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Editorial Open Access

Type 2 Diabetes and Multiple Myeloma: The Latest Insights

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Editorial

Type 2 Diabetes (T2D) is a complex disease that is typically diagnosed in midlife and is characterized by progressive defects in insulin secretion and action [1]. T2D is the most common type of diabetes and is preceded by a lengthy asymptomatic stage, termed prediabetes, which is characterized by mild hyperglycemia, insulin resistance, and early decrements in insulin secretory capacity. The number of people with T2D is growing rapidly worldwide. The most recent estimates indicate that 8,3 % of adults (382 million people) have diabetes, and the number of people with the disease is set to rise beyond 592 million in less than 25 years. In human as well as financial terms, the burden of diabetes is enormous, provoking 5.1 million deaths and taking up some USD 548 billion dollars in health spending (11% of the total spent Worldwide) in 2013 [2].

The increasing global prevalence of T2D is tied to rising rates of obesity. A person's risk of T2D or obesity reflects the joint effects of genetic predisposition and relevant environmental exposures [3]. Despite advances in understanding of the importance of insulin resistance and β-cell dysfunction to the pathogenesis of T2D, the disease process is clearly heterogeneous [4], and includes other pathogenic factors. Obesity is a strong modifier of T2D risk, and can account for a large proportion of the epidemic of T2D, including the ever-increasing number of adolescent with T2D. Genes and the environment together are important determinants of insulin resistance and β-cell dysfunction. Advances in technology and analytical approaches have identified genes linked with T2D. Interaction of genes that affect body adiposity with environmental factors results in development of obesity and associated insulin resistance. However, only when genes for abnormal β-cell function are present along with those for body adiposity does interaction with the environment result in development of T2D [5]. A recent meta-analysis quantified the risk of T2D preceded by body weight gain in the general population [6]. Obesity is associated with increased mortality in the general population but, paradoxically, with decreased mortality in persons with diabetes. Selection bias may be a simple explanation for this "paradox" [7]. Results of a detailed analysis of the association between body-mass index (BMI) and the risk of death among participants with incident diabetes from two large prospective cohort studies indicate a J-shaped relationship between BMI at the time of a diabetes diagnosis and the risk of death from all causes, with the lowest risk observed among normal-weight group. The authors suggest that the maintenance of a healthy body weight should remain the cornerstone of diabetes management [8]. Like in many other complex diseases, genetics, epigenetics will contribute to increase our current understanding of T2D pathophysiology as well as its clinical and molecular heterogeneity. Recently, Genome-Wide Association Studies (GWAS) have extended the number of loci robustly implicated in T2D risk to more than 60 [9].

Multiple Myeloma (MM) is a very heterogeneous disease from both clinical and molecular point of view [10]. Evidence for genetic predisposition to MM has been recently demonstrated [11,12]. MM is considered an incurable disease, but outcome in terms of overall survival (OS) is increasingly improving and early mortality, that is mainly associated with renal failure, is being reduced [13]. The prognostic impact of comorbidity in MM is an area of great interest [14]. We have recently highlighted the role of obesity as risk factor as well as prognostic factor in MM [15]. T2D could have a similar behavior in this way. Regarding T2D as possible risk factor for MM, the first meta-analysis aiming to find such association including ten studies [16] showed a statistical trend toward significantly increased odds of MM in patients with T2D, pooled OR 1.22 (95% CI, 0.98-1.53; p=0.08). Although the effects of age, sex and geographic region were likely accounted for in this study, no other important factors such as obesity, diet or physical activity were considered. The possible interaction among these factors, MM incidence and T2D should be further investigated.

On the other hand, there are increasing evidence to point out T2D as a prognostic factor in MM. Chou et al. [17] in a study of 310 patients with MM of which 40 (12.9 %) had T2D, showed that pre-existing T2D had a significantly higher all-cause mortality risk, HR 1.51 (95% CI, 1.02-2.22; p=0.037). We did not find statistically significant median OS in a study of 309 MM patients of which 63 (20.4%) had T2D [14]; however, OS curves tend to gradually separated over time, suggesting that T2D has a progressive impact on mortality with prolonged follow-up. More recently, Wu et al. [18] in a retrospective study of 1240 MM patients of which 136 (12.6 %) had T2D and 344 (31.7%) steroid-induced diabetes (SID), were able to show a significantly shorter OS in the combined T2D/SID group. SID was a significant predictor of poor OS whereas T2D was not when compared with non-diabetic group. Furthermore, in multivariate analysis SID was a significant predictor of decreased OS. Interestingly, 60 % of patients in the T2D group were also obese comparing to 31 % in the non-T2D group (p<0.001); however, OS among obese and non-obese patients in this study were similar without statistically significant difference. Metformin predicted an increased OS whereas use of insulin/analogues predicted a decreased OS.

The prevalence of T2D in MM patients is variable among different studies [14,17,18] but is expected to increase owing to the increasing global prevalence of T2D and obesity. Currently, the clinical management of MM patients with T2D remains a challenge. Insulin is a potent growth factor and survival factor for MM [19]. The insulin and insulin-like growth factor I receptor family is now known to have a role in the important relationships between macronutrient intake and cancer, diabetes and cancer, and obesity and cancer [20]. Until now, the role of T2D in MM risk and MM prognosis is a debatable and open question, waiting for new evidence and more mature data. At the moment, T2D cannot be considered an independent risk factor and/or an established prognostic factor for MM, but increasing evidence suggests that T2D could be considered as a potential risk factor for MM. Controversy remains about the role of T2D as an independent prognostic factor in MM but current data point out in this direction.

T2D and MM are complex diseases and the majority of T2D patients are also obese. GWAS have discovered common genetic variants associated with susceptibility for several complex diseases. However, variants that have been identified appear to explain only a small proportion of genetic heritability, even for diseases that clearly have a major genetic component. Rare variants, structural variations, epigenetic effects, gene-gene, and gene-environment interactions have all been proposed as phenomena that may contribute to the low yield of GWAS [21]. These GWAS-discovered variants are relatively weak risk factors ant its chief utility is likely to be in improved understanding of disease mechanisms and potentially in identification of persons at higher or lower risk of specific diseases [22]. The complex pathogenesis of T2D remains a matter of debate, but the evidence supports a strong environmental influence interacting with genetic predisposition in a synergistic fashion. A large portion of the heritability is unaccounted for, and many of the genes commonly found have small effects. Genes identified by GWAS using diagnosed T2D as the phenotype have mainly been associated with β-cell failure but have only accounted for less than 5% of the heritability [23]. It's time to look back but also forward. There is a growing body of evidence to support a connection between T2D and cancer, through several pathophysiological mechanisms including insulin resistance and hyperinsulinemia, enhanced inflammatory processes, dysregulation of sex hormone production and hyperglycemia; in addition, a number of common risk factors, including obesity, may be behind the association between T2D and cancer [24]. The same can apply to MM, to a certain point. A deeper understanding of the pathogenesis of T2D is needed to better define a potential role of T2D in the myelomagenesis process. GWAS and gene-gene or gene-environment interaction studies may help us to unravel the role of T2D on the risk of MM. In the meantime, some intervention strategies for the prevention of T2D should be considered [25].

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