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Introduction

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The American Diabetes Association (ADA) stated in 2017 that diabetes is a complex, chronic illness requiring continuous medical care with multifactorial risk-reduction strategies beyond glycemic control, including continuous patient self-management education and support as critical issues to prevent acute complications and reduce the risk of long-term complications [1]. At the same time, the International Diabetes Federation (IDF) defined diabetes as a pandemic disease and the major cause of cardiovascular (CV) disease (CVD), chronic renal disease, blindness, and amputation. In 2017, 425 million people were affected by diabetes worldwide [2].

One of the main priorities agreed on at the 2013 United Nations high-level meeting on non-communicable diseases (NCDs) was to halt the number of people living with diabetes as in 2010 [3]. Despite these efforts, the number of diabetic patients is expected to continue growing, reaching 629 million in 2045, regardless of country of residence, sex, race, social, or income levels [2]. Data from the NCD Risk Factor Collaboration (NCD-RisC) showed that the global age-standardized prevalence of diabetes between 1980 and 2014, rose from 4% to 9% in men, and from 5% to 8% in women [4].

Despite a multitude of investigators around the world working extensively on a cure for diabetes, using different approaches, from islet transplantation to stem-cell therapies, progress is slower than anticipated, and a definitive cure is currently not available and actually still far in the future. Indeed, diabetes is a plague due to the increased risk of multiple micro- and macrovascular conditions, dementia, cancers, and infectious diseases. Notably, people with diabetes are supposed to have double the risk of CVD as compared with sex-, age-, and body mass index (BMI)-matched people with no glycemic derangements [5].

Even if women have historically poorer risk factor profiles, they usually receive lesser CV care compared with men, despite no differences in the safety and effectiveness of medication between women and men [6]. It is noteworthy that women with diabetes have a 44% greater risk of coronary artery disease as defined by the presence of angina, heart failure, and/or myocardial infarction [7], and a 27% greater risk of stroke than men [8], independent of sex differences and other major risk factors. Interestingly, the increased risk of microvascular chronic complications in diabetes has been shown to be a “phenomenon
with a memory”. The first evidence was reported in a study from Dr. Lorenzi’s group in the 1980s in which the authors elegantly showed that the microvascular changes induced by hyperglycemia persisted after restoration of normoglycemia [9]. Indeed, on the one hand, these observations have been replicated in humans within the Diabetes Control and Complications Trial (DCCT) 30-years follow-up study [10], and on the other hand, these observations represent the foundation of the study of the alterations induced by diabetes to the epigenome [11]. Therefore, in this complex clinical setting, the prevention of the chronic complications of diabetes is one of the main therapeutic goals. Currently, the only available approach to achieve this goal is an adequate management of blood glucose levels, and good control of blood pressure, cholesterol, triglycerides, and body weight through balanced diet and lifestyle changes [12]. Noteworthily, therapeutic patient education is now considered a crucial element in the treatment and prevention of diabetes: several trials have shown that education is able to improve clinical, lifestyle, and psycho-social outcomes, but so far they have not clarified the ideal characteristics of a comprehensive patient education program in clinical practice [13, 14].

In the past, microvascular disease was thought to affect the smallest blood vessels after a long history of diabetes, while stroke and heart attacks were considered classical manifestations of macrovascular disease [15]. In 2000, the first edition of the Diabetes Atlas well described microvascular complications as abnormally thick but weak walls of the vessels, leading to bleeding, leaked proteins, and the slowing of the flow of blood through the body. Diabetic retinopathy (RD), nephropathy, neuropathy, and food lesions (up to amputations) were considered the peculiar manifestations of this condition [15]. However, in the past decade, increasing evidence has been published indicating that functional and structural abnormalities of the coronary microvascular district cause myocardial perfusion impairment and, finally, ischemia [16]. Hyperglycemia causes microvascular dysfunction, modifying several physiological pathways, such as NO and arachidonic acid metabolism, and, consequently, generating increased oxidative stress [17]. At early stages, patients with subclinical levels of diabetes-induced myocardial changes (atherosclerotic changes of coronary arteries and microvascular endothelial dysfunction) are usually asymptomatic. Therefore, if not precociously detected, the disease may advance rapidly, leading to heart failure and death [18].

Intriguingly, hallmark studies such as the DCCT/EDIC (Epidemiology of Diabetes Interventions and Complications) and the ACCORD-MIND (Action to Control Cardiovascular Risk in Diabetes – Memory in Diabetes), have demonstrated a link between diabetes and cognitive dysfunction [19, 20]. In addition, other more recent cohort studies highlighted a strong correlation between both type 1 and type 2 diabetes and the development of dementia, especially of vascular origin [21, 22]. The hypothesis of an association between cognitive impairment and microvascular derangement has been finally confirmed by the observations of a solid correlation between RD, the most frequent microvascular complication, and poor neurocognitive performance in patients with diabetes [23–26], with alterations of both gray and white matter structure [27, 28]. It has been proposed that inflammation may also play a key pathophysiological role in this clinical context. Indeed, it is well known that diabetes is associated with high levels of pro-inflammatory cytokines; accordingly, high levels of inflammatory markers in the cerebrospinal fluid and in the circulation have been related to both RD and cognitive impairment [29, 30].
This thorough and comprehensive book integrates new and accessible material on diabetic microvascular comorbidities. It will help investigators, clinicians, and students to improve their understanding, providing additional knowledge, assembled in an easily consultable manner, on pathogenesis, diagnosis, research, and cure of microvascular complications.

References

the INdividual Therapeutic Education in Newly Diagnosed type 2 diabetes (INTEND) randomized controlled trial. *Endocrine* 60: 46–49.


