

## STATE-OF-THE-ART REVIEW

# Diabetes Care in Republic of Macedonia: Challenges and Opportunities



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### Abstract

**BACKGROUND** The Republic of Macedonia (RoM) has experienced a rapid rise in the prevalence of type 2 diabetes (T2D) over the past 2 decades, a period characterized by significant social, political, and economic change. RoM now has one of the highest rates of diabetes in Europe.

**OBJECTIVES** To explore the modifiable conditions that may underlie and exacerbate the T2D epidemic; describe the state of diabetes care; and consider improved mechanisms for prevention and treatment, including research priorities, in RoM.

**METHODS** Methods included data mining from reliable sources and collaboration of authors to consider and describe applications of research from outside RoM and to identify evidence-based strategies to reduce the burden of T2D in RoM.

**FINDINGS** In 2014, the national prevalence of diabetes was 11.44% of the population (20–79 years) of RoM. Per capita caloric intake has increased significantly over the past 2 decades, with the majority of these calories coming from sugar, pork, chicken, beef, and sunflower oil. Excess calories, in the form of nutrient-deficient foods, animal products, and added oils promote insulin resistance and T2D. Tobacco use and lack of physical activity also contribute to the diabetes epidemic. Insulin, especially insulin analogues, are widely available and used to manage diabetes, often over other interventions that are more appropriate for patients with T2D, and more frequently than in other more developed countries, resulting in higher and unsustainable related costs.

**CONCLUSIONS** A new National eHealth System allows for better identification and monitoring of citizens with diabetes. However, the rapidly growing expense of insulin in the past has been unsustainable. The potential exists for a stronger role for lifestyle interventions in prevention and treatment of T2D. Significant changes in dietary patterns parallel the rise in diabetes prevalence and are likely a leading cause of diabetes and its complications. Research in RoM is needed to determine the impact and acceptability of dietary interventions for prevention and treatment of T2D, as a first step toward reduction of diabetes prevalence and its complications and controlling spiraling health care costs.

**KEY WORDS** cardiovascular disease, high prevalence, insulin consumption, Macedonia, plant-based dietary intervention, type 2 diabetes, vegan, vegetarian

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## INTRODUCTION

It is now widely accepted that worldwide diabetes prevalence is surpassing even the most pessimistic projections from the past. For example, in 2004, it was estimated that diabetes prevalence in 2030 would reach 334 million people, whereas the actual prevalence of 387 million people with diabetes was already reached in 2014, and the new projection for 2035 is 592 million, almost double what was estimated only 10 years ago.<sup>1,2</sup>

The Republic of Macedonia (RoM) is a landlocked country located east of Albania and north of Greece (Fig. 1), with an estimated population of 2.06 million and covering an area of 25,220 square kilometers.<sup>3</sup> Escalating rates of type 2 diabetes (T2D) are worrisome and have significant ramifications for the future well-being of the country and its citizens. The estimated total diabetes prevalence, of both diagnosed and undiagnosed cases, in RoM was around 80,000 people in 2004, whereas the estimated total diabetes prevalence in 2014 was 180,180 (90,020 men and 90,160 women). RoM has a national diabetes prevalence of 11.44%, which is the third highest in Europe, behind just Turkey and Montenegro, and a comparative (age-adjusted) diabetes prevalence of 9.76%, or the second highest in Europe, after Turkey.<sup>2</sup> The estimated total diabetes prevalence for RoM in 2035 is 223,780.

It was projected there were 2300 (1.3%) patients with type 1 diabetes (T1D) in RoM in 2013.<sup>2</sup> T1D is characterized by autoimmune destruction of the insulin-producing beta cells of the pancreas.<sup>4</sup> RoM still remains a “cold spot” (ie, low prevalence rate region) for T1D in Europe.<sup>5</sup> In contrast, the prevalence of T2D in RoM is strikingly high. T2D is characterized by insulin resistance and a progressive decrease in insulin secretion.<sup>4</sup> Overweight, obesity, and a lack of physical activity increase the risk of T2D. Basic diabetes-related data for RoM are presented in Table 1.

## METHODS

Information from the International Diabetes Federation (IDF), RoM Ministry of Health database, and other sources were used to compile the most up-to-date information on the prevalence of diabetes and its complications, along with associated costs in RoM. Consensus among the authors was used to describe the potential implications of specific evidence-based lifestyle interventions and to lay the foundation for necessary clinical research.

## DISEASE DRIVERS

There are many factors responsible for the rising prevalence rate of diabetes in RoM. One reason for such steep growth in T2D, especially in the past 25 years, might be the societal transition from a centrally planned economy guaranteeing jobs and income in the socialist period before 1990, to a market economy with job and income insecurity afterward. This “transitional economy” has led to an unprecedented rise in unemployment and associated stress, especially among the middle-aged population. In addition, RoM is one of the top 10 countries of the world in smoking prevalence. This is important when taking into consideration that in 2014, the US Surgeon General’s Report identified for the first time that cigarette smoking not only raises the risk of vascular and other complications of diabetes, but that it is a direct causative factor for T2D, and furthermore, that the risk of developing diabetes is 30%–40% higher for active smokers than nonsmokers.<sup>6,7</sup> The nation is also struggling with a typical sedentary lifestyle, despite recent efforts to increase the number of hours of physical activity as part of compulsory education.

Another explanation for the risk in diabetes prevalence is offered by the similarity of the dietary habits and lifestyle to those of the population in Turkey, a country with the highest diabetes prevalence in Europe.<sup>2</sup> This might be due to the fact that the Ottoman Empire had occupied the Balkans, and the territory of modern RoM, for more than 5 centuries until beginning of the 20th century, exerting a huge influence on the diet and lifestyle of the local population. Such a diet is mainly based on nonintegral wheat flour, bread, pastry, lots of sweets, high-fat meals, and a lifestyle characterized by no or inadequate physical activity.

The dramatic shift in dietary patterns since the early 1990s, when RoM gained its independence from the former Yugoslavia, warrants a closer look, because these have paralleled the rising rates of overweight (53% of the population in 2014<sup>8</sup>), obesity (20% of the population in 2014<sup>8</sup>), and T2D over this period. Total daily calories per person have risen from 2250 in 1993 to almost 3000 in 2011 (Fig. 2), with no concurrent increase in physical activity. Centrifugal (refined) sugar consumption rose rapidly between 1991 and 1999 (Fig. 3). Consumption of sugar has remained high but steady since 1999 and does not begin to account for all of the increased calories in diets in RoM. Beef and veal intake have increased from 15 to 19 metric tons



**Figure 1. Map of the Republic of Macedonia.**

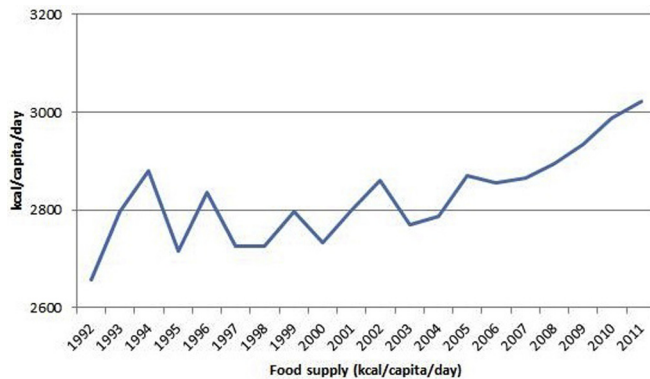
(MT) carcass weight equivalent (CWE), though not to the extent of swine and poultry consumption (Fig. 4), both of which have more than doubled over this relatively short period. These represent

significant increases in the intake of saturated fat and cholesterol. Intake of sunflower seed oil, another high-fat, high-calorie food, has also more than doubled (Fig. 5).

**Table 1. Diabetes-related demographic data of the country**

Total population	2,058,539
National diabetes prevalence (20-79 y)	11.44%
Comparative diabetes prevalence (age-adjusted)	9.76%
Total diabetes patients (both diagnosed and undiagnosed)	180,180
Patients with diagnosed diabetes	84,568 (46.9% of total patients)
Patients with diabetes on insulin treatment	37,011 (43.8% of diagnosed patients)
Patients with diabetes on insulin analogues treatment	27,370 (74.0% of insulin treated patients)
Patients with type 1 diabetes	2,300 (1.3% of total patients)
Patients with type 1 diabetes on insulin pump	172 (7.5% of type 1 diabetes patients)

Source: National eHealth System. [www.mojtermin.mk](http://www.mojtermin.mk) Accessed July 1, 2015.



**Figure 2. Changes in food supply in the Republic of Macedonia.** Source: Food and Agriculture Organization of the United Nations, Statistics Division, 2015. [http://faostat3.fao.org/browse/FB/\\*E](http://faostat3.fao.org/browse/FB/*E). Accessed October 6, 2015.

### CARDIOVASCULAR DISEASE AND DIABETES

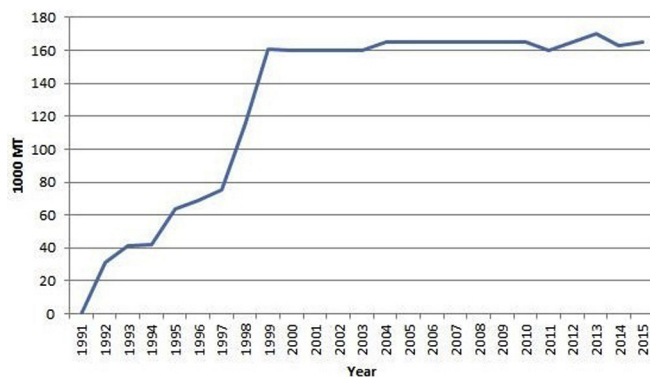
A related concern is the prevalence of cardiovascular disease, which is the most dominant cause of mortality in RoM (59% of all cases), now categorized as a very high risk country for cardiovascular mortality with a rate of 553/100,000 persons.<sup>9,10</sup> Diabetes-associated cardiovascular disease, such as coronary artery disease, stroke, peripheral artery disease, cardiomyopathy, and congestive heart failure, are the main causes of morbidity and mortality in patients with T2D.<sup>11,12</sup> It is estimated that 80% of patients with T2D would die from cardiovascular events, and the risk for developing coronary artery disease in patients with T2D is at least 2-fold higher in men and at least 4-fold higher in women compared with those without T2D.<sup>11,12</sup>

Such a strong association between diabetes and cardiovascular disease further contributes to the

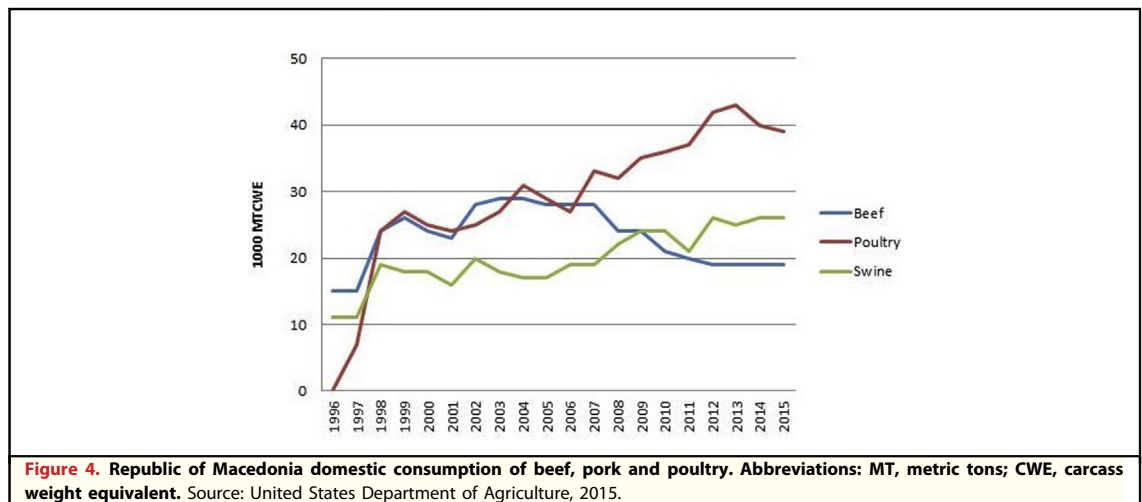
complexity of the diabetes burden on the socioeconomic state of the country. As discussed earlier, the same lifestyle changes that have contributed to the rising rates of diabetes are also a significant factor in cardiovascular disease. Fortunately, diet, tobacco use, and physical activity are highly modifiable risk factors. The World Health Organization identified unhealthy diets as a major cause of diabetes and other chronic diseases.<sup>13</sup>

### INSULIN USE

As the number of diabetes cases in RoM has risen, there has also been an increase in insulin use of more than 50% in the period from 2005 to 2011.<sup>5</sup> In one study of 30 diabetes clinics involving almost 2200 patients, 48.7% percent of people with diabetes used insulin,<sup>14</sup> compared with only 30.8% of people with diabetes in the United States.<sup>15</sup>



**Figure 3. Centrifugal (refined) sugar consumption in the Republic of Macedonia.** Abbreviation: MT, metric tons. Source: United States Department of Agriculture, 2015.



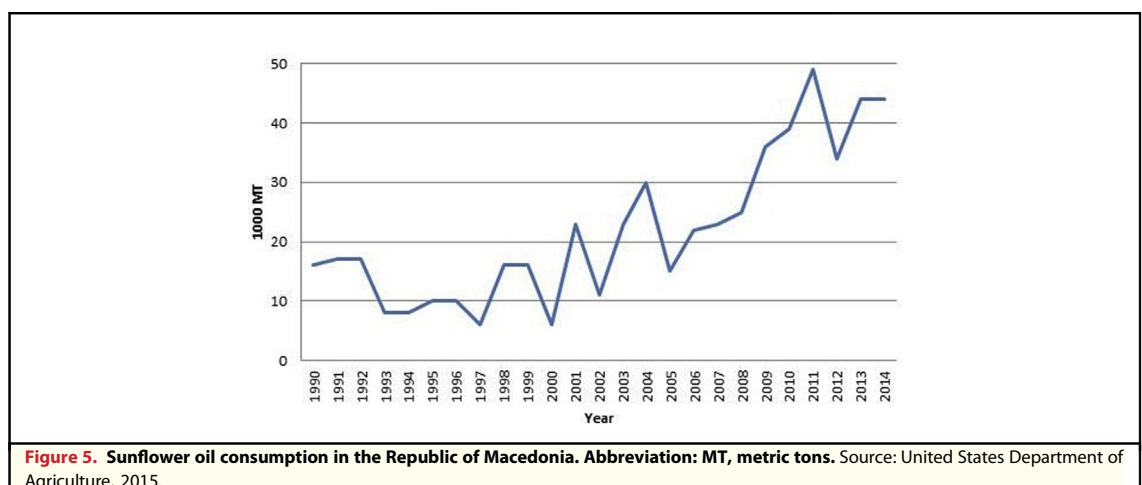
Exogenous insulin is associated with weight gain and hypoglycemia.<sup>16</sup> Considerable growth of the use of insulin analogues (an 8.6-fold increase) has occurred in RoM in the same period. Increases in the diabetes prevalence and high penetration of insulin analogues led to the enormous increase in the cost of insulin treatment (2.5-fold increase) in the period 2005–2011.<sup>5</sup> This largely is due to prices of analogues 2–4 times higher than human insulins, coupled with a >13-fold increase in analogue cost in this period.<sup>5</sup>

By 2012, insulin consumption in RoM was characterized by exceptionally high insulin analogue penetration, both in terms of volume and value, compared with European Union/European Economic Area countries, particularly so if the financial strength of the national health care system was taken into consideration. Cost of insulin and

insulin-related supplies (eg, needles, test strips, glucagon, insulin pumps, and related supplies) amounted to 21% of the total cost for medications covered by the Healthcare Insurance Fund or government programs in 2012, not including the cost for oral antidiabetic drugs or direct and indirect costs related to diabetes complications.<sup>5</sup> Given the very high prevalence and very high costs for the diabetes treatment, diabetes has been posing a threat not only to the national health care system but also to the society as a whole.

#### THE NATIONAL HEALTH CARE SYSTEM

One revolutionary step in monitoring and improving of performance of the national health care system was the introduction of the National eHealth System on July 1, 2013. This consisted of a



comprehensive electronic health care record system covering all citizens from RoM across all 3 levels of health care: primary care provided by family physicians, secondary care provided in general and regional hospitals, and tertiary care provided in university clinics. The National eHealth System is an internationally recognized achievement, as stated in the European Healthcare Consumer Index (EHCI) Report for 2014: “The FYR [Former Yugoslav Republic of] Macedonia is making the most remarkable advance in the EHCI scoring of any country in the history of the Index, from 27th to 16th place, largely due to more or less eliminating waiting lists by implementing their real time e-Booking system.”<sup>17</sup>

This step represents significant progress. Some additional strengths for RoM have been identified by the International Diabetes Federation (IDF),<sup>18</sup> including: a National Diabetes Plan; existing prevention policies on overweight/obesity, smoking, and the harmful use of alcohol; and promotion policies on healthy foods, dietary patterns, and physical activity. This IDF publication also mentioned that stakeholders recognized diabetes as a major problem in RoM, being high on the political agenda because of increasing rates of prevalence and associated costs.<sup>18</sup> As for shortcomings, this IDF publication specified there are no nationally reported data on total prevalence and incidence, with the existing national diabetes registry following only people on insulin therapy and thus remaining incomplete.<sup>18</sup> Furthermore, this IDF publication found that diabetes education is available mainly to people treated in large clinics and medical centers, with a lack of time and shortages in human resources in diabetes education offered to the larger population of people with diabetes and their relatives.<sup>18</sup>

Facing such tremendous challenge for the society, diabetes, as a specifically designated medical condition, has been included in the recently adopted amendments on the Law on Healthcare.<sup>19</sup> International guidelines have been accepted as national guidelines for diabetes care and treatment, and, in addition, have been published in the *Official Journal of RoM*, where laws and bylaws are published, further emphasizing the importance attributed to diabetes as a nationwide condition.<sup>20</sup> Amendments on the law also stipulated formation of the National Diabetes Committee to oversee the implementation of a national guideline for diabetes care and treatment.<sup>19</sup>

Since the beginning of 2015, data for all diabetes patients have been integrated in the National

eHealth System, together with a National Diabetes Register, enabling numerous analyses on a national level. For the first time ever, it has been possible to provide nationally reported data on diabetes prevalence in diagnosed cases at the level of 5.0% in the adult population (20–79 years). However, initial results of a diabetes screening program at the primary care level suggest diabetes prevalence in undiagnosed cases of 6.5%, resulting in total diabetes prevalence for ROM of 11.5%, almost identical to the one estimated by IDF, sending an alarming message that more than half of the patients with diabetes in RoM are, in fact, undiagnosed.<sup>20,21</sup>

## SOLUTIONS

**Economic.** The struggle for sustainable diabetes care resulted in considerable reduction of insulin and insulin-related costs in the period 2012–2015, despite the fact that insulin and related supplies (eg, test strips, insulin pumps and related supplies, needles, and glucagon) are entirely free to all citizens of RoM and the insulin volume has increased in the same period with a cumulative annual growth rate of 5%.<sup>5</sup> There has also been an increase in the number of patients with T1D on insulin pumps, whereas relatively high insulin analogue use has been preserved and all first-generation analogues have been available. In addition, there has been increase in the number of free test strips for patients with T2D on insulin treatment from 4 to 30 per month, while preserving the number of 125 free test strips per month for patients with T1D.<sup>5</sup>

This cost reduction, along with promoting diabetes care, has been primarily achieved through parallel imports and competition, as well as through supervision of rational use of insulin analogues by the National Diabetes Committee. However, in RoM there is still a significant discrepancy between diabetes care in early stages compared with contemporary global T2D guidelines.<sup>4,22</sup> This is particularly true at the primary care level, where formalized, evidence-based approaches to lifestyle change have the potential to obviate high utilization rates of insulin on a national scale.

## PLANT-BASED DIETARY PATTERN

Could an improved dietary pattern reduce the need for so much insulin? It is evident that shifting dietary patterns contribute to rates of overweight/obesity, T2D, and cardiovascular disease in RoM, as

they have in other parts of the world. However, no clinical studies of dietary or lifestyle intervention have been undertaken in RoM. Around the world and in RoM, diabetes nutrition recommendations encourage reduced total calories and control of the quantity of carbohydrates as primary dietary interventions, along with reduced saturated fat intake, akin to an “all things in moderation” approach. These evidence-based strategies can improve body weight and glycemic control.<sup>23</sup> However, these strategies fail to treat the cause. They do not address the significant, unhealthful dietary changes in RoM: a dramatic increase in consumption of animal products, oil, and sugar that preceded the diabetes epidemic, the growing rates of cardiovascular diseases, and the need for insulin injections. A growing body of evidence suggests that use of a plant-based dietary pattern, with emphasis on whole grains, vegetables, legumes, fruits, and nuts, may offer significant additional advantages.

The Adventist Health Study-2 (AHS-2), a prospective cohort study of 96,000 Canadian and American adults, found that body mass index and prevalence of diabetes increased as the amount of animal products in the diet increased.<sup>24</sup> This same study found that avoidance of any types of meat promoted longevity: vegetarian (those who consume vegetables, legumes, grains, fruits, nuts, seeds, dairy products, and eggs, but no animal flesh) men lived 9.5 years longer and vegetarian women lived 6.1 years longer than their meat-eating counterparts.<sup>25</sup> In people diagnosed with T2D, a vegan diet (a vegetarian diet that also excludes animal flesh, dairy, and eggs) has been found to improve weight and plasma glucose concentrations.<sup>26</sup> Vegan and vegetarian diets have been reported to reduce cardiac risk factors, particularly blood pressure<sup>27</sup> and cholesterol.<sup>28</sup>

Furthermore, a plant-based dietary pattern with very low (<10%) fat content is the only dietary pattern that has been found to reverse coronary heart disease,<sup>29,30</sup> the leading cause of death in people with diabetes.<sup>31</sup> After an analysis of almost 20 years of data that demonstrated effectiveness at halting the progression of coronary heart disease, reducing the need for coronary bypass surgery, and reducing the need for percutaneous coronary interventions, the US Congress approved 2 intensive dietary- and lifestyle-focused cardiac rehabilitation programs for Medicare recipients.<sup>32</sup> The many cardiac-related benefits of this approach have led the president of the American College of Cardiology to state, “I often discuss the benefits of adopting a plant-based diet with patients who have high cholesterol, diabetes,

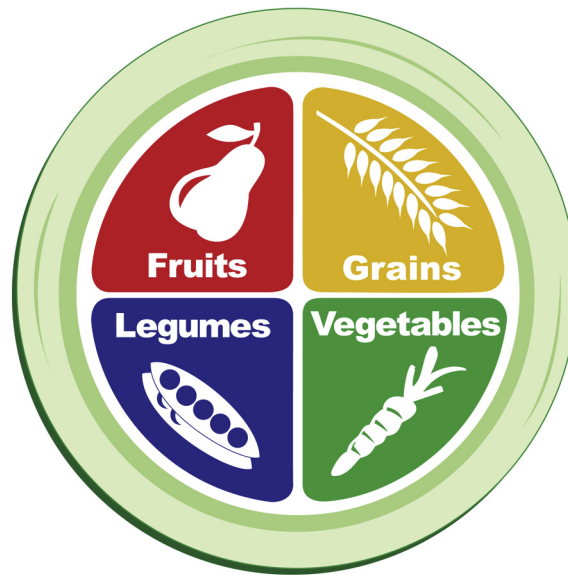
hypertension, or coronary artery disease,” and to follow this dietary pattern himself.<sup>33</sup>

A plant-based dietary pattern has been found to have many nutritional advantages.<sup>34</sup> Although it might sound challenging to those who are unfamiliar with it, a plant-based diet has been found to have an acceptability that is similar to that of “conventional” diets for diabetes.<sup>35</sup> Lower rates of a range of common cancers and improved cancer survival are also observed among people who eat a plant-based diet.<sup>36,37</sup>

Perhaps of greatest immediate interest to the situation in RoM is evidence of the effectiveness of a plant-based dietary pattern to reduce the need for medication in people with T2D. As Barnard et al<sup>26</sup> demonstrated in a study in the United States, funded by the National Institutes of Health, comparing a conventional diabetes diet with a low-fat, low glycemic index, vegan dietary pattern, during the initial 22 weeks, 43% of participants reduced their diabetes medications, whereas 8% increased their medications. At 74 weeks, net dosages of medications for glycemic control were reduced in 35% of participants, increased in 14%, and unchanged or mixed (changes in opposite directions in  $\geq 2$  medications) in the remainder.<sup>26</sup> It should be noted that medications were adjusted in this study according to an a priori protocol or for hypoglycemia.

**Education.** According to the IDF, one of the challenges facing RoM in addressing diabetes is lack of time and shortages of personnel to offer diabetes education.<sup>18</sup> Diet counseling in patients with T2D is currently provided by diabetes specialists (specialists in internal medicine, endocrinologists, and diabetologists) and diabetes nurses generally concentrated in urban areas and limited to people who take insulin. Dietitians are not involved in diabetes treatment at the present time. Physician education in RoM includes very little practical instruction on the role of nutrition in disease prevention or treatment. Furthermore, the IDF has identified a shortage of registered nurses with training in diabetes.<sup>18</sup>

Unlike a more complicated dietary regimen of restricted portion sizes and carbohydrate counting, a plant-based dietary pattern, as used by Barnard et al,<sup>26</sup> is easy to teach, utilizes a simple graphic for meal planning termed the Power Plate (Fig. 6), and incorporates *ad libitum* consumption of plant-sourced foods.<sup>38</sup> Weekly group instruction in lunchtime sessions held at workplaces is a cost-effective model that is successful at improving behaviors and health outcomes.<sup>39</sup> Foods to avoid



**Figure 6. Power Plate.**

and a sample of healthful regional meal ideas are provided in [Table 2](#).

The National eHealth System remains the key platform supporting National Diabetes Committee activities in its main mission of improving glycemic control in patients with diabetes by adhering to national diabetes care and treatment guidelines while preserving the sustainability of the health care system. The National eHealth System could be used for monitoring progression of patients from prediabetes to overt T2D, while also focusing preventive activities in people with prediabetes. This platform also enables monitoring of metabolic control and risk factors to focus preventive activities on avoiding or delaying diabetic complications in diagnosed patients. This platform can also be used for

monitoring diabetes risk in undiagnosed patients with diabetes, as well as the complication risk in diagnosed patients with diabetes. In effect, this approach advances personalized diabetes care based on glycemic control and concomitant management strategies of individual patients as data becomes available to caregivers across the spectrum of health care levels in RoM. Furthermore, there is a potential to add new scientifically sound and approved biomarkers at a patient level nationwide to further personalize diabetes care.

**Research.** A randomized trial is needed within RoM to determine the effectiveness of a whole foods plant-based dietary intervention and moderate exercise to improve (or maintain) glycemic control and other metabolic measures while

**Table 2. Food Choices in the Republic of Macedonia**

Problem Foods	Healthful Plant-Based Options
<ul style="list-style-type: none"> <li>● White bread with margarine</li> <li>● Pastries</li> <li>● Meat and processed meats</li> <li>● Fried foods</li> <li>● Oil</li> <li>● Cheese and other dairy products</li> <li>● Sugar-sweetened beverages</li> </ul>	<p>Breakfast:</p> <ul style="list-style-type: none"> <li>● Oatmeal with fruit</li> <li>● Whole grain toast</li> </ul> <p>Lunch and dinner:</p> <ul style="list-style-type: none"> <li>● Salad with beans and grains</li> <li>● Baked beans</li> <li>● Lentils with beets and greens</li> <li>● Baked pumpkin with walnuts</li> <li>● Grain-vegetable stuffed peppers</li> <li>● Cheeseless vegetable pizza</li> </ul>



concurrently determining if the intervention can reduce the need for or reliance on insulin injections for people with T2D. This intervention diet would focus on culturally familiar dishes made from legumes, vegetables, whole grains, fruits, nuts, and seeds, with generally recognized exercise requirements for those who are physically able to do so: at least 150 minutes of moderate activity, such as walking, along with muscle strengthening activities 2 days per week. This proposed study would also include assessments of the intervention's acceptability and sustainability and would develop specific guidelines for "deprescribing" insulin. If shown to be effective in improving measures of health and reducing insulin requirements, this lifestyle intervention strategy could become a model for a diabetes intervention to be implemented in primary care and specialty medical practices across many different scenarios and cultures worldwide.

Given the fact that a lifestyle-focused intervention has not been previously tested in RoM and therefore effects on insulin requirements are not yet known, an initial brief (2- to 3-week) residential treatment, led by knowledgeable and enthusiastic health educators familiar with the interventional dietary pattern, followed by a multi-month period of outpatient support is recommended. The Physicians Committee for Responsible Medicine has extensive experience designing plant-based dietary protocols and trainer education programs for research and community settings and can provide assistance. Prior residential studies of plant-based diet interventions have been very successful and well accepted.<sup>40-43</sup>

## CONCLUSIONS

RoM ranks third in comparative diabetes prevalence among European countries. A new National eHealth System allows for better identification and monitoring of citizens with diabetes. However, the expense of insulin is unsustainable. Significant changes in dietary patterns parallel the rise in diabetes prevalence and are likely a leading cause of the diabetes epidemic. The potential exists for a much stronger role for nutrition in prevention and treatment. Adding education on nutrition to medical school curricula and increasing the number of registered nurses with training in diabetes, especially in lifestyle interventions, would benefit people and reduce over-reliance on medication. Plant-based dietary patterns have worked well elsewhere for diabetes prevention and treatment, as well as preventing and treating other chronic diseases, including heart disease. Local research is needed to establish an insulin-avoidance or reduction protocol and to determine the impact and acceptability of dietary interventions for treatment of T2D, as a first step toward reducing diabetes prevalence and its complications and controlling spiraling health care costs in RoM.

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