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SOCIEDAD ESPAÑOLA DE DIABETES

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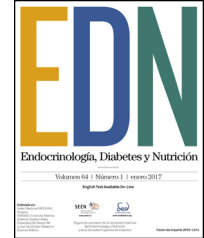Endocrinología, Diabetes y Nutrición

REVIEW ARTICLE

Epidemiological bases and molecular mechanisms linking obesity, diabetes, and cancer[☆]

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Abstract The association between diabetes and cancer was hypothesized almost one century ago. Today, a vast number of epidemiological studies support that obese and diabetic populations are more likely to experience tissue-specific cancers, but the underlying molecular mechanisms remain unknown. Obesity, diabetes, and cancer share many hormonal, immune, and metabolic changes that may account for the relationship between diabetes and cancer. In addition, antidiabetic treatments may have an impact on the occurrence and course of some cancers. Moreover, some anticancer treatments may induce diabetes. These observations aroused a great controversy because of the ethical implications and the associated commercial interests. We report an epidemiological update from a mechanistic perspective that suggests the existence of many common and differential individual mechanisms linking obesity and type 1 and 2 diabetes mellitus to certain cancers. The challenge today is to identify the molecular links responsible for this association. Classification of cancers by their molecular signatures may facilitate future mechanistic and epidemiological studies.
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Bases epidemiológicas y mecanismos moleculares implicados en las asociaciones de obesidad y diabetes con cáncer

Resumen   Hace casi un siglo que se hipotetizó la asociación entre la diabetes y el cáncer. Hoy, numerosos estudios epidemiológicos sostienen que las poblaciones con obesidad y/o diabetes poseen una mayor predisposición a padecer cáncer en órganos específicos. Los mecanismos moleculares subyacentes se desconocen. Las alteraciones metabólicas, hormonales e inmunológicas que comparten la obesidad, la diabetes y el cáncer pueden contribuir a justificar la relación existente. Por otra parte, la influencia de los tratamientos antidiabéticos en la aparición/evolución de algunos cánceres y la inducción de la diabetes por los tratamientos antineoplásicos han despertado una gran controversia debido a las implicaciones éticas y los intereses comerciales asociados. Esta actualización de los datos epidemiológicos presenta un enfoque mecanístico que sugiere la existencia de múltiples mecanismos comunes y diferenciales que asocian la obesidad y la diabetes tipo 1 y tipo 2 a ciertos cánceres. Identificar los mecanismos responsables de la asociación diabetes-cáncer es un reto de la investigación actual; la clasificación de los cáncer por sus firmas moleculares podría facilitar futuros estudios mecanísticos y epidemiológicos.

Introduction

Obesity, diabetes, and cancer are metabolic disorders. Obesity predisposes to diabetes, and both obesity and diabetes are risk factors for many types of cancer.[1] According to the World Health Organization (WHO), 39% of the world's adult population are overweight, and more than 13% are obese; these figures have doubled since 1980. Among adults, 9% are diabetic; this figure is expected to double by 2030 (http://apps.who.int/iris/bitstream/10665/148114/1/9789241564854_eng.pdf). Similarly, the WHO expects a 70% increase in cases of cancer by 2030 (http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2014).

Both type 1 (T1DM) and type 2 diabetes mellitus (T2DM) share with cancer hormonal (defects in the insulin/IGF-1 and leptin/adiponectin axes),[2] metabolic (affecting carbohydrates and lipids), and immune (increased circulating inflammatory cytokines)[3] changes.

Human health epidemiological studies try to elucidate the impact of disease, social and environmental factors, *etc.* on the population's health. One way to measure this impact is to estimate the increase or decrease in the relative risk (RR) of developing another condition. This requires large populations of cases and controls (prospective or retrospective), but has the advantage that the results may be generalized to the overall population. The drawback is that in order for a study to achieve statistical significance, the population size must be extremely large, which is sometimes possible only by combining different studies—so-called meta-analyses. The problem with meta-analyses is that they compare studies that were not defined or corrected with the same parameters, which may lead to errors in interpretation. This has usually been the case with epidemiological studies of diabetes-cancer and obesity-cancer.

Neither diabetes nor cancer should be treated as single diseases. Diabetes encompasses several metabolic and hormonal disorders (such as T1DM, T2DM, or gestational diabetes) with shared features, such as hyperglycemia. Similarly, lung cancer and color cancer are two distinct diseases that cannot be analyzed together. Some diabetes-related factors, such as obesity or treatment, may greatly affect the diabetes-cancer association, but not all studies included in a meta-analysis take this into consideration.

The present review discusses current epidemiologic evidence regarding the association of obesity and diabetes with cancer, and provides an overview of the potential mechanisms implicated in such an association.

Analysis of epidemiological data linking obesity, diabetes, and cancer

A systematic review is provided of epidemiological data collected from studies conducted over the past 10 years, which are summarized in Fig. 1. The meta-analyses with the most cases and which incorporated the largest number of corrections for possible confounding factors were selected. The association with different types of cancer of T1DM, T2DM and obesity—defined as the body mass index (BMI) $\geq 30\,\mathrm{kg/m^2}$—was analyzed. The panel on the right details the relative risks and their statistical significance in each type of cancer for populations with obesity, T1DM, or T2DM.

Obesity and cancer

The link between obesity and cancer has long been known,[4] and has been confirmed in more recent meta-analyses.[5] Fig. 1 shows that the obese population shows a statistically significant increase in the RR of developing the analyzed types of cancer, except for lung cancer. The increased RR is particularly important for endometrial cancer[6] (up to 2.54