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Editorial
PREVENTION OF DIABETES AND 4P MEDICINE

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Introduction

In the last decades (more visibly in the last 20 years), there has been a progressive increase in the prevalence and incidence of Diabetes Mellitus (DM) on a global scale, irrespective of the economic development of various regions (high, middle or low income countries), especially in developing countries. "It may yet be, along with obesity, the greatest chronic disease epidemic in the history of human existence" [1].

The International Diabetic Federation (IDF) has reported for 2015, globally, a number of 415 million adults (aged between 20 and 79), with DM (8,8%), estimating an increase to 642 million by 2040 [2]. This increase is mainly due to the surge in the number of people with Type 2 DM but also to the rise in incidence of Type 1 DM and gestational DM, a form of diabetes which is still under-investigated and under-diagnosed. The prevalence of Type 2 DM increases with age, being more frequent in men in comparison with women; overweight and obesity as well as unhealthy lifestyle are important factors of this rise [1,2]. DM is associated with a high risk of morbidity and premature mortality, especially due to cardiovascular reasons, complex health care teams being needed to train the patient suffering with diabetes the way they should permanently adapt medication to their type of diet, the level of physical exercises, the various events which can produce a diabetes' temporary imbalance.

It is well known that the patients who suffer from DM need more outpatient consultations, show a greater number of days of hospitalization, and the occurrence of the devastating chronic complications (micro, macrovascular) or comorbidity severely affects the health state of these relatively young patients, their work ability decreases, being often in need of a companion. The mortality of patients suffering from DM exhibits an increasing tendency and exceeded, in 2015, the figure of 5 million, compared to 1,5 million in 2012 and 1,1 million in 2005 [2,3].

Necessity of prevention

The inexorable and unsustainable progression of this disease is becoming more and more apparent, which more and more clearly requires a coherent international policy of prevention against DM [1]. At present, the majority of states provide 5-20% of their health budget for the care of these patients [2]. IDF estimates that there are approximately 315 million people with Impaired Glucose Tolerance

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(IGT), who have a major risk of developing DM in the near future [2]. There is no consensus regarding defining and diagnosing prediabetes, as it follows from the analysis of clinical studies: some states report only the persons who show IGT, Impaired Fasting Glucose (IFG) or their association (IFG+IGT) or the value of HbA1c. On the other hand, the criteria defining prediabetes used by ADA doubles the cases diagnosed with prediabetes, comparing to the criterias of the WHO [4]. The studies regarding the prevention of DM, which included people with prediabetes, showed that DM can be prevented or that the onset of the disease can be delayed, if some lifestyle changes are being made or if some medication is being used, especially Metformin. "Preventing or delaying Type 2DM has become an international priority" [4]. Barry et al. published the results of two meta-analyses, in which they included all the eligible studies, no matter of the publication language, concluding that the screening tests which were used in the majority of the studies have significant limitations; A1c is neither sensitive nor specific for detecting prediabetes and fasting glycaemia is specific but not sensitive. The consequences are twofold: a great number of people who do not suffer from prediabetes can be diagnosed with the disease. On the other hand, some patients will remain undiagnosed. As a result, no prevention program will be applied and they will not be considered as being at risk of developing diabetes [4].

Zimmet et al. states that approximately 20% of the population, at a global level, shows increased risk of developing DM and they represent the source of 50% of the new diabetes cases, the other 50% being part of the population with a low to moderate risk, although many of them do not go through the stage of prediabetes, rapidly developing DM [1,4]. This is why we cannot help but ask this legitimate question: Why the implementation of the prevention programs are justified only for the high risk classes, even if there are more and more studies which show that the people with a very high risk of DM (old age, IFG+IGT, the decrease in insulin secretion, insulin resistance, the presence of Non Alcoholic Fatty Liver Disease – NAFLD, etc.) normalise the glycemic response in a much smaller percentage than the rest of the population? [5].

It is already well known the fact that prediabetes is a heteregenous state, with various pathogenetic mechanisms, which can predict DM. This is why Norbert S et al. propose the establishement of some accurate prediabetes phenotypes which can stratify and predict the risk of the disease, imposing personalized preventive measures. The authors also propose that after the presence of IFG, IGT or IFG+IGT is established, the metabolic phenotypes of each person suffering from prediabetes (insulin resistance, insulin secretion failure, NAFLD and visceral obesity) should be studied; in this way, it will become more and more clear that no matter of the Body Mass Index (BMI) there can be people with high cardiometabolic risk, including the people with normal weight and new preventive personalized strategies can be adopted due to knowing these facts, without passively waiting for the onset of the disease [5].

4 P Medicine

It is more and more obvious that, for preventing a disease, a precocious intervention is needed, and this can be made through the elimination of the causes, the intervention in the disease's physiopathogenic mechanisms, at a cellular and molecular level, long before the occurrence of a clear symptomatology [6].

Therefore, the introduction of a new health care system is required, which is named

"Medicine 4 P" (predictive, preventive, personalized and participatory) or the "medicine of the future", developed as a result of the "digital revolution", which radically increased the collecting, incorporation and data storage capacity, analyzing with great complexity and communicating data and information resulted from both clinical and fundamental research. More and more inhabitants of this planet will have "Personal Data Cloud (PDC)", which will be filled during their lifetime. The data will contain complex information, starting from the family and personal history of each individual, including information regarding the lifestyle (diet, sedentariness, sleep, stress, alcohol consumption etc.), followed by blood measurements, genomic, transcriptomic, metabolomic, proteomic, gut microbiomic data, etc.

Both Biology Systems and Medicine Systems as well as PDC will permanently update the data, as new research results appear, respectively new feedbacks from as many PDC as possible (whether as a result of the application of personalized prevention measures to each individual, as it has been concluded after the integration of PDC in the Medicine System). Biology Systems are the result of data collection from the multiple level networks, from a molecular level to cellular, tissue, organism, and population level.

The integration of the biological data and people's colaboration, which is becoming more and more productive, between scientists, doctors, informaticians, mathematicians, engineers makes the prediction and the control of the activities of the Biology System possible to be made in a much more detailed way.

Medicine Systems are about the application of the biological systems into the human pathology.

The doubts regarding the application of 4P Medicine to any of its sub-points (predictive, preventive, personalized and participatory), will soon be eliminated due to the technological and scientific progress; the people will not be genetically labeled, the data will be interpreted depending on the intervention of the environmental factors and of the epigenetic ones. Therefore, Medicine Systems will be able to establish, for each „PDC", what is the risk of developing diabetes (predictability), what would be the optimal prevention modality (preventibility), the personalization of the intervention depending on the analysis of the data from the Medicine System (the personalization of the intervention); healthy people and patients would be able to knowledgeably access the database from home, work, or school, without having to go to their doctor in order to receive answers to their various anxieties and questions [6].

Risk factors for diabetes, Clinical studies

Over time, a series of factors which favor the onset of DM have been identified. Some of them are not liable to influence (ethnicity, family history of Type 2DM or cardio-vascular diseases, age, gender, history of gestational diabetes, polycystic ovary syndrome), others can be liable to influence (insulin resistance, overweight/obesity/visceral obesity, insulin secretion failure, NAFLD, Metabolic syndrome, sedentary lifestyle, smocking, IGT and/or IFG, hypertension, decreased HDL cholesterol, increased trigylcerides, unhealthy diet, intrauterine environment, inflammation, stress, alcohol consumption, antidepressant drugs, statin use, etc).

Since 1993, a series of inter-conventional clinical studies have been carried out at an international level in order to demonstrate the role of lifestyle's optimization ± medication in

the prevention of DM. The first study, Finnish Diabetes Prevention Study (DPS) lasted for 3.2 years and followed its subjects for up to 13 years. The study was coordinated by the National Public Health Institute, took place in 5 locations around Finland and contained 522 subjects, overweight men and women with high risk of DM, of average age. The subjects were divided, randomly, in 2 groups: a control group "standard care" and "an intensive lifestyle intervention" group. The last group benefited from a complex educational program which pursued a weight loss of ≥ 5 kg. A ≥30 min/day work-out was recommended, a hypocaloric diet was implemented with a <30% fat quantity of daily calories intake, with <10% saturated fats of daily calories intake and ≥ 15g/1000 kcal of dietary fibers. The glycemic balance was monitorized through the procedure of glucose tolerance test with 75 g of annually anhydrous glucose. The DPS results were encouraging: there were 58% less cases of DM during those 3.2 years, while after 13 years another 39% less patients with DM in the interventional group, in comparison with the control group.

In 2002, the results from the US Diabetes Prevention Program (DPP) were published, and they also showed a decrease by 58% of diabetes risk, proving that the optimization of lifestyle is more efficient than medication [7-9]. The number of people who needed to be treated to prevent one DM case was, in both studies 7, indicating that DM was prevented for 1 out of 7 subjects for whom the prevention program was implemented [8]. Da Quing Study demonstrated, after 20 years, a 43% DM reduction [9].

The clinical studies, regarding the medication recommended in prevention, show that metformin is the best ranked and can be recommended to people suffering from prediabetes especially when the Body Mass Index (BMI) ≥35kg/m², to women who had gestational DM and to people who have an increasing HbA1c, even though the prevention program is respected [9].

Unfortunateley, a series of subjects, especially the ones with a higher risk of developing DM, do not respond to the prevention programs, even if they follow the recommendations and lose as much weight as they need to. This is why it is neccessary to imply personalized prevention programs, starting from various phenotypes and physiopathogenic mechanisms [8]. There are many gene variants which are known to associate with DM; they can influence one another and, incretin and fatty acids also playing an important role in insulin secretion [8-13]. The disparate analysis of BMI only, cannot offer enough data regarding the risk of diabetes, even if it is already known that approximately 25% of the overweight patients are metabolically healthy at a given moment – metabolically healthy obesity – MHO, while some of the subjects with normal weight can be metabolically unhealthy at one moment or another–MUHL. Complex explorations (magnetic resonance spectroscopy and a series of other explorations) can identify the existence of a various phenotypes of prediabetes, which influence more or less the response to the prevention programs [8]. NAFLD, which induces insulin resistance, IGT and in time Type 2 DM, does not usually improve after the optimization of lifestyle, especially to the increase of physical activity. Clinical studies, accompanied by hepatic biopsy to subjects with prediabetes and NAFLD, showed a different participants' response in studies, some with a good response to hypolipidemic diet, others to hypoglycemic diet, both types of diets being hypocaloric and both inducing the same weight loss [8,14-17].

Conclusions

The epidemic rise of DM must be stopped due to both severity of this disease, induced by the presence of associated chronic complications and the presence of comorbidities, and also because of the huge costs.

Prevention studies demonstrated that diabetes can be prevented in a limited percentage; the medicine of the future – 4P can bring incalculable benefits for both general population (regarding prevention and DM treatment, accompanied by other chronic diseases), and also for the limitation of the huge costs associated with treatment and prevention.

The prevention programs are more and more recommended to be used for the entire population, no matter the risk, as precocious as possible, starting even from the intrauterine life, when a series of phenotypes (and also genotypes) which will guide each person for the entire life, are being established [1,18].

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