Epidemiology of Lean/Normal-Weight Type 2 Diabetes

Subjects: Endocrinology & Metabolism

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Several epidemiologic data have continued to support the existence of lean diabetes in populations living in low-income countries of Asia and Africa, and others studies pointed to a high prevalence of diabetes in normal-weight non-white populations, even in high-income settings such as the U.S.

type 2 diabetes mellitus | normal-weight | pathophysiology

1. Introduction

The ongoing dramatic increase in incidence and prevalence of type 2 diabetes (T2D) is largely explained by the global epidemic of obesity, due to the known linkage between these two conditions [1]. It has been recently observed that any pattern of life-course exposure to obesity, i.e., thinness increasing weight or overweight from both early and late adulthood trajectories, may raise the risk for T2D development with respect to a stable normal body mass index (BMI) [2]. On the other hand, most overweight and obese individuals never develop diabetes, and conversely some normal-weight individuals are diabetic so that obese and non-obese subclasses of T2D are currently used in clinical practice.

An adult-onset non-insulin-dependent diabetes with low/normal BMI has been known since 1955, when Hugh-Jones first reported it in Jamaica as a unique form of diabetes among lean individuals that lacked the clinical features of both type 1 diabetes (T1D) and T2D [3]. Over the following decades, cases of leanness-associated diabetes emerged in many other low- and middle-income countries from Asiatic and African continents. In 1985, the WHO officially recognized a “malnutrition related diabetes mellitus” (MRDM) characterized by a resistance to the development of ketosis, partial resistance to insulin action, extreme degree of wasting and emaciation, and onset of symptoms before the age of 35 years [4]. In 1999, this clinical entity was dropped from WHO classification of diabetes due to a lack of substantial evidence for malnutrition or protein deficiency as independent causes of disease [5]. However, several epidemiologic data have continued to support the existence of lean diabetes in populations living in low-income countries of Asia and Africa, and others studies pointed to a high prevalence of diabetes in normal-weight non-white populations, even in high-income settings such as the U.S. [6][7][8][9][10]. More recently, some authors have classified the entire population of subjects with diabetes, both T1D and T2D, into five clusters based on the presence of six variables (age at diagnosis, BMI, glutamate decarboxylase antibodies,

HbA_{1c}, β-cell function, and insulin resistance). Those subgroups seem differently associated with diabetes complications and the classification could help clinicians identify patients at higher risk and tailor therapy [11].

Nevertheless, the lean/normal-weight T2D remains, to date, an understudied topic that deserves consideration for at least two reasons. Firstly, the largest increase in diabetes prevalence in the coming years is expected in non-obese, non-white individuals who represent the majority of the world if considering that nearly half of the globally estimated 463 million adults with diabetes live in India and China [12]. Due to the continuous migratory flows of Asian and other ethnic groups such as asylum-seekers refugees from conflict areas in the Middle East and Northern Africa, the number of people with diabetes will dramatically increase even among non-white ethnic minorities living in high-income Western countries [13][14]. A second point for interest is the still dilemmatic “obesity paradox”. Decade ago, a great sensation was raised by the results of a pooled analysis of longitudinal observational studies showing that adults with normal weight at the time of diabetes appearance had higher mortality than those overweight or obese [15]. Similar results were reported in other studies on individuals with diabetes [16][17]. In recent large meta-analyses, U-shaped associations between BMI and all-cause mortality in people with diabetes were observed with nadirs in the range of overweight or mild obesity [18][19][20]. Other authors did not confirm the phenomenon, or remarked the poor appropriateness of BMI as a measure of adiposity [21]. Moreover, they observed that most studies did not control for preexisting chronic illness and smoking status, or suffered from other limitations such as reverse causation, selection and treatment bias, and a one-time measurement of weight [22]. Even taking into account these opposite data, a protective effect of excess weight on mortality in diabetes cannot be denied with certainty and the question remains unsolved [23].

Whereas scientists from all over the world have spent great efforts to understand the mechanisms linking obesity to diabetes, the pathophysiology of lean T2D is still debated. Knowing eventual specific metabolic and physiologic drivers of the disease in normal-weight individuals is of great relevance for implementation of an effective prevention and an individualized clinical management in order to reduce the global burden of diabetes [24].

2. Epidemiology of Lean/Normal-Weight T2D

A few studies have assessed the frequency of T2D in white normal-weight populations, for example those documenting a prevalence of 5.1% in Australian adults and an incidence of 15% in a male Swedish cohort [25][26].

According to data collected in the last twenty years, populations from Asia and Africa are at risk for T2D at much lower levels of BMI than other ethnic groups, suggesting the need for lowering their current targets for ideal body weight [27][28].

A 2.1% incidence of MDRD was reported in a sub-Saharan African rural area, and a study examining the T2D prevalence in Zambia and Western Cape of South Africa found values of 2.9% and 9.4%, respectively, two-thirds of which were associated to under- or normal-weight [8][29].

In a nationally representative sample from China, T2D prevalence was 4.5% in individuals with a BMI < 18.5 kg/m^2 and 7.6% in those with a BMI of 18.5–24.9 kg/m^2 [7]. A similar 7.8% prevalence was found in subjects with a BMI < 25 kg/m^2 in a nationally representative survey from mainland China [30]. In an underdeveloped area of South China, 68.2% of instances of newly detected T2D were from non-obese diabetics [31]. In a Japanese population, over 60% of the subjects with diabetes were not obese [32].

India is referred as one of the T2D capitals, with a predicted prevalence of 151.4 million indigenous South Asians affected by 2045 [33]. A study in semi-urban/rural India found most hyperglycemia in undernourished people [6]. Overall, T2D in Asian Indians is characterized by younger age of onset and relatively low BMI [34]. An analysis of the U.K. Biobank containing four large ethnic groups, established that to have the same diabetes risk as white participants with a BMI > 30 kg/m^2, the equivalent BMI in South Asians was only 22 kg/m^2 [35]. Cross-sectional analyses using representative samples of Asian Indians (South Asia CARRS-Chennai Study) and whites (U.S. NHANES Survey) demonstrated a significant ethnic difference in T2D prevalence in men, 5.4%/23.5% in under- and normal-weight Asian Indians and 0.0%/6.1% in their white counterparts. In women, the prevalence was 5.6%/13.6% in under- and normal-weight Asian Indians and 2.3%/2.8% in whites [36].

Most data come from ethnic minorities living in high-income Western countries. A study cohort of 18,000 T2D patients living in Chicago showed that around 13% had a BMI ranging from 17 to 25 kg/m^2 and that Asians had a five-fold higher prevalence in the lean group (17% vs. 4%) [9]. In a large racially/ethnically and geographically diverse cohort of adults who were all members of integrated health care systems to correct for disparities in access to services, the age-standardized prevalence of diabetes increased across BMI categories among all groups. However, the prevalence of diabetes and prediabetes at low to normal BMI was 3.5 and 5%, respectively, in white subjects, and 7.3 to 10.2% and 9.6 to 18% in the various racial/ethnic groups, being the higher values registered in Hawaiians/Pacific Islanders and Asians [10]. A recently published systematic review and meta-analysis of prospective cohort studies (minimum 12-month follow-up, over 2.69 million participants from 20 countries) using ethnic-specific BMI categories, emphasized the crucial role of obesity demonstrating an increasing T2D risk of 0.93 for underweight, 2.24 for overweight, 4.56 for obesity, and 22.97 for severe obesity with respect to normal-weight. Interestingly, the underweight resulted a protective factor against T2D only in non-Asian people (RR = 0.68, 95% CI: 0.40–0.99, I^2 = 56.1%, *n* = 6) [37].

Overall, these results suggest that environmental and genetic factors beyond obesity may contribute to the disproportionate burden of disease in non-white populations with ancestry from low- and middle-income countries.

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