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Diabetes Type 2 and Physical Activity Program: Potential Application of Risk-Engine UKPDS Score in Out-Patient Context

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Abstract: Diabetes mellitus Type 2 (DMT2) carries a high risk of cardiovascular (CV) morbidity and mortality. Physical activity (PA) is widely prescribed for this population. However, detection of the eventual risk level and the potential additional increase through physical exercise are of paramount importance in these patients. A model for predicting absolute risk for coronary artery disease in diabetes has been provided in the investigation by the UKPDS (United Kingdom Prospective Diabetes Study). The present study aims to verify the potential feasibility of the UKPDS calculation in an out-patient context, where patients with DMT2 can be selected for an exercise prescription program. All patients investigated were consecutively enrolled in the study at the time of the first clinical check-up in the outpatient center of the University of Perugia-Internal Medicine Department. A group of 101 Caucasian patients (62 males; 39 females; aged 67 ± 2 years) were studied. In agreement with the UKPDS score, gender, age, ethnicity, Body Mass Index, systolic blood pressure and smoking habits were considered. The global mean cardiovascular risk calculated by the UKPDS risk-engine was 25.8% of a first cardiovascular event within 10 years after the initial observation. Despite an absence of symptoms, the risk was globally high and in agreement with current literature. Conclusion: The data are suggestive of a potential large clinical application of UKPDS risk-engine score in an outpatient context, especially in those asymptomatic DMT2 patients potentially enrolled in a physical activity program. This pilot investigation supports the importance for immediate estimation of cardiovascular risk in DMT2 subjects to implement basic therapeutic strategies such as physical activity.

Keywords: type 2 diabetes; UKPDS score; exercise; cardiovascular risk

1. Introduction

DMT2 (Diabetes Mellitus Type 2) carries a high risk of cardiovascular (CV) morbidity and mortality [1], especially if associated with a negative lifestyle [2]. Correct lifestyle behaviors are widely promoted to reduce both diabetes and cardiovascular disease (CVD) in healthy individuals [3]. There is some evidence supporting the effects of lifestyle changes on CVD outcomes, even though some limitations such as self-reporting life style measurements are often recognized [4,5].

The intensity of the exercise prescribed is also important to reach the goal of exercise as therapy, but the level of the physical effort can expose asymptomatic subjects to acute CV events.

Even though the literature supports glycated hemoglobin (HbA1c) plasma level as the main parameter for detecting global vascular dysfunction [1,2,6,7], it cannot be considered sufficient to correlate with the multiple CV risk factors present in this disease [6], especially if DMT2 is associated with negative habits and consequently leads to a progressive increase in events of acute CV [6,7] and coronary artery disease (CAD) [8,9]. Physical activity (PA), especially at moderate intensity, is normally prescribed to limit the progression of the complications of chronic metabolic diseases [10]. The indications are actually for all those subjects in a clinical stable condition and completely asymptomatic, especially regarding acute coronary artery disease events. It is therefore important to evaluate global CV risk before commencement of a PA program and to consider the potential negative and unpredictable impact of training in this population. The UKPDS (United Kingdom Prospective Diabetes Study) has supported the importance of using a risk-score in DMT2 asymptomatic patients [11] when they have been affected by the disease for at least 10 years. The purpose of our work was to verify the potential clinical applicability of the UKPDS calculator to identify DMT2 subjects at high risk before commencing an exercise as prescription program in an outpatient context, where patients can be consecutively enrolled. Our intention is to investigate whether the UKPDS application gives evidence of the absolute CV risk in a DMT2 population before commencing regular exercise training. This could be particularly helpful for adequately planning the intensity of exercise, even when the subjects are asymptomatic.

2. Materials and Methods

2.1. Population Studied

In the period between January and June 2016, a group of 101 Caucasian patients (62 males and 39 females, aged 67.2 ± 2.0 years) were enrolled for the investigation.

All patients investigated were consecutively enrolled in the study at the time of the first clinical check-up in the outpatient center at Perugia University Internal Medicine Department, dedicated to the periodical follow-up of DMT2 patients.

Inclusion criteria were the presence of DMT2 for at least 10 years, and being asymptomatic for any acute cardiovascular events, or an any abnormal rise in blood pressure.

Subjects with recent acute CV events were excluded from the study as well subjects with ascertained DMT2 for less than 10 years before the start of the observation.

All patients gave their formal consent to participate in the study and produced at the onset of the study, in the 2016.

2.2. Procedures

After a first clinical examination during which general data were collected, an update of the patient's history was carried out. A questionnaire was used to investigate when subjects had contracted diabetes, and the eventual presence of symptoms.

No specific evaluation of lifestyle or habits with respect to PA or dietary habits was made. To detect the level of daily physical activity, an informal interview was held during the first check-up, at which self-perception of daily physical activity was reported [12].

After a first clinical examination, where inclusion criteria and principal confirmation of DMT2 diagnosis needed to be satisfied, general data were collected. Some specific parameters were measured for the score application.

2.3. UKPDS (United Kingdom Prospective Diabetes Study) Model

The UKPDS risk-engine calculator estimates CV risk in terms of a potential first cardiovascular event, for at least 10 years following the onset of disease [13]. This model for absolute CV risk incorporates multiple risk factors as well as HbA1c values. This is the most important aspect that differentiates UKPDS with respect to the Framingham equations [14] for diabetic patients and these differences have been widely debated. The UKPDS method has a double interface: the first part is dedicated to the insertion of general data and the second part is a session where the score is calculated. Risk is calculated based on ten factors: age, gender, smoking habit, duration of diabetes, total cholesterolemia and HDL (high-density lipoprotein), systolic blood pressure, HbA1c, atrial fibrillation, and ethnicity.

The HbA1c was measured by HPLC (Diamat Automated Glycosylated Haemoglobin Analyzer, Bio-Rad, Hercules, CA, USA), non-diabetic range 4.5 ± 6.2%. Biochemistry methodology for the lipid profile was measured by Lipoprint® LDL Subfractions Kit (HDL-C < 40 mg/dL and LDL-C > 160 mg/dL are associated to high risk). The systolic and diastolic blood pressure was recorded manually for every patient as the mean value of three measurements taken during the same clinical check-up. Diagnosis of diabetes was confirmed based on at least 2 subsequent measurements over a week of fasting blood glucose at 126 mg/dL, or clinical history of diabetes. The definition of a smoker is someone who smokes every day (even one cigarette) or has stopped for less than 12 months. The definition of a non-smoker is someone who has never smoked or was a former smoker but who has stopped smoking for more than 12 months. To assess the correlation between cardiovascular risk and body mass index (BMI), we measured the patient's height and weight. Body weight measurement was performed using a calibrated scale. The subject was positioned standing barefoot at the center of the scales, arms by the sides of the body, wearing lightweight clothes without shoes. Measurement was carried out in fasting conditions. Height was measured using a measuring stick. The subject stood barefoot on a horizontal platform, touching the wall behind with his back and with heels together.

2.4. Statistical Analysis

The Shapiro–Wilk test was applied to assess the normal distribution of variables. Due to their asymmetrical distribution, the Mann–Whitney test was used to compare the values for the clinical variables; the relationship between variables were tested using Spearman's rho coefficient analysis. To simplify, all values were expressed as the mean ± SD (standard deviation). Statistical analysis was performed using IBM-SPSS® version 23.0 (IBM Corp., Armonk, NY, USA, 2015) and two-sided probability values $\leq$0.05 were considered to be statistically significant.

3. Results

The general characteristics and the principal parameters included in the score are reported in Table 1. The results are reported based on gender. The group of 101 subjects was composed of 62 males and 39 females, aged around 67.2 ± 2 years, with a body composition in the overweight range. Systolic and diastolic blood pressure values were at the upper limits of the acceptable normal level for diabetes (Table 1) and therefore not higher than 135/85 mmHg. Regarding smoking habits, only 14 subjects declared they were smokers, while 52 subjects were non-smokers and 35 ex-smokers. For the PA level, the group was homogeneous. All subjects were inactive, according to the interview, with respect to the eventual programmed PA model; therefore, it was estimated that the amount of PA was lower than two Metabolic Equivalent (MET). No subjects followed a specific diet, with the exception of the nutritional indication of a restriction of the assumption of glucose and carbohydrates.

Table 1. Characteristics of the Type 2 diabetes population investigated.

Group Investigated	Overall	Males	Females
Patients °	101	62	39
Age *	67.23 ± 2	67.35 ± 2	67.03 ± 3
BMI * (Kg/m^2)	28.66 ± 2	28.17 ± 3	29.46 ± 4
Systolic Blood Pressure * (mmHg)	131.1 ± 2	130.6 ± 4	131.7 ± 5
Diastolic Blood Pressure * (mmHg)	85.1 ± 3	84.6 ± 4	85.7 ± 5
Cholesterol * (mg/dL)	182 ± 3	181 ± 2	184 ± 4
HDL * (mg/dL)	49.7 ± 3	49.6 ± 5	49.9 ± 2
HbA1c * (%)	7.25 ± 2	7.39 ± 1	7.03 ± 3
Time from onset of T2D * (years)	12.4	11.6	12.7
Smokers °	14 (13.9)	8 (12.9)	6 (15.4)
Non-smokers °	52 (51.5)	24 (38.8)	28 (71.8)
Ex-smokers °	35 (34.6)	20 (32.3)	5 (12.8)

° Counts (%); * Mean ± SD.

Based on the parameters included, the mean global cardiovascular risk calculated by the UKPDS risk-engine of a potential first cardiovascular event after 10 years from the contraction of the disease was found to be 25.8%, as represented in Figure 1.

The specific evaluation of the risk profile distinguished by gender demonstrates a higher risk value in females (29.7%) than in males (19.6%). A specific impact could be due, primarily, to the high level of cholesterol found in the females of this sample (Figure 2).

Smokers and non-smokers, including ex-smokers, showed similar lifestyle habits. From the UKPDS risk analysis, the latter appear to run a higher risk compared to the former. Non-smokers have a greater risk (26.5%) than ex-smokers (26.2%) and a higher risk vs. smokers (22.2%), although these risks were not significant. For other parameters (systolic and diastolic blood pressure, BMI, glycated hemoglobin, and duration of diabetes), no significant differences emerge. In addition, the UPKS cardiovascular risk score does not show any significant variations with respect to the BMI values (Table 1).

Some correlations have been found: as expected, systolic pressure is directly correlated to age (rho = 0.229; p = 0.001) as reported in Figure 3. However, systolic pressure inversely correlates to HDL (rho = −0.203; p = 0.003). The latter correlates inversely with BMI (rho = −0.165; p = 0.017). The BMI itself correlates with HbA1c level (rho = 0.148; p = 0.033) and globally cardiovascular risk correlates with age, systolic pressure, HDL and duration of diabetes.

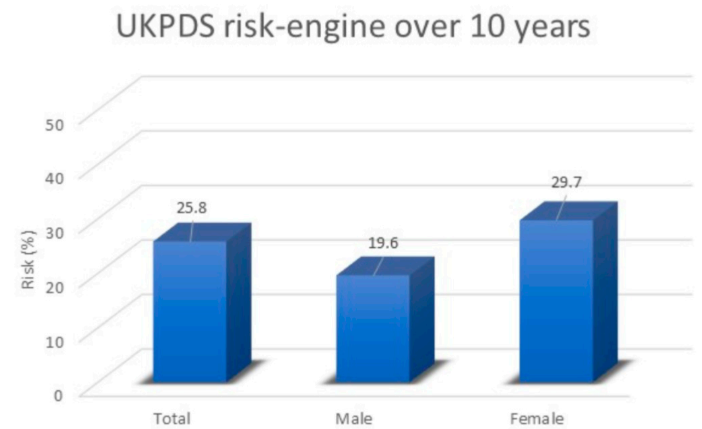

Figure 1. Estimated CV (cardio vascular) risk calculated by the UKPDS risk-engine, more than 10 years from the onset of diabetes. The graph shows the mean risk expressed in percentage is higher in females vs. males (p = 0.005). The laboratory's data were partially concordant with these results: total cholesterol is significantly higher in females compared to males, and the HDL (high density lipoprotein) cholesterol was also significantly higher in females when compared to males.

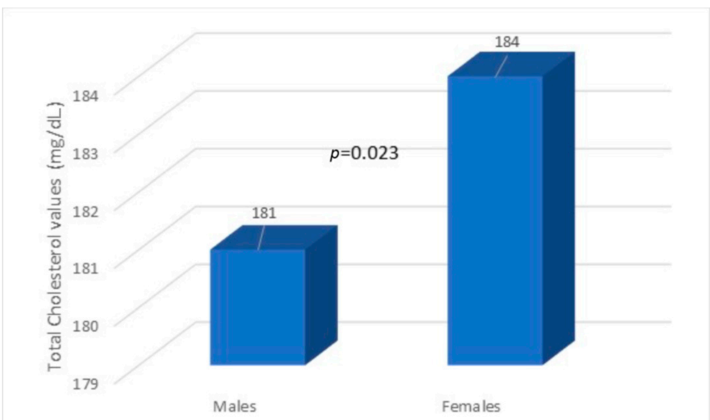

Figure 2. Total cholesterol values in males and females. Total cholesterol values are higher in females compared to males (p = 0.023) and females have a higher value of HDL (p = 0.009).

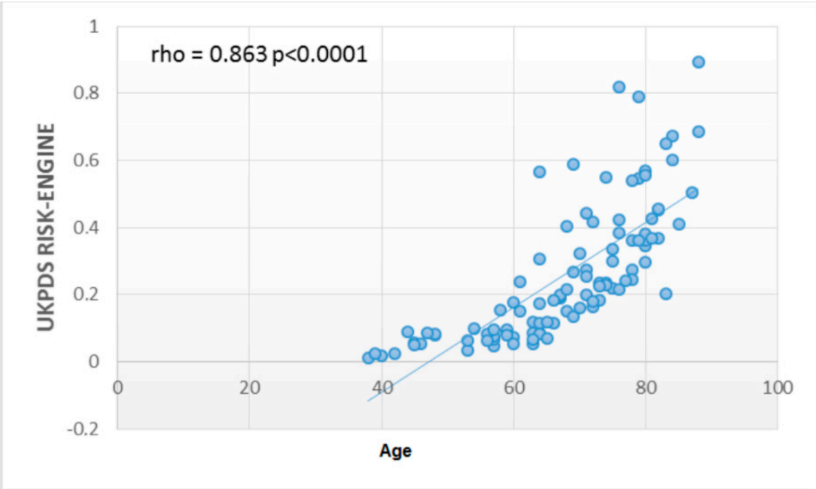

Figure 3. Age and CV risk correlation. Correlation of UKPDS risk engine with age.

4. Discussion

DMT2 is a high CV risk disease, and evidence shows it is increasing. Treatment has recently been updated with the inclusion of regular physical activity that is normally represented in a supervised model, in many programs. There is strong evidence that correct lifestyle can produce benefits in the diabetic population [15], and it is widely recognized that moderate physical activity is associated with benefits, especially in many metabolic chronic diseases. Treatment guidelines include regular PA to reduce the risk of complications [16] and to maintain a high quality of life [17]. Studies and trials support the evidence of the importance of a correct control of the metabolic aspect to prevent complications [10]. However, few data of the global outcome of the diabetes patients are available when a physical activity program is allowed in an unsupervised form.

A deep risk stratification analysis is often requested when the subjects involved in the exercise prescription activity are asymptomatic and the exercise program is proposed for a long time. Even when at moderate level, PA is not completely free of risk, especially in those subjects having disease at high CV risk component.

The daily level of glycate hemoglobin (HbA1c) is the expression of the amount and quantity of glucose circulating in the blood, particularly in the previous three months. However, it cannot be considered a sufficient parameter to estimate global CV risk.

From the current literature, it emerges that a standardized lifestyle intervention program needs the support of the CV risk stratification. This is especially important when the lifestyle adaptation can prevent the complications of DMT2 [18].

The measure of the CV risk before the individual exercise intervention is the basic approach to permit a physical exercise program to reach the target and to drastically reduce the incidence of acute events. There is in fact a kind of "escalation" of anti-diabetic treatment that has to take into account the progression of the disease, adapting, over time, the use of different and increasingly intensive therapeutic tools, from diet, to pads and, finally, insulin, with the constant support of regular PA.

Particularly in asymptomatic patients who have been affected by DMT2 for 10 years, screening CV risk before commencing an exercise program is often induced to reduce the excessive prescription of many specific but expensive tests such as the ergometric test or echocardiographic stress test. The UKPDS method is largely used in the context of CV risk even though it is known that it tends to overestimate global CV risk.

The data of the level of risk obtained in the present investigation are substantially in agreement with literature [8], and they correlate with gender, age, total cholesterol, HDL, systolic pressure, duration and time of diabetes. The specific evaluation of the risk profile distinguished by gender demonstrates a 29.7% risk value in diabetic females compared to 19.6% found in males: this is not completely in agreement with the data in the literature [8]. The group investigated is probably too small. All these parameters are, however, closely affected by regular physical activity.

Smoking and non-smoking subjects need special consideration; at present, the particular and apparently paradoxical behavior of the risk value found in them is not completely understood. There are insufficient data to assess the real impact of smoking data on the score: the results could be influenced partially by the small sample investigated and mainly by the length of time the subjects had the disease, which has a major impact on CV risks factors.

The data require a larger population of subjects, and a new investigation will be necessary to consider some specific aspects regarding other risks factors related to the lifestyle.

Other limit regards the missing data about the number of patients definitely excluded from the protocol. This could be an important aspect in a longer follow-up evaluation. The data are going to be implemented for this aspect.

Another important limit could be represented by the fact that the algorithm calculation was developed by data obtained from a UK population and therefore not an Italian one.

A specific aspect regards the single parameters used in the UKPDS that could be further modulated in terms of a range of values to better and sooner discover the eventual multifactorial risk in the case of different kinds of population investigated.

As reported in the literature, the Framingham Risk Score is a gender-specific algorithm used to stratify the cardiovascular risk as low, medium, and high in the past 10 years of a population studied.

Different versions of the Framingham Risk Score have been published, however, in the last update, DMT2 has been excluded because it was considered to be a CHD Risk Equivalent, having the same 10-year risk as individuals with prior coronary heart disease. For this reason, in this study, no comparison between the two score has been made even though it could be a potential investigation in future and in a larger population of out-patients.

In this study, the data regarding the BMI value does not correlate with an increase of cardiovascular risk up to ten years of observation. Overall, these data can support the strong capacity of the score to highlight some risk factors in asymptomatic diabetes, especially those such as BMI and blood pressure, potentially modified by regular physical training.

In any case, this investigation has to be considered a pilot study, conducted in a restricted area of DMT2 out-patients. The potential comparison of the UKPDS score with other CV risk stratification models such as those studied in the Framingham coronary heart risk score [19] could be very helpful, especially in this kind of population, where the involvement in exercise prescription models is important.

A wider study involving patient will be planned to avoid eventual inconsistencies and overcome limits.

5. Conclusions

Generally, from this pilot study, even though it is a restricted investigation, the UKPDS method seems to offer some larger clinical applications for reducing costs and easily screening the effective risk. The potential clinical application could address the specific investigations to more selected subjects, and limit the eventual additional investigations, especially in a restricted group of diabetes.

The results provide insights for wider use of the score, even in a sports medicine context where PA is now considered to be the main therapeutic approach for many chronic degenerative pathologies such as diabetes.

Considering in any case the positive experience of the application of this model, it is hoped that this approach is shared among other disciplines and potentially implemented, based on gender.

Other data are necessary for a long-term evaluation of the impact of the model in the diabetic population regularly submitted to physical exercise as therapy, especially considering that, even though constant and regular exercise at moderate intensity induces positive effects and it is protective in a population at high CV risk such as DMT2, out-patients represent a special context where the initial clinical approach cannot be sufficient to create a long term security of the exercise, especially if the exercise is allowed on an at-home basis, i.e., not in a gym.

We can conclude by asserting that the UKPDS risk-engine represents an excellent support for the management of Type 2 diabetes mellitus, when the therapeutic approach is implemented with new strategies, such as supervised or non-supervised physical exercise programs. The benefits of this tool include considering certain parameters such as glycated hemoglobin and duration of diabetes, not included in other diabetes-specific methods, and that are in any case available in the out-patient context.

Author Contributions: Cristian Petri conceived and wrote the study; Alice Tantucci, Gaia Angeloni and Giacomo Bomboletti carried out patient evaluations and wrote the manuscript; Gabriele Mascherini contributed to update the literature and to implement the main message of the study; Vittorio Bini elaborated the data and contributed to writing the manuscript; Massimiliano De Angelis supervised and directed the study; Giorgio Galanti revised and approved; and Laura Stefani coordinated the author contributions, wrote, revised and approved the final version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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