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Obesity and Multiple Myeloma: What Do the Data Tell Us?

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Obesity is a major public health problem throughout the world. It is defined as an excess accumulation of adipose tissue, which is considered as a heterogeneous and highly active endocrine and metabolic organ [1]. Obesity predisposes individuals to an increased risk of developing many diseases, including atherosclerosis, non-alcoholic fatty liver disease, Type 2 Diabetes (T2D), asthma and cancer; it is also associated with altered functioning of circulating immune cells [2]. The Body Mass Index (BMI) is one of several indicators of body fat, which is calculated as weight in kilograms divided by height in meters squared and categorized as defined by the World Health Organization as "underweight" (BMI<18.5 kg/m^2), "normal weight" (BMI 18.5 to 24.9 kg/m^2), "overweight" (BMI 25.0 to 29.9 kg/m^2), and "obesity" (BMI ≥ 30.0 kg/m^2). Using BMI, a large number of studies have highlighted a causal link between obesity and several human cancers, including hematological malignancies. One out of every five cancer cases is estimated to be caused by being obese, but the prevalence of obesity is steadily increasing in most developed countries; in this way, the impact can be even greater in the future. The biological mechanisms linking obesity to cancer susceptibility are related to the hormonal and/or metabolic abnormalities prevalent in obesity (mainly hyperinsulinemia and insulin resistance, insulin-like growth factor 1, sex steroids and adipokines), but a set of novel candidate mechanisms has been proposed [3].

Multiple Myeloma (MM) is the second most common cancer of the blood and accounts for 1% of all malignancies. MM is a very heterogeneous disease from both clinical and molecular point of view. Its pathogenesis remains poorly understood and it is considered an incurable disease. The molecular epidemiology of MM is an exciting area of research. Major advances have been made in recent years highlighting the need to face the disease through common efforts within large cooperative groups [4]. There is a set of accepted risk factors for MM like increasing age, male gender, black race, positive family history or having a Monoclonal Gammopathy Of Uncertain Significance (MGUS) [5]. In addition, an emerging group of new risk factors should be taken into consideration. Interestingly, a growing body of evidence points out to obesity as a consistent risk factor for MM. Four meta-analysis have found a positive association between obesity and MM risk [6-9]. Moreover, MGUS is also associated with obesity, supporting the hypothesis that obesity is etiologically linked with myelomagenesis [10]. The largest prospective investigation of the impact of BMI at different ages and MM risk has also found a modest positive association, suggesting that excess body weight in both early adulthood and later in life is a risk factor for MM [11]. The circulating levels of adiponectin, the most abundant adipokine, are negatively correlated with obesity. The first prospective study of circulating adipokines and MM showed a clear inverse relationship between adiponectin levels and subsequent risk of MM, suggesting that adiponectin may play a role in the underlying biologic mechanisms linking obesity to myelomagenesis, by suppressing production of pro-inflammatory cytokines, inducing other anti-inflammatory cytokines and inhibiting NF-Kappa B activation, thereby affecting transduction pathways associated with survival and proliferation of malignant plasma cells [12]. In our recent study [13], approximately one third of MM patients are obese. Obesity could now be considered the only preventable MM risk factor. Controlling obesity epidemics could be a potential effective tool for MM prevention, to a certain point.

Besides the evidence of obesity as a MM risk factor, obesity could have a role as a prognostic factor in MM. We showed a significant shorter Overall Survival (OS) in obese MM patients comparing to patients with a normal weight (median OS 34 vs. 61 months, respectively) [13]. In this study we also highlighted the prognostic impact of disease-related weight loss before the diagnosis of MM, which occurred in 25,7% of the patients; moreover, we found a markedly short OS in MM patients with an underweight at the moment of the diagnosis. Beason et al [14] have recently analyzed the influence of BMI on OS in a large retrospectively assembled cohort of MM patients. Median OS was 28.6 months. They also found significant increased mortality for the underweight group and for patients with weight loss ≥ 10% in the year before diagnosis. Remarkably, the obese patients had better OS than those in the other BMI groups; a potential explanation is that obese patients were significantly younger. However, they did not give information about cytogenetics by fluorescent *in situ* hybridization or International staging system, the current standard combination for risk stratification in MM. In the Stem Cell Transplantation (SCT) setting, controversy remains about the role of obesity as a risk factor in both autologous and allogeneic SCT [15,16].

Attempts have been made to apply a specific comorbidity score to MM, but a standardized approach is still lacking. The prognostic impact of comorbidity in MM must be taken into account in a comprehensive way [17]. The magnitude of the interactions between the associated conditions should be explored. Obesity and T2D share close ties. Approximately one fifth of MM patients have T2D in our study. It is well known that obesity is a risk factor for T2D, so obesity can be frequently associated to T2D in the same patient. In fact, body weight gain in early rather than middle-to-late adulthood play an important role in developing T2D [18]. The association between T2D and MM has been evaluated in a meta-analysis [19] showing a statistical trend toward significantly increased odds of MM in patients with T2D. The possible biologic links between T2D and MM are greatly shared with

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those of obesity and MM. Moreover, T2D is also a condition associated with immunosuppression, chronic inflammation, and B- and T-cell dysfunction. A recent study points out to T2D as a prognostic factor in MM patients, showing a significantly lower median OS (11.7 vs. 22.4 months; p=0,037; HR=1.509; 95% CI=1.023-2.225) [20]. Nevertheless, currently, it is difficult to ascertain the role of T2D in MM patients. More studies are needed before considering T2D as an independent risk factor and/or a prognostic factor for MM.

In conclusion, there is a close link between obesity, with or without T2D, and MM. On the one hand, a large body of evidence supports obesity as a risk factor for MM. In addition, obesity could be considered a potentially preventable risk factor for MM. On the other hand, new data points out to obesity as a prognostic factor for MM, but controversy remains at this moment. In any case, BMI should be carefully measured at diagnosis of MGUS or MM and at every inflexion point in the evolution of the disease. In view of the global expansion of obesity prevalence, large prospective clinical trials are needed to highlight the impact of obesity on MM. From a molecular point of view, MM and obesity are highly heterogeneous and complex diseases in which several metabolic pathways are involved. More studies are warranted at genomic level to define the role of obesity and T2D in the myelomagenesis process.

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