components of personalized medicine. All of the above leads to the necessity of the development and improvement of methods for determining the levels of TMAO in the biological material.

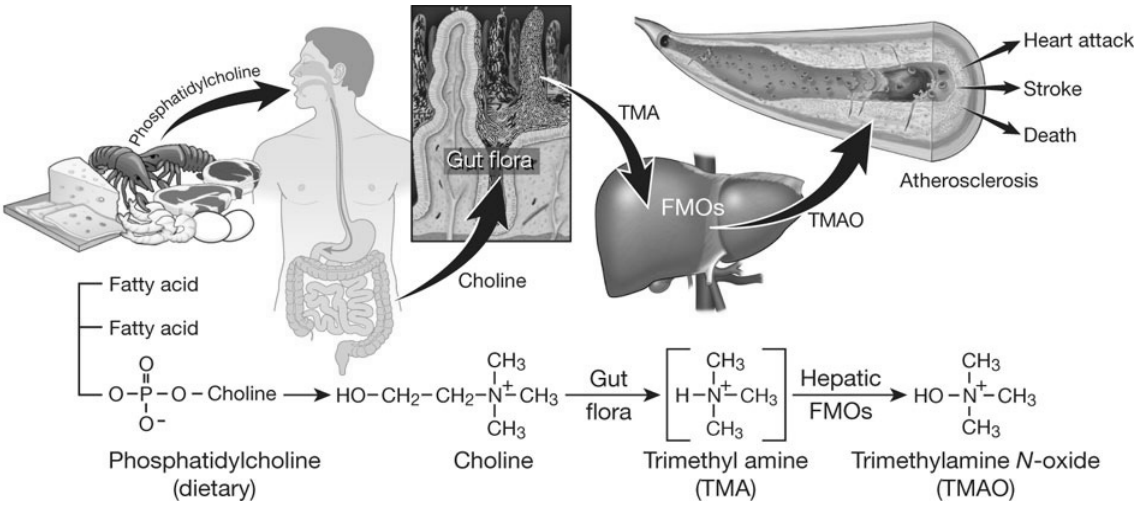

Figure 1. TMAO generation in human organism [1, 2]

Among the first researchers, who had synthesized TMAO and spent its qualitative and quantitative determination in 1962, were the scientists from the University of California (USA) J.R. Baker and S. Chaykin. The purpose of their study was to determine the type of liver enzymes and their effect on detoxification (oxidation) of trimethylamine (TMA) to trimethylamine N-oxide (TMAO). The material, in which the level of tertiary amine determines, was the microsomal fraction of pork liver. Preparative liquid chromatography was used, followed by analysis on paper chromatography [6].

In modern time the level of TMAO is usually defined for diagnosis of Trimethylaminuria. The syndrome of disagreeable fish odor (also known as fish odor syndrome or Trimethylaminuria) is the index of metabolic disorder and is characterized by the presence of abnormal amounts of dietary origin tertiary amine, trimethylamine (TMA) in urine, sweat, exhaled air and other secretions. Trimethylamine has a strong smell of rotting fish, and it has on a person, suffering from this disease, a devastating psychological impact on all spheres of life (personal, social, labor). In 2004 Marcus A. Bain et al. [7], based on the earlier experience of their foreign colleagues, who determined the level of TMAO in urine by gas chromatography (GC) [8, 9], high performance liquid chromatography (HPLC) [10], with various detection methods, developed their own methodology using GC. This method using solid phase microextraction (SPME) allowed determining the level of TMAO in human plasma. During the work, it was used gas chromatograph Varian Star 3400 CX with column SPB-1 sulfur (30 m × 0.32 mm, 4.0 μm) and mass-detector Varian Saturn 2000. Evaporator temperature was 250 ºC, the column temperature — 120 ºC, as a carrier gas it was used the isothermal helium with the delivery of 60 ml/min. Carboxy-polydimethylsiloxane fiber (75 μm) was used for SPME. 0.01 M of hydrochloric acid and titanium sulfate (III) dissolved in sulfuric acid (10 μL, 45 % w/v) were poured to plasma. As internal standards the deuterated TMA and TMAOwere used, quantitative calculation was based on the calibration line.

With the aim of the diagnosis of Trimethylaminuria, as well as for studying of the role of betaine and its metabolites in the development of vascular disease, in 2006 the team of scientists from New Zealand conducted the validation of method of 1H NMR-spectroscopy, which, according to their opinion, allows the more efficient identification of methylamine metabolites at the study of their level in urine [11]. Sample preparation was carried out by adding of 1M of hydrochloric acid solution, containing 25 mM of acetonitrile (as an internal standard), into the test material (urine). Also the internal standards of methylamines were used. All spectra were registered and were recorded on a high-resolution investigated liquid phase NMR-spectrometer Varian INOVA 500 at the temperature of 23 ºC in the 5 mm NMR-tubes with deuterated 3 mm lock inserted in them. For measuring it was used 90° RF pulse with duration of 8.1 microseconds. The delay between the pulses was 5 seconds, the detection time 1,982 seconds, the width of the fluctuation band — 8000 Hz. The duration of the analysis was less than 5 minutes. The limit for TMAO detection was 3,37 ppm (15 μM) that, according to the authors' opinion, was above the detection limit using HPLC. The same method, but in more expanded version (with detection of TMAO level not only in the urine and blood), was patented in 2015 by the team of scientists from North Carolina (USA) headed by James D. Otvos [12].

Due to the need to improve the diagnosis of Trimethylaminuria, the scientists from many countries introduced new and technically more simplified methods of qualitative and quantitative determination of TMA and TMAO levels. One of these was David W. Johnson, who in 2008 proposed thread-injection electrospray ionization tandem mass-spectrometry for the simultaneous determination of TMA and TMAO in urine for the first time [13].The analysis was performed on the equipment Applied Biosystems/MDS Sciex API 4000. The gas for the collision was nitrogen. A sample (20 μL) was placed through 96-well autosampler Gilson 215, with mobile phase at a rate 150 μL/min (supplied by Agilent 1100 of HPLC-system). The time for the analysis of one sample was 2 minutes. TMAO and TMA marked ^{2}H were used as an internal standard. Sample preparation was carried out in several stages. The internal standards $^{2}N_9$TMA (1 μL, 1 mg/ml in water) and $^{2}H_9$-TMAO (2 μL, 1 mg/ml in water) dissolved in hydrochloric acid were poured to the test material (urine), then it was added concentrated ammonia solution (1 μL) and ethyl bromoacetate (30 μL, 20 mg/ml in acetonitrile). After 30 minutes, the solution of mobile phase containing acetonitrile/water/formic acid (50:50:0.025) was added.

Subsequently it was conducted 100x dilution of 10 μL of received solution by mobile phase (MP). The following data were obtained for TMA (146,1, 118,1, 400 m/z), 2H9-TMA (155,1, 127,1, 400 m/z), TMAO (76,1, 58,1, 100 m/z) and 2H9-TMAO (85,1, 66,1, 100 m/z). The quantitative calculation was based on the calibration line. Two years later, the team of scientists from Canada used the method of direct input of electro-spray quadrupole time-of-flight mass-spectrometry to determine the TMA and TMAO in urine in order to improve and simplify the given analysis [14]. The difference with the method developed by David

W. Johnson (described above) was in radioactive isotopes, with which the desired material was labeled. Orval A. Mamer and co-workers used the isotope ^{15}N instead the isotope ^{2}H.

In order to protect the human from the use of poor fish and to improve the quality of life of people with Trimethylaminuria the Chinese scientists have developed a method of determining the levels of TMAO, TMA, dimethylamine, formaldehyde in seafood [15]. For this it was used the method of ion chromatography with non-suppressed conductivity. The analysis was performed on the equipment ICS-2000 using theprotective pre-column Dionex Ion-Pac CG17 guard column (50 mm × 4 mm i.d.) and the analytical column DionexIonPac CS17 (250 mm × 4 mm i.d.). The column CS17 has been selected on the basis of benefits at the analysis of organic amines in the method of ion chromatography with not-suppressed conductivity. Mobile phase (MP) consisted of a solution of methanesulfonic acid 3.0 μmol/L. Separation was performed in isocratic mode at 30 ºC temperature of column and MP flow rate 0.8 ml/min. Sample preparation was carried out by homogenization of raw material (finely chopped pieces of fish) in 10 ml of 7.5 % cold trichloroacetic acid (TCA), followed by centrifugation 4000 rpm/min for 15 minutes at 4 ºC. The sediment was subjected to a double back-extractingof 5 ml of 5 % TCA with the repeat centrifugation. All supernatants were mixed with deionized water with subsequent filtration through a fine pore filter paper (20–25μL). The time of TMAO retention was 15,91 min. The quantitative determination was carried out on the calibration line.

The scientists from the University of California (USA) in 2010 at the head of Mark E. Erupe among the first used the above method to determine the level of TMAO (in combination with other amines) in the atmospheric air. This study was conducted for determination of the role of organic nitrogen in the composition of atmospheric aerosols, which plays a significant role in formation of the environment and affecting the climate and human health as a whole [3]. The analysis was performed on the equipment Metrohm 761 Compact IC with protective pre-column Metrosep RP (with steel mesh filter) and analytical column Metrohm-Peak Metrosep C2 (250 mm × 4 mm i.d.). As an eluent was thesolution of 3 mM nitric acid and 3.5 % acetonitrile with mobile phase at a rate of 1 ml/min. The sample was injected manually; the analysis time was 15 minutes. Separation was performed in isocratic mode at a column temperature of 20 ºC. The mix of methylamines (including TMAO) was used as a marker. The samples were taken from the filter of the smoke chamber for sample preparation, then it was conducted the extraction in 10 ml of ultrapure water (Millipore) by ultrasonic dispersion for 30 minutes. The quantitative calculation was based on the calibration line. The lower limit of TMAO detection was 72 μg/L, the retention time — 12 minutes. According to the authors, this method is easy to use and applicable for the determination of the desired substances in low concentrations due to the low detection threshold.

Since 2011 the level of TMAO in the human body is given a new meaning. A number of researchers have proven the relationship of TMAO high titers as the end product of metabolism of choline and betaine with an increased risk of developing of cardiovascular diseases, myocardial infarction and stroke [1, 2, 4]. This fact has increased the interest in the improvement of methods for determining the level of these substances in biological samples.

Thus, Zeneng Wang et al., were among the first to carry out this analysis as part of their research work with reference to cardiovascular risk. The liquid chromatography coupled with electrospray ionization spectrometry was used to determine the metabolic profile. Structural identification of targeted analytes was performed using a combination of methods: HPLC/MS/MS, multinuclear NMR-spectroscopy and GC/MS. Sample preparation was carried out by deproteinization of plasma by means of ice-cold methanol. After centrifugation, the supernatant was introduced into Rexchrom Phenyl column (4,6×250 mm, 5 μm) with a flow rate of MP 0.8 ml/min. Gradient elution was used, at first 10 mM ammonium formate was used longer than 0.5 minutes with the transition to 5 μM of ammonium formate, 25 % methanol and 0.1 % formic acid (for 8 minutes), after it was used 100 % methanol and the water for analytes separation [1]. In analysis mode of MS1 positive ions they were obtained the analytes with m/z 76, 104, 118. d9-TMAO was used as the internal standard. The quantitative determination was carried out on the calibration line.

The same group of authors refined the method of determining the TMAO level in the biological material in 2013 [16]. The analysis was conducted using a pump system 4LC-20AD Shimadazu, autosampler SIL-HTC and system switching the valve of double columns connected with the mass-spectrometer API 4000 Q-TRAP. Sample preparation consisted of mixing of 20 μL of the test plasma with 10 μM of internal standard (d9-TMAO) in 80 microliters of methanol with followed centrifugation for 10 minutes at 20000g speed at 4 ºC. The resulting supernatant was injected into the column Luna silica (4,6×250 mm, 5 μm) at a rate of MP 0.8 ml/minute at gradient elution. Discontinuous gradient used for better separation of analytes by mixing a composition of eluent «A» (0.1 % propanoic acid in water) with eluent «B» (0.1 % acetic acid in meth-

anol) in different ratios, ranging from 2 % «B» linearly to 15 % «B» within 11 minutes, then linearly to 100 % «B» for 5 minutes with the followed return to 2 % «B». The desired substance was monitored using electrospray ionization in the mode of positive ion with multiple reaction monitoring (MRM) with typical product-ion transitions m/z 76→58 and 85→66 amu. Retention time was ≈ 9 minutes, the minimum quantification threshold of detection was 0.05 μM, max > 200 μM[16].

A similar method, but with some modifications, was used by Liam M. Heaney et al. in 2015. Differences with the method created by Zeneng Wang were as follows: the composition of MP, as the solvent «A» the mixture of 0.025 % ammonium hydroxide with 0.045 % formic acid (pH 8.1) was used, the solvent «B» was acetonitrile, the characteristics of the used column Acquity UPLC BEH HILIC (130 Å, 2,1 mm × × 100 mm, 1.7 μm). The analysis results were similar to the previous method.

Later they began to appear the new works confirming the correlation of TMAO high titers with the development of atherosclerosis [17–19], heart failure [20], inflammatory bowel disease (Crohn's disease, ulcerative colitis) [21], the more detailed description of the metabolic pathway of TMAO formation on the basis of nutritional factor [22–24]. All of these moments give scientists new tasks to increase the number of simultaneously defined TMAO metabolites and precursors, to reduce the time of analysis, to increase the sensitivity of the method, including the simplification the methods of analysis and at the same time the optimization of its reliability.

For example, the team of Latvian scientists have developed and conducted the validation of the method for the simultaneous determination of TMAO level in combination with L-carnitine and its biological precursor γ-butyrobetaine (GBB) in human plasma using HPLC/MS/MS [25]. For the sample preparation 900 μL of solution of acetonitrile and methanol (3:1 v/v) containing the tap (200 ng/ml) was poured the 40 μL of plasma. Supernatant was used for analysis after centrifugation (13000g, 10 minutes). The system Acquity HPLC with column Acquity HILIC BEH (2,1×50 mm, 1.7 μm) was used for the separation of analytes. Elution was conducted by the gradient principle from 75 to 55 % acetonitrile in 10 μM of aqueous solution of ammonium acetate (pH4) at a rate of MP 0.25 ml/minute. The analytes were monitored using electrospray ionization in the positive ion mode with multiple reactions monitoring on a triple quadrupole mass-spectrometer. The mass-spectrometer was configured as follows: capillary voltage 3,3 kV, desolvation and source temperature 120 and 350 ºC respectively. Nitrogen flow rate 500 L/h. The product-ion transitions for TMAO amounted m/z 75,8 → 58,3, for L-carnitine — m/z 146,11 → 87,11, for GBB — m/z 175,44 → 86,0. The time TMAO detection was 1,95 min, L-carnitine — 1,85 min, GBB — 2,21 min. The quantitative determination was carried out on the calibration line.

All of the following methods for determining of the level of choline structural metabolites are largely identical. Analysis was performed using HPLC/MS/MS in the positive ion mode. Relative differences were presented in the composition and the speed of mobile phase, in the type of analytical column and the time ofanalytes retention in accordance with applied chromatographic systems.

One of the latest it is possible to mark the work of Xueqing Zhao et al [26], which improved method for determination of choline, betaine, TMA and TMAO to diagnose diseases associated with nutrition, bowel diseases and the risk of life-threatening diseases. Sample preparation was carried out as follows: acidified test material (plasma, urine) was extracted, and then derivatization using tert-butylbromoacetate in acetonitrile and ammonium hydroxide in water was performed. After the centrifugation, the supernatant was transferred to a vial for subsequent analysis. Chromatographic separation was performed on the column Atlantis Silica HILIC (4,6×50 mm, 3μm). Column temperature was 40 ºC, the eluent flow rate 1 ml/minute. The solvent «A» was the composition of acetonitrile and water (1:9) with 10 μM of ammonium formate and 0.125 % formic acid. The solvent «B» consisted of acetonitrile and water (9:1) with 10 μM of ammonium formate and 0.125 % formic acid. The gradient elutionwas used. The analytes and their respective isotopes were monitored by specific ion transitions: 104→45 for choline, 118→59 for betaine, 174→59 for TMA, 76→58 for TMAO. The retention time for TMAO was 2,41min.

Steuer et al. [27] using the same clinical objectives conducted another improvement of the analysis abovelisted substances in plasma, serum and human urine. They proposed the method for rapid and simultaneous determination of compounds of quaternary ammonium of phosphatidylcholine origin such as choline, betaine, O-acetyl-L-carnitine, L-carnitine and TMAO. Plasma, serum, urine were deproteinized with methanol with following centrifugation and the supernatant sampling. The column Phenomenex Luna-HILIC (4,6×150 mm, 3 μm) was used for the separation of substances, the detection and quantitative analysis was performed by LC-MS/MS electrospray ionization in the positive ion mode recording. The temperature of column was 35 ºC, mobile phase flow rate — 0.75 ml/min. The analysis was conducted using a gradient elution. Solvent «A1» con-

sisted of 10 μM ammonium acetate in 90 % acetonitrile with water (9:1), the solvent «B1» consisted of 10 μM acetate buffer with pH 4. The second mobile phase consisted of «A2» of 10 μmol of ammonium formate and 90 % acetonitrile and «B2» — 10 μmol of ammonium formate in water at pH 3. Autosampler temperature was set to 10 ºC. Validation method was carried out in accordance with international guidelines regarding selectivity, consistent contamination of samples, the limit of quantitation (LQ), linearity, accuracy, reliability, reproducibility and stability of the treated sample. Ionic analytes transitions made the identical performance to the above methods. The retention time for TMAO was 7.27 min.

Conclusions

Thus, by analyzing all of the above, it is found that the level of trimethylamine N-oxide exceeding the threshold is a precursor of a number of diseases, leading to disability and death, in this context, the definition of titers and the normalization of its levels in the body are one of the stages of preventive medicine. High performance liquid chromatography is mainly used in world practice for quantitative determination of TMAO in biological material. Given the structural features of TMAO the detection is performed using tandem MS/MS-spectroscopy and nuclear magnetic resonance spectroscopy in some cases. It should be noted that such equipment is very expensive, so it is not always available. Taking into account the multicomponent composition of the research material the time-consuming sample preparation and complex combinations of the composition of the mobile phase are used for efficient separation and obtaining of reliable results.

Nevertheless, the problem of the quantitative and qualitative determination of TMAO and his predecessors not only hasn't lost the relevance, but has acquired the new horizons to improve this analysis in view of recent events in the scientific world. Speaking about the evolution of techniques, it is clear that the work aimed at their improvement, due to changes of technical component of analysis, the number of simultaneously defined analytes, reducing time of analysis, and also the improvement of the method of sample preparation and the composition of the mobile phase for the separation.

The development of rational sample preparation and efficient methods of quantitative determination of TMAO in plasma using HPLC-MS/MS for the early diagnosis of diseases of the circulatory system is carried out in the Share laboratory of the Scientific-research Center of Karaganda state medical university.

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А.Б. Марченко, С.А. Ивасенко, А.А.Турмухамбетова

Биологиялық материалда триметиламин оксиді деңгейін және оның метаболитті орынбасушыларын анықтау

Триметиламин оксиді көптеген аурулардың бастамасы болып өлім мен жұмысқа қабілетсіздікке әкеліп соғады. Профилактикалық медицинаның ең маңызды рөлдерінің бірі титрлеу мен ағзадағы қалыпты деңгейін анықтау болып табылады. Берілген шолуда ТМАО деңгейін анықтау әдісі мен биологиялық материалдағы оның метаболитті орынбасушылары көрсетілген. Бүгінде биологиялық материалдағы ТМАО санын анықтауда жоғары дейгейдегі сұйықты хроматография тандемін, яғни спектроскопия MS/MS және кей жағдайларда резонанстық ядролық спектроскопия әдістерін, қолданады. Ұтқыр фазаның күрделі комбинациялық құрамы тиімді бөлініп, сенімді нәтижелер алуға көмектеседі, сол себепті жоғары сұранысқа ие болады.

А.Б. Марченко, С.А. Ивасенко, А.А. Турмухамбетова

Определение уровня окиси триметиламина и его метаболических предшественников в биологическом материале

Окись триметиламина является предшественником многих заболеваний, приводящих к нетрудоспособности и смерти. В этом контексте определение титров и нормализация его уровней в организме являются одной из важных задач профилактической медицины. В настоящем обзоре представлены методики для определения уровней ТМАО и его метаболических предшественников в биологическом материале. Сегодня главным образом используются высокоэффективная жидкостная хроматография для количественного определения ТМАО в биологическом материале, тандемная спектроскопия MS/MS и в некоторых случаях — спектроскопия ядерного магнитного резонанса. Подготовка проб и сложные комбинации состава мобильной фазы применяются для эффективного разделения и получения надежных результатов, благодаря чему являются весьма востребованными.

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