DOI: 10.15386/cjmed-406

EFFECT OF THE EARLY INTENSIVE MULTIFACTORIAL THERAPY ON THE CARDIOVASCULAR RISK IN PATIENTS WITH NEWLY DIAGNOSED TYPE 2 DIABETES: AN OBSERVATIONAL, PROSPECTIVE STUDY

RAMONA MARIA STEFAN[1], CRISTINA NITA[2], ANCA CRACIUN[3], ADRIANA RUSU[4], NICOLAE HANCU[3]

[1]Diabetes, Nutrition and Metabolic Diseases Department, County Emergency Hospital, Bistrita-Nasaud, Romania
[2]Diabetes, Nutrition and Metabolic Diseases Department, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca and Private Practice, Baia Mare, Romania
[3]Diabetes, Nutrition and Metabolic Diseases Department, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca and Private Health Network Regina Maria, Cluj-Napoca, Romania
[4]Clinical Consulting SRL

Abstract

Background and aims. *We assessed if early intensive interventions improve the glycemic control and the modifiable cardiovascular diseases risk factors in Romanian patients with newly diagnosed type-2 diabetes during the first year follow-up period.*

Patients and methods. *This was an observational, prospective study: 69 subjects were included in the analysis; each of them received intensive multi-factorial pharmacologic treatment and therapeutic education targeting hyperglycemia, weight, hypertension and dyslipidemia. Disease monitoring was done at months 0, 1, 3, 6 and 12 by assessment of anthropometric measurements, arterial blood pressure and biochemical parameters. The cardiovascular diseases risk factors were calculated using the United Kingdom Prospective Diabetes Study Risk Engine.*

Results. *The mean age at diagnosis was 53.61±10.66 years. All anthropometric variables (body weight, body mass index, waist circumference, visceral fat area, percentage of body fat), except for skeletal muscle mass, significantly decreased overtime. The majority of the biochemical parameters significantly decreased overtime. The non-fatal/fatal coronary heart disease risk significantly decreased at month 12 (9.74 [p<0.05] and 4.84 [p<0.05], respectively) compared to month 0 (19.66 and 11.10, respectively); a similar trend of the non-fatal/fatal stroke (risk at month 12, 8.30 [p<0.05] and 1.04 [p<0.05], respectively, while at month 0, 7.89 and 1.38, respectively) was recorded.*

Conclusions. *Early multi-factorial treatment and intensive lifestyle interventions in patients newly diagnosed with type-2 diabetes could decrease with approximately 50% the rate of cardiovascular disease risk.*

Keywords: type-2 diabetes, newly diagnosed patients, cardiovascular risk, multi-factorial therapy.

Background and aims

Diabetes is a major public health problem worldwide and it is considered the most frequent metabolic, chronic and non-communicable disease [1,2,3]. The most recent data provided by the International Diabetes Federation (IDF) indicate a number of 382 million persons diagnosed with diabetes and it is estimated that the number of people suffering from this disease will increase to 592 million by 2035. In 2013, the regional estimates of IDF classify Europe on the second place worldwide, with 56.3 million people with diabetes in the 20–79 years old age category, of which 851,07 (1000s) were diagnosed in Romania [4].

Manuscript received: 28.01.2015
Received in revised form: 23.02.2015
Accepted: 03.03.2015
Address for correspondence: stefanramonamaria@yahoo.com

A significant imbalance has been observed between the prevalence of type 1 and type 2 diabetes, as approximately 90% of the diabetic population is diagnosed with type 2 diabetes (T2D) [5,6]. This lifelong disease is associated with severe microvascular and macrovascular complications such as retinopathy, nephropathy, neuropathy, and cardiovascular disease [7,8,9].

One of the major goals of the diabetes treatment is the reduction of diabetes-related complications, which have been shown to be associated with increased morbidity and mortality, heavy economic burden and decreased quality of life [9]. Given this, early prevention or delaying diabetes-related complications including cardiovascular diseases is an imperative goal to be achieved.

Currently, it has been demonstrated that glycemic control can decrease the risk of microvascular complications [10]. Large trials as Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Veteran Affairs Diabetes Trial (VADT) were not able to demonstrate that glycemic control could reduce the incidence of cardiovascular complications [11,12,13]. One of the possible explanations is that these studies enrolled patients with long-term duration of T2D and it was observed that chronic exposure to hyperglycemia may cause a negative metabolic memory [10]. Metabolic memory is a phenomenon suggesting that early glycemia normalization is able to interrupt the hyperglycaemia-related pathological processes associated with increased oxidative stress and glycation of cellular proteins and lipids. This phenomenon has been recently described following the observations of large randomized studies, where has been established that early intensive glycaemic control reduces the risk of chronic diabetic complications [14].

The UK Prospective Diabetes Study (UKPDS) enrolled patients with newly diagnosed T2D which were followed for 10 years and showed that intensive glycemic control significantly decreased the risk of microvascular complications, but had no impact on the risk of macrovascular complications [15]. To overcome this challenge, the STENO-2 trial focused its research on the intensive multi-factorial therapy in patients with T2D and microalbuminuria and showed that intensive interventions decreased the risk of cardiovascular events and death by 50% over a 7.8 year follow-up period [16,17].

The purpose of the current study was to assess if early intensive multi-factorial treatment associated with lifestyle management could improve the glycemic control and the modifiable cardiovascular diseases (CVD) risk factors, in Romanian patients with newly diagnosed T2D, during first year follow-up period.

Patients and methods

This was an observational, prospective study. The analysis was performed on data collected from 69 subjects with newly diagnosed T2D at "Regina Maria" Private Practice during January 2010 – January 2012 time period. T2D was diagnosed based on the criteria published by IDF in 2009 [18].

The study inclusion and exclusion criteria are presented in Table I.

Study procedures: Multi-factorial treatment was focused on glycemic, lipids and blood pressure control associated with intensive therapeutic patient education, during a 1 year follow-up period. At **visit 1** (Month 0), individual lifestyle was assessed based on a questionnaire including information regarding the age, sex, dietary pattern, socio-economic status, family history, smoking status, habitual physical activity, medical history and other relevant information if any. Body height and weight were measured using standard procedures. Body mass index (BMI) was calculated using the following formula: [weight (kg)/height^2 (m)]. Body composition measurements were performed by using the bioelectrical impedance analysis (InBody 720, Biospace, Korea). Waist circumference, visceral fat area (VFA), percentage of body fat (PBF), skeletal muscle mass (SMM) and body fat mass (BFM) were recorded. Systolic and diastolic blood pressure were assessed using a standard mercury sphygmomanometer in sitting position. Hypertension was defined as systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥80 mm Hg or previous prescription of antihypertensive therapy [7]. The following biochemical parameters were measured by using fully automated analyzer (Cobas Integra 400 Plus, Roche): blood glucose, HbA1c, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), nonHDL-C; Reaven score was calculated using the formula TG/HDL. Diabetes treatment was prescribed and therapeutic education was performed based on the relevant clinical factors, cost-effectiveness and in accordance with American Diabetes Association/ European Association for the Study of Diabetes (ADA/EASD) guidelines at the time of diagnosis [19,20]. At **visit 2** (Month 1), weight, BMI, waist circumference, systolic and diastolic blood pressure were recorded together with blood glucose and HbA1c

Table I. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Newly diagnosed type 2 diabetes	Other type of diabetes diagnosed
Age >30 years	Ketoacidosis as diabetes complication
Body mass index ≥25 kg/m^2	Body mass index <25 kg/m^2
Acceptance to be included in the study	Chronic debilitating disorders in late stages
	Insulin therapy recommendation
	Refusal to be included in the study

monitoring.

At **visits 3 and 4** (Month 3 and 6, respectively) all body composition measurements, biochemical parameters and arterial blood pressure were recorded. In addition, therapeutic education was performed and the treatment was modified according to patient's need if necessary.

At **visit 5** (Month 12) all parameters including weight, BMI, anthropometric measurements, blood pressure, blood glucose, HbA1c, total cholesterol, triglycerides, HDL-C, LDL-C, nonHDL-C and TG/HDL-C were recorded.

CVD risk assessment: The one-year modelled CVD risk was calculated by using the model of the UK Prospective Diabetes Study (UKPDS) Risk Engine [21]. This is a diabetes-specific risk-assessment engine that can predict the absolute risk of fatal or non-fatal CVD within a defined time period up to 20 years [22,23]. The analysis included all the subjects with complete data on the UKPDS score variables at baseline. The occurrence risk of fatal or non-fatal coronary heart disease (CHD) and stroke was calculated at visit 5 based on the following risk factors included in the model: age, time from T2D diagnosis, gender, atrial fibrillation diagnosis, ethnicity, smoking status, alcohol consumption, systolic blood pressure, total cholesterol and HDL-C. These variables were selected due to their relevance to cardiovascular health in patients newly diagnosed with T2D.

According to the UKPDS score, CVD (CHD and stroke) risk are classified as follows [21]:

<15%: decrease risk of CVD;

15–30%: moderate risk of CVD;

≥30%: high risk of CVD.

The study protocol was approved by the ethical committee of the "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca and the informed consent form was obtained from all subjects before any study procedure was performed.

Statistical analysis: All statistical analyses were performed using the SPSS software for Windows version 13.0 (SPSS Inc., Chicago, IL, USA).

The quantitative data were expressed as mean ± standard deviation (SD) and the categorical data were expressed as percentages.

Analysis of variance (Friedman's test) test was performed to compare continuous variables measured at different time points. The Friedman's test ($\chi 2$ test) is a non-parametric test equivalent to one-way ANOVA with repeated measures and it allows the comparison of continuous variables in a group. P-value was considered statistically significant if $p < 0.05$.

The General Linear Model within-subjects factors was used to calculate the repeated measures ANOVA and the independent variable was time. This test was performed to examine the changes from each time period to the next one for the following dependent variables: blood glucose, LDL, PBF and SMM. P-value was considered statistically significant if $p < 0.05$.

To evaluate the CVD factor risk changes, the data were compared using the non-parametric Wilcoxon Signed Ranks Test and p-value was considered statistically significant if $p < 0.05$.

Results

Demographic characteristics

A number of 69 subjects newly diagnosed with T2D were included in the analysis. The mean age at diagnosis was 53.61±10.66 years and ranged between 30 and 76 years. The sample included three times more men than women and a higher percentage of subjects from urban area than from rural area. At baseline, CVD were identified in 56.5% of subjects, and obesity and dyslipidemia in 62.3%. The detailed description of the subjects' characteristics at diagnosis is provided in Table II.

Type 2 Diabetes treatment and monitoring

The anti-diabetic treatment was recommended individually according to the parameters changes overtime and in association with intensive therapeutic patient education, including dietary recommendation. In table 3 are presented the number (percentage) of subjects receiving an anti-diabetic specific medication by time point.

Table II. Participants' characteristics at diagnosis.

Variable	N=69
Age (years); mean ± SD	53.61±10.66
Men; n (%)	52 (75.4%)
Urban area; n (%)	41 (59.4%)
Education level; n (%)	
High school graduate	24 (34.8%)
College grad or higher	45 (65.2%)
Smoking status; n (%)	
Non-smoker	31 (44.9%)
Quit smoking for >6 moths	16 (23.2%)
Smoker	22 (31.9%)
Alcohol consumption; n (%)	
Yes	30 (43.5%)
Medical history; n (%)	
Cardiovascular disease	39 (56.5%)
Dyslipidemia	43 (62.3%)
Obesity	43 (62.3%)
Other*	37 (53.6%)
Self-monitoring	50 (72.5%)
Family history; n (%)	
Type 2 diabetes	16 (23.2%)
Cardiovascular disease	21 (30.4%)
Obesity	25 (36.2%)

*Other includes health issues that were present in the patient history such as: pancreatic abscess, asthma, mammary cyst, ovarian cyst, gastritis, pancreatitis, psoriasis, etc.; N, total number of subjects included in the analysis; n (%), number (percentage) of subjects included in a given category; SD, standard deviation.

In addition, they received antihypertensive treatment, including diuretics (14 [20.3%] at visit 1, and 11 [15.9%] at visit 5), angiotensin-converting enzyme

inhibitors (ACEI) (30 [43.5%] at visit 1, and 27 [39.1%] at visit 5), angiotensin receptor blockers (ARBs) (6 [8.7%] at visit 1, and 7 [10.1%] at visit 5), calcium channel blockers (14 [20.3%] at visit 1, and 10 [14.5%] at visit 5), beta-blockers (22 [31.9%] at visit 1, and 21 [30.4%] at visit 5). Approximately 50 (72.5%) of the subjects were on antiplatelet treatment, and 51 (73.9%) and 26 (37%) on dyslipidemia treatment, including statin and fibrate, respectively.

Diabetic polyneuropathy and retinopathy were recorded as complications in 8 (11.6%) and 2 (2.9%) subjects till the end of study.

Anthropometric and biochemical changes over time

Weight, BMI, anthropometric measurements, blood pressure, blood glucose, HbA1c, total cholesterol, triglycerides, HDL-C, LDL-C, nonHDL-C and TG/HDL-C were monitored overtime. For all parameters an overall decrease was recorded (except for skeletal muscle mass that was comparable with the one recorded at visit 1, and HDL-C that slightly increased) up to visit 5 (Table IV).

Friedman's test showed a statistically significant decrease of body weight and BMI at visit 5 compared to visit 1. Similar results were obtained for body composition measurements (waist circumference, BFM, and VFA). Blood pressure and insulinemia results were not included in this statistical analysis as data from visit 4, and visits 4 and 5, respectively, were missing. Regarding the biochemical parameters, a statistically significant decrease of the HbA1c, total cholesterol, nonHDL-C, triglycerides, TG/HDL-C and a statistically significant increase of HDL-C were recorded (Table IV).

The General Linear Model analysis showed a significant decrease overtime of blood sugar, LDL and PBF. The SMM values were comparable at different time points (Table IV).

Cardiovascular disease risk analysis

Figure 1 shows the changes in CVD risk from baseline to 1-year follow-up.

The non-parametric Wilcoxon Signed Ranks Test indicated a statistically significant decrease of the CHD and fatal CHD risks at visit 5 (mean value: 9.74 and 4.84, respectively) compared to visit 1 (mean value: 19.66 and 11.10, respectively), $p < 0.05$ for both variables. A similar

Table III. Number (percentage) of subjects on anti-diabetic treatment by drug category and time point.

Category	N	Visit 1 n (%)	Visit 2 n (%)	Visit 3 n (%)	Visit 4 n (%)	Visit 5 n (%)
Biguanides	69	64 (92.8%)	64 (92.8%)	63 (91.3%)	63 (91.3%)	64 (92.8%)
Sulphonylurea	69	18 (26.1)	16 (23.2%)	13 (18.8%)	9 (13%)	9 (13%)
DPP-4 inhibitors	69	7 (10.1)	12 (17.4%)	14 (20.3%)	15 (21.7%)	15 (21.7%)
GLP-1 agonists	69	0 (0%)	0 (0%)	2 (2.9%)	2 (2.9%)	2 (2.9%)

N, total number of subjects with available results; n (%), number (percentage) of subjects in a given category; DPP4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide.

Table IV. Anthropometric and biochemical characteristics of the study subjects by time point.

Category	N	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	p-value
Weight (kg)	69	97.10±22.91	93.31±21.10	89.60±19.21	88.96±18.06	87.87±16.54	<0.05
BMI (kg/m2)	69	32.86±7.27	31.73±6.81	30.49±6.24	30.01±5.77	30.02±5.49	<0.05
Waist circumference (cm)	69	111.99±13.99	108.93±12.95	105.64±11.79	102.66±16.55	103.52±10.40	<0.05
VFA (cm^2)	67	178.48±43.57	-	147.02±44.89	139.83±41.55	140.77±39.66	<0.05
PBF (%)	67	36.13±8.75	-	31.67±9.09	30.59±9.35	30.94±9.51	<0.05
SMM (kg)	52	34.51±7.36	-	34.35±6.75	34.46±6.57	34.08±6.74	=0.173
BFM (kg)	52	36.64±16.87	-	29.96±15.07	28.34±13.74	28.57±13.18	<0.05
Blood pressure (mm Hg)							
Systolic	69	141.06±18.22	129.16±11.97	122.25±18.51	-*	126.39±15.06	NA
Diastolic	69	87.57±10.30	83.01±10.89	93.62±96.47	-*	82.74±9.78	NA
Blood glucose (mg/dl)	69	174.25±45.32	118.93±19.98	126.13±120.16	108.07±17.02	106.65±19.54	<0.05
HbA1c (%)	69	8.11±1.35	6.99±0.75	6.15±0.61	6.02±5.33	5.99±0.65	<0.05
Insulinemia	5	18.48±11.49	-	8.22±4.39	-*	-*	NA
Total Cholesterol (mg/dl)	69	221.84±69.72	-	155.62±37.07	160.27±36.77	165.83±38.28	<0.05
Triglycerides (mg/dl)	69	263.80±249.37	-	137.22±63.14	127.56±46.35	123.92±52.01	<0.05
HDL-C (mg/dl)	69	42.76±13.78	-	44.94±11.62	46.65±0.60	49.17±11.22	<0.05
LDL-C (mg/dl)	63	132.88±40.27	-	89.01±30.56	92.59±33.83	94.78±35.40	<0.05
nonHDL-C (mg/dl)	69	174.42±64.06	-	109.78±33.61	113.29±35.60	117.56±38.27	<0.05
TG/HDL-C	66	5.54±3.51	-	3.51±3.38	3.22±3.27	3.05±3.69	<0.05

Values are expressed as mean ± standard deviation (SD). *Missing data; NA, not applicable as data were missing at marked time points; N, maximum number of subjects with available results; BMI, body mass index; VFA, visceral fat area; PBF, percentage of body fat; SMM, skeletal muscle mass; BFM, body fat mass; HbA1c, glycated hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; nonHDL, non high density lipoprotein.

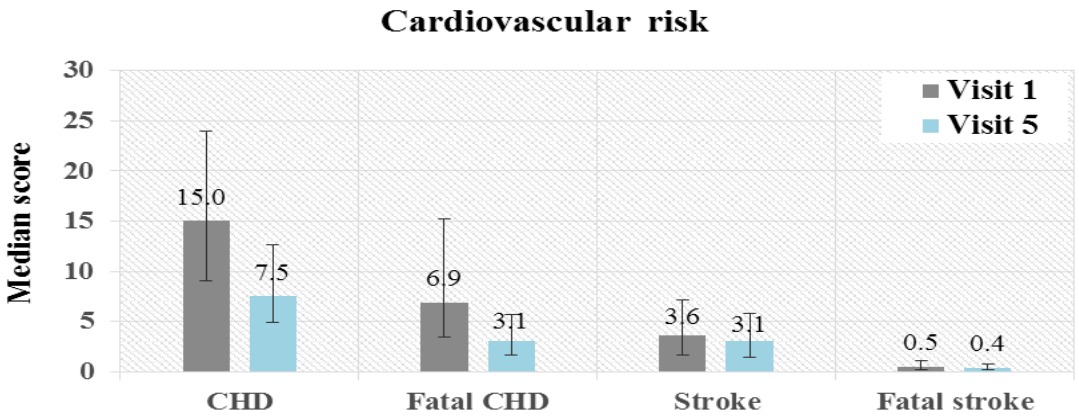

Figure 1. Cardiovascular disease risk changes.
Error bars represent the interquartile (Q1 and Q3) ranges; CHD, coronary heart disease.

trend was observed in the risk of stroke and fatal stroke; the mean value at visit 5 (8.30 and 1.04, respectively) was statistically significant decreased compared to the mean value at visit 1 (7.89 and 1.38, respectively), $p<0.05$ for both variables.

Discussion

In the present study, we demonstrated that intensive multi-factorial treatment and life-style management recommendations, provided during a 1-year follow-up period, contributed to the reduction of cardiovascular diseases risk in patients newly diagnosed with T2D.

It is well known that T2D is a major social and economical problem worldwide being considered an "epidemic disease" [24]. In 2011, Danaei *et al.* showed the imperative need of effective preventive interventions in T2D management due to its dreadful complications and its sequelae, including microvascular and cardiovascular events [24,25,26].

Multiple trials have been conducted to address these needs [27]. The UKPDS was the first that provided strong evidence that glycemic control in newly diagnosed patients with T2D (average HbA1c was 7.0% in the intensive treatment group receiving sulfonylurea or insulin) could lead to a significant decrease of the diabetes-related complications over a 10-year follow-up period. They demonstrated that glycemic control significantly reduced (with 25%, p=0.0099) the microvascular complications, but the reduction of the myocardial infarction risk was not statistically significant (16%, p=0.052) [15]. In addition, after a post-trial monitoring during a 10 year period it has been shown that persistence of the improved glucose control (in groups with intensive sulfonylurea–insulin treatment and metformin treatment) leaded to a continuous reduction of microvascular complications risk (with 24%, p=0.001 and no significant risk reduction, respectively) and myocardial infarction risk (with 17%, p=0.01 and with 33%, p=0.005, respectively). These findings sustain the metabolic legacy effect suggesting that the persistence of glycemic control benefits were related to intensive therapy, especially for CVD risk reduction in overweight patients on metformin treatment [28].

Other trials as Kumamoto study [29] and PROactive trial [30] were not able to demonstrate that glycemic control could provide a strong benefit regarding the reduction of CVD risk. As previously mentioned, the STENO-2 trial showed that an intensified multi-factorial treatment in patients with T2D and microalbuminuria reduced the relative risk of CVD with approximately 50% (hazard ratio, 0.47; 95% confidence interval, 0.22; 0.74; p=0.01), and the relative risk of diabetic nephropathy, retinopathy and progression of autonomic neuropathy with approximately 60%, during a 7.8 years follow-up period. In this trial, 160 Danish patients with T2D and microalbuminuria were randomized to receive either intensive or conventional multi-factorial therapy with the aim to evaluate the impact on modifiable risk factors for cardiovascular disease. The conventional treatment was the one recommended by the Danish Medical Association at the beginning of the study period. The intensive control consisted in a combination of medications and behavior modification aiming to achieve multiple targets according to the guidelines of the American Diabetes Association (glycated hemoglobin [HbA1c] <6.5%, a fasting serum total cholesterol <175 mg/dl, fasting serum triglyceride <150 mg/dL, systolic blood pressure <130 mm Hg, and a diastolic blood pressure <80 mm Hg). Additionally, due to their microalbuminuria and regardless of blood pressure, all patients in this group received blockers of the renin–angiotensin system and low-dose aspirin as primary prevention [16,17].

Although we did not assess the incidence of CVD during a long-term follow-up, we have demonstrated that the improvement of individual CVD risk factors during the 1 year follow-up period by intensive education regarding

the lifestyle management and medication led to a 50% decrease of calculated CHD and fatal CHD scores [from 15.0% and 6.9% to 7.5% and 3.1% ($p < 0.05$) respectively] and of stroke and fatal stroke by [from 3.6% and 0.5% to 3.5% and 0.4% ($p < 0.05$), respectively].

Our multi-factorial approach and structured management of patients with type 2 diabetes significantly improved the majority of modifiable risk factors and clinical outcomes of CHD and stroke. We have also recorded a significant decrease of BMI (from 32.86±7.27 kg/m^2 at visit 1 to 30.02±5.49 kg/m^2 at visit 5), VFA (from 178.48±43.57 cm^2 at visit 1 to 140.77±39.66 cm^2 at visit 5), triglycerides (from 263.80±249.37 to 123.92±52.01), LDL-C (from 132.88±40.27 mg/dl to 94.78±35.40 mg/dl) and Raven score (from 5.54 at visit 1 to 3.05 at visit 5). Our results are in accordance with the ADA and IDF guidelines regarding the control of CVD in subjects with T2D [31,32,33] and with other studies on early lifestyle interventions in patients newly diagnosed with T2D [34,35,36].

In addition to the routine medical practice, we focused our attention on the body composition measurements, especially VFA monitoring, because even if BMI is considered one of the best measure of overweight and obesity (overweight: BMI ≥25 kg/m2 and obesity: BMI ≥30 kg/m2) [37] and in the Framingham Heart Study has been shown that obesity is a critical risk factor for CVD [38], recent studies reported that VFA could have a higher atherogenic potential compared to general obesity [39]. A positive association was reported between elevated VFA and LDL-c, because an increased VFA leads to extensive lipolysis mediated by insulin resistance. The excess of free fatty acids (FFA) are involved in TG synthesis in the liver, and prolonged exposure to high level of FFA increases HDL-c synthesis and concomitantly, an increase in LDL-c [40], which is considered the predominant risk factor for atherosclerosis and CVD [41].

Considering all this, we assume that intensive patient monitoring by body composition measurements and individual treatment based on associated glucose-, lipid− and blood pressure-lowering medication associated with dietary and physical activity recommendations could lead to CVD risk decrease and it could elevate the quality of life.

Conclusions

The significant improvement of the majority of the CVD risk factors together with the significant decrease of non-fatal/fatal CHD and stroke risk during the 1-year follow-up period in newly diagnosed patients with T2D suggests that associated treatment and the intensive lifestyle intervention could decrease the rate of cardiovascular disease risk.

We think that healthcare professionals should be encouraged to recommend the T2D treatment together with the treatment of multiple cardiovascular risk factors and lifestyle management early in the diabetes disease trajectory. Early appropriate strategic healthcare planning could prevent or postpone diabetes-related complications by reducing significantly the risk of CVD.

Refecrences

1. Kazemi E, Hosseini SM, Bahrampour A, Faghihimani E, Amini M. Predicting of trend of hemoglobin a1c in type 2 diabetes: a longitudinal linear mixed model. Int J Prev Med. 2014;5(10):1274–1280.
2. Bhutani J, Bhutani S. Worldwide burden of diabetes. Indian J Endocrinol Metab. 2014;18(6):868–870.
3. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus-present and future perspectives. Nat Rev Endocrinol. 2011;8(4):228–236.
4. Sixth edition of the International Diabetes Federation Atlas, 2013. Available from: http://www.idf.org/sites/default/files/EN_6E_Atlas_Full_0.pdf.
5. Wu Y, Ding Y, Tanaka Y, Zhang W. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. Int J Med Sci. 2014;11(11):1185–1200.
6. Black JA, Sharp SJ, Wareham NJ, Sandbæk A, Rutten GEHM, Lauritzen T, et al. Does early intensive multifactorial therapy reduce modelled cardiovascular risk in individuals with screen-detected diabetes? Results from the ADDITION-Europe cluster randomized trial. Diabetic Med. 2014;31(6):647–656.
7. American Diabetes Association. Standards of medical care in diabetes—2013. Diabetes Care. 2013;36:S11–S66.
8. Zhao Y, Jiang Z, Guo C. New hope for type 2 diabetics: Targeting insulin resistance through the immune modulation of stem cells. Autoimmun Rev. 2011;11:137–142.
9. Mahajan A, Sharma S, Dhar MK, Bamezai RNK. Risk factors of type 2 diabetes in population of Jammu and Kashmir, India. J Biomed Res. 2013;27(5):372–379.
10. Bianchi C, Del Prato S. Metabolic memory and individual treatment aims in type 2 diabetes – outcome-lessons learned from large clinical trials. Rev Diabet Stud. 2011;8(3):432–440.
11. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358(24):2560–2572.
12. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129–139.
13. ACCORD Study Group. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358(24):2545–2559.
14. Otto-Buczkowska E, Machnica L. Metabolic memory - the implications for diabetic complications. Endokrynol Pol. 2010;61(6):700–703.
15. Intensive blood glucose control with sulfonylureas or insulin compared with conventional treatment and risk for complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:837–853.
16. Gaede P, Vedel P, Larson N, Jensen GVH, Parving H, Pederson O. Multifactorial intervention and cardiovascular disease in patients with type II diabetes. N Engl J Med 2003;348–393.
17. Gaede, P, Vedel, P, Parving, HH, Pedersen, O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised

study. Lancet. 1999;353:617–622.
18. IDF Diabetes Atlas 4th Edition, International Diabetes Federation, 2009. Available from: www.diabetesatlas.org.
19. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, et al. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy. Diabetologia. 2009;52:17–30.
20. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35(6):1364–1379.
21. Risk calculator UKPDS. Available from: http://integrate.ccretherapeutics.org.au/Calculator/UkPds.aspx
22. Black JA, Sharp SJ, Wareham NJ, Sandbæk A, Rutten GE, Lauritzen T, et al. Change in cardiovascular risk factors following early diagnosis of type 2 diabetes: a cohort analysis of a cluster-randomised trial. Br J Gen Pract. 2014;64(621):e208-216.
23. Stevens RJ, Kothari V, Adler AI, Stratton IM; United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin Sci (Lond). 2001;101(6):671–719.
24. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. Lancet. 2011;378:31–40.
25. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Phys Ther. 2008;88:1254–1264.
26. Emerging Risk Factors Collaboration, Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med. 2011;364:829–841.
27. Cerghizan A, Bala C, Nita C, Hancu N. Practical aspects of the control of cardiovascular risk in type 2 diabetes mellitus and the metabolic syndrome. Exp Clin Cardiol. 2007;12:83–86.
28. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359(15):1577–1589.
29. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Longterm results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. Diabetes Care. 2000;23:B21-B29.
30. Dormandy JA, Charbonnel B , Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitazone Clinical Trial In macroVascular Events): a randomized controlled trial. Lancet. 2005;366:1279-1289.
31. International Diabetes Federation. Guideline for the management of post-meal blood glucose. 2007. Available from: http://www.idf.org/webdata/docs/Guideline_PMG_final.pdf.
32. American Diabetes Association. Standard of Medical Care in Diabetes-2012. Diabetes Care. 2012;35[Suppl 1]: S11–S63.
33. International Diabetes Federation. Clinical Guideline Task Force. Global Guidelines for type 2 diabetes. 2012; Available from: http://www.idf.org/sites/default/files/IDF%20T2DM%20Guideline.pdf
34. Andrews RC, Cooper AR, Montgomery AA, Norcross AJ, Peters TJ, Sharp DJ, et al. Diet or diet plus physical activity versus usual care in patients with newly diagnosed type 2 diabetes: the Early ACTID randomised controlled trial. Lancet. 2011;378:129–139.
35. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358:580–591.
36. Florea M, Niţă C, Florea R, Hâncu N. Cardio-metabolic risk factors control in newly diagnosed type 2 diabetic subjects. Rom J Diabetes Nutr Metab Dis. 2013;20(3):279–286.
37. Ross TA, Boucher JL, O'Connell B (Eds.) American Dietetic Association Guide to Diabetes: Medical Nutrition Therapy and Education. Chicago: American Dietetic Association; 2005;217–218.
38. Dawber TR, Meadors GF, Moore FE Jr. Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health Nations Health. 1951;41:279–281.
39. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, et al. Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. Circulation. 2007;116:39–48.
40. Luo Y, Ma X, Shen Y, Hao Y, Hu Y, Xiao Y, et al. Positive relationship between serum low-density lipoprotein cholesterol levels and visceral fat in a Chinese nondiabetic population. PLoS ONE. 2014;9(11):e112715.
41. Kastelein JJ, van der Steeg WA, Holme I, Gaffney M, Cater NB, Barter P, et al. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. Circulation. 2008;117:3002–3009.