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http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **20**(4):409-418
doi: 10.2478/rjdnmd-2013-0041

THE PREVALENCE OF OVERWEIGHT AND OBESITY IN NEWLY DISCOVERED DIABETIC PATIENTS

Simona Carniciu ✉***, Elena Caceaune, Andrada Mihai, Cornelia Zetu, Constantin Ionescu-Tîrgovişte***

National Institute of Diabetes, Nutrition and Metabolic Diseases "N. C. Paulescu", Bucharest, Romania

received: November 12, 2013 *accepted*: November 29, 2013
available online: December 15, 2013

Abstract

Background and aims. *The aim of this paper was to make a comparison between the main clinical characteristics (especially age at onset and body mass index - BMI) of newly diagnosed diabetic patients based on the analysis of our current data, our previous data and data from international literature.* ***Materials and method.*** *We analyzed a cohort of 1463 (757 males and 706 females) recorded between 2010-2012 and compared it with the previous cohorts of diabetic patients belonging to the same "Ion Pavel" Diabetes Centre, Bucharest and whose characteristics were published along the years. We divided patients according to age, sex and type of diabetes.* ***Results.*** *Our data showed that the main clinical characteristics (the decrease of the age at onset and the increase in BMI) in the recent cohort of diabetic patients can be related to the lifestyle changes and the increased prevalence of overweight and obesity in the general population.* ***Conclusions.*** *The pathogenesis of type 2 diabetes is closely related with a negative effect of overweight on the β-cell function, suggesting that prevention of diabetes must be based on a decrease in BMI induced by an appropriate change in the modern pathogenic lifestyle.*

key words: *Type 2 diabetes, obesity, adipocytes, β-cell function*

Background and aims

The association between type 2 diabetes (T2D) and obesity is known for a long time. Already, between 1877-1883, Lancereaux [1,2] made a refined observation on the signification of diabetes sustaining with several clinical arguments that this strange disturbance called diabetes is not a disease according to the classical concept, but it is a ***syndrome***, due to the heterogeneity of its clinical manifestations. Among these forms (suggesting that there are many) there are two which by their contrast can be easily identified. For the cases with the onset at young ages, severe symptoms associated with weight loss and rapid evolution, he gave the name of "***thin diabetes***"; while for the cases with insidious onset in older ages and with "undefined evolution" [2] he gave the name "***fat diabetes***". In this distinction we can recognize what is called today type 1 (T1D) and type 2 diabetes (T2D) [3].

In the third volume of the encyclopedic "*Textbook of Medicine Lancereaux-Paulesco*"

✉ I.L. Caragiale Street, No.12, Bucharest, Romania; Tel: 0721337712;
corresponding author e-mail: cassimona@yahoo.com

[4] we found the distribution of the 86 cases of diabetes admitted in the authors clinic of internal medicine during the last quarter of 19th century: 7 patients with age 30 to 40 years old, 18 with age 40 to 50, 22 with age 50 to 60, 30 with age 60 to 70 and 9 with ages between 70 to 80 years. As we will see later on, the number of diabetic patients diagnosed after the age of 30 years increases dramatically due to the progressive increase of the prevalence of T2D. For type 2 diabetic patients, 90% of cases were shown to be or to have been obese [5]. If this association was easy to be proved, its pathogenic mechanism has been sporadically approached before the discovery of the complex secretory function of the adipocyte [6]. The first pathogenic defect associated with T2D was a defect in β-cell function [7-12]. After the secretory function of adipocytes was established, the pathogenesis of diabetes was thought as a binomic approach: β-cell dysfunction and adipocyte dysfunction [13,14]. Despite the high interest for understanding the pathogenesis of diabetes, there are 3 questions that are not answered yet: why ~ 10% of T2D cases are not associated with obesity; why only ~30% of all obese became along their life diabetics and finally, why ~90% of the T2D patients were or have been obese on the time of clinical onset of this phenotype.

The aim of this study was to analyze the distribution of overweight/obesity in a cohort of 1475 patients, registered in a single office by the same team from "Ion Pavel" Diabetes Centre belonging to National Institute of Diabetes, Nutrition and Metabolic Diseases "N. C. Paulescu" Bucharest and compare it with the two previous similar cohorts recorded in 1976 [5] and 1994 in the same outpatient department [16].

Materials and methods

We evaluated 1463 newly discovered patients from the cohort 2010-2012 evaluated in only one office of the "Ion Pavel" Centre of Diabetes. There were 27 patients (13 males and 14 females) with T1D and 1436 (744 males and 692 females) with T2D. We evaluated the age at diabetes onset of patients on 5 years age groups, according to sex. In T2D patients we divided the patients according to their age at onset and Body Mass Index (BMI).

It is worthy to note that the majority of primary insulin-dependent patients (mainly T1D) were not included in this study since these patients were mainly registered during their first "in patient" hospital admission for the standard educational program in which are included all these patients. However, in a small number of T1D patients (usually young adults) we started insulin therapy in our outpatient department. They represent a thin black line in Figure 1(A).

In the 2001 cohort [16], the authors evaluated 6294 newly discovered diabetic patients recorded in the "Ion Pavel" Diabetes Centre in Bucharest. Patients were divided by sex (3038 males and 3256 females), age groups of 5 years and type of diabetes. The slight female predominance may be explained only by the higher number of females in the general population.

Previously, a cohort of 10.000 diabetic patients [5] were recorded between Nov. 1968 and Dec. 1974 (5.198 males and 4.802 females) in the "that time" Antidiabetic Centre from Bucharest. Patients were divided by onset age and according to the classification of diabetes used in that time: *juvenile* diabetes (0-20 years); *young adult* diabetes (21-40 years); *maturity onset* diabetes (41-65 years) and *senile* diabetes (>65 years). BMI was calculated individually using the Broca formula, which is quite similar to the BMI formula (kg/m^2).

Results

As can be seen in Figures 1 and 2, the distribution of T2D patients according to the age at onset is quite similar along the years, but with

a very interesting observation: the maximum incidence of diabetes (which in 1975 was recorded around the age of 65 years [5]) has decreased progressively up to 55 years during the last years, as confirmed by the analysis of the 2010-2012 cohort.

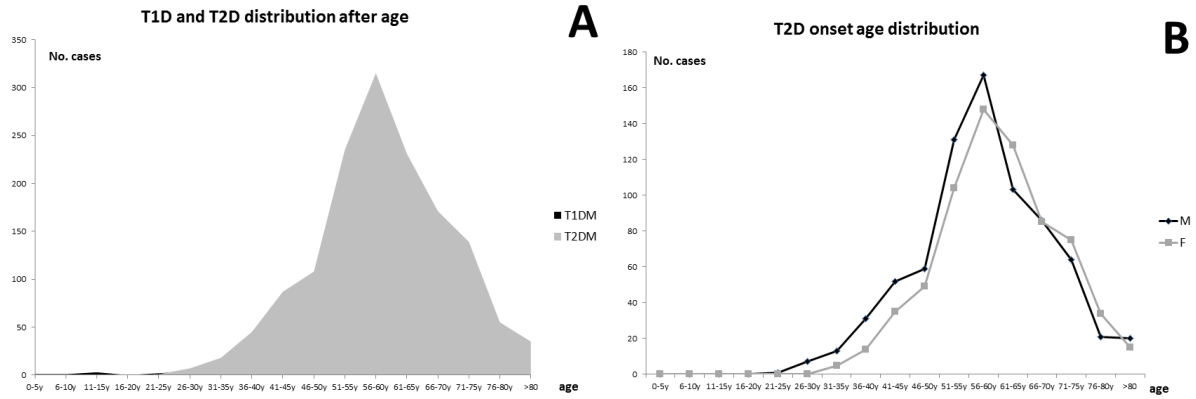

Figure 1. *Distribution of subjects according to the age at onset (A) and sex (B) in patients from the 2010-2012 cohort (A) and sex (B).*

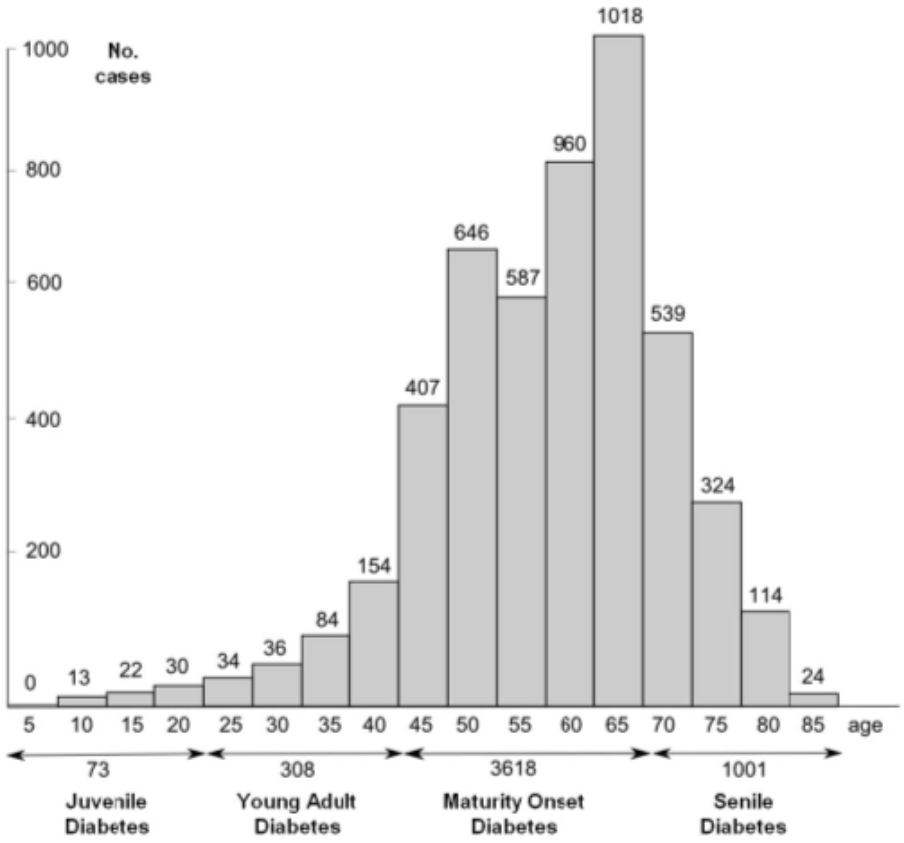

Figure 2. *Distribution of diabetic patients according to the age group at onset in the 1968-1974 cohort. Adapted after* [5].

Our current data (Figure 1A) show that by the age of 20 years the incidence of diabetes is low. It rises slowly in the age groups 21-40 years, it rapidly increases at 45-50 years, reaching a peak between 55 and 60 years and decreases progressively to the age group of > 80 years. Notably, the onset age in males was constantly lower than in females (Figure 1B).

In the previous Cohorts, the distribution according with sex was in favor of women (51% M/49% M) (Figure 3B). In the present study, the number of males was higher because it did not

reflect the general distribution of diabetes in Bucharest, due to a preferential attending of patients in this office.

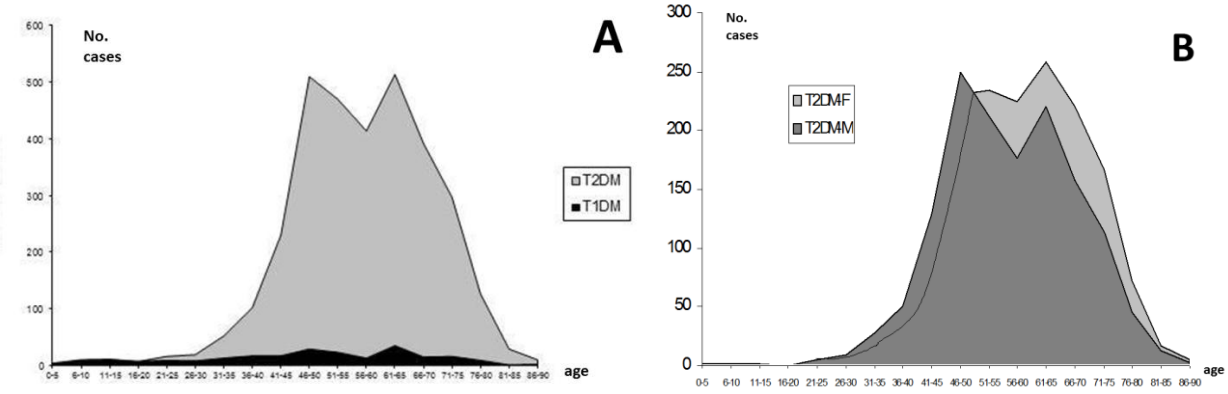

Figure 3. *Distribution of subjects (both T1D and T2D) according to the age at onset (A) and sex (B) in patients from the 2001 cohort. T1D represent ~ 7% of total. Adapted after* [16].

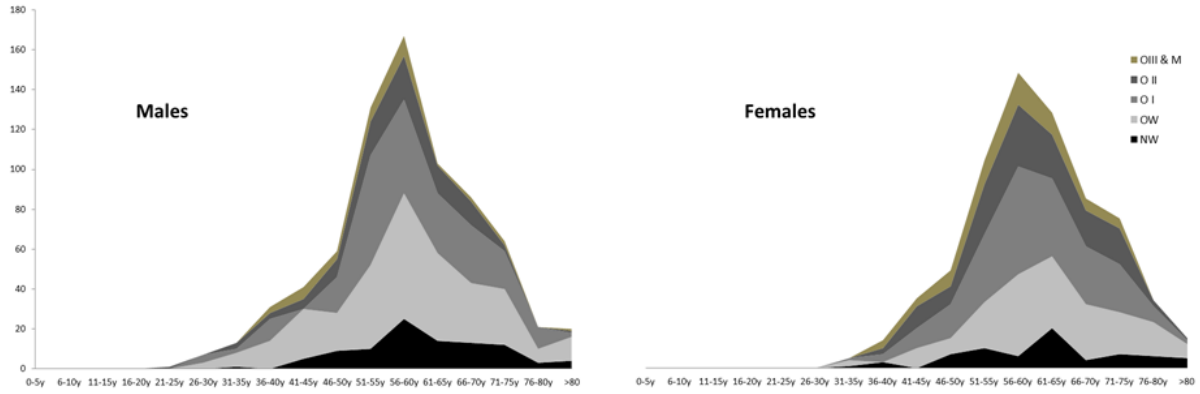

Figure 4. *Distribution of subjects (Males and Females) according to their weight status and age groups in patients from the 2010-2012 cohort (NW = normal weight; OW = overweight; OI, II, III, M = obesity grade I, II, III).*

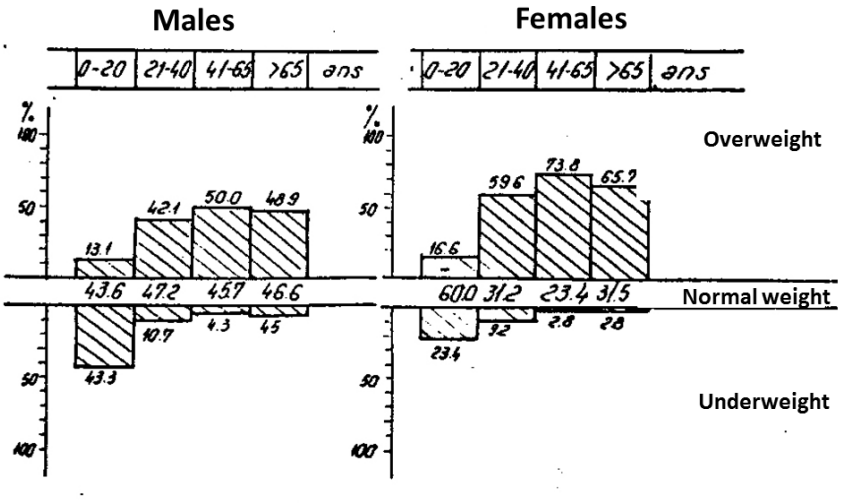

Figure 5. *Distribution of subjects (Males and Females) according to their weight status in patients from the 1968-1974 cohort. Adapted after* **[**5**]**

As can be seen in Table 1 and Figure 4, in the current (2010-2012) cohort, about 13% of males and 10% of females were normal/underweight, including also the T1D cases.

Table 1. Distribution of patients according to weight status.

TOTAL (1447 patients)		**NW**		**OW**		**O I**		**O II**		**O III**	
M	F	M	F	M	F	M	F	M	F	M	F
47.82%	52.18%	12.9%	9.97%	39.5%	28.03%	30.64%	32.08%	12.09%	20.37%	4.86%	9.55%

NW – Normal weight; OW – Overweight; O I – Grade I Obesity; O II – Grade II Obesity; O III – Grade III Obesity

Overweight was higher in males than in females, but obesity was higher in females than in males.

As it can be seen in Figure 5, in the 1968-1974 cohort, underweight was very high in the age group 0-20 years and significantly decreased in the 20-40 and 40-60 decades.

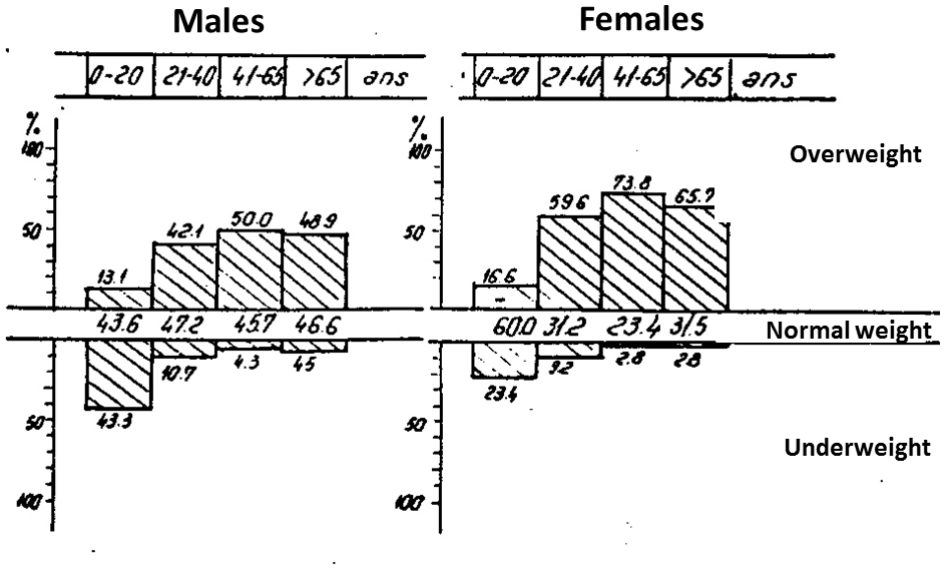

Figure 5. *Distribution of subjects (Males and Females) according to their weight status in patients from the 1968-1974 cohort. Adapted after* [5].

Discussions

The "Paulescu Institute" school of diabetes repeatedly mentioned that a distinction must be made between the clinical onset of diabetes based on blood glucose level (hyperglycaemia) and the real onset of diabetes, i.e. the moment when the declining β-cell function/mass reaches less than 50% of the normal [17-20]. This process starts months or years before the clinical onset of the disease in T1D and years or decades in T2D [13,21-23]. It is obvious that the proposal for a change in both the definition of diabetes and its classification is a difficult task [13,24,25]. Recently, genetic revolution added new objective arguments in this respect [26-31], showing that the vast majority of genes associated with T2D are related with *β-cell function* and not with the hypothetical *insulin resistance* [14,30-32]. This confirmed the concept of "Paulescu Institute" team, that the main defect occurring early in the natural history of T2D is related to the *incomplete maturation of the secretory vesicles* [21,25,33-36]. This defect leads finally to the decrease or absence of the

oscillatory insulin secretion [37-40] and to the decrease or even disappearance of the first phase insulin secretion response [40], all these preceding with many years or even decades the decompensation of blood glucose regulation. The proposal to replace hyperglycaemia (which is only an epiphenomenon) as diabetes diagnosis criterion with the phenomenon itself (decrease in β-cell function / mass) is one of the tasks of the "Paulescu Institute" school of diabetes [23-25]. Such proposal has not only an academic significance, but also a practical one. In a recent paper published in *Nature Reviews Endocrinology*, Phillips and Olson [41] made a plea for a more carefully identification of IFG and IGT (inappropriately included in "prediabetes") in order to act earlier in the natural history of the disease. They correctly sustained that "*Prediabetes and early T2DM are a continuum and their adverse impact begins early in their natural history*". It was found that some "prevention" programs for T2D [42-45] focused on populations with pre-final decompensation of blood glucose regulation can have a measurable efficacy by delaying the clinical onset of diabetes and improving the metabolic profile of the patients. Because lifestyle optimization decreases the overload of the already dysfunctional β-cell, an improvement in β-cell function is highly expected.

One major clinical indicator referring to the efficacy of such prevention measures is a decrease in the body weight and the increased capacity of physical activity. Our current data show that overweight/obesity which is associated with T2D in more than 90% in our older epidemiological study [5], is also present in approximately the same percentage in our study.

The relationship between β-cell function and adipose tissue mass was well identified by Sims et al [46] in 1968 in an interesting study carried out on volunteers. In this study, in parallel with an induced weight gain by a hypercaloric diet, the authors also noted an increase in the plasma insulin levels, proving that the small increase in plasma insulin is related to increased numbers of adipocytes during the weight gain. On the contrary, the reduction in body weight by a hypocaloric diet is accompanied by a decrease in plasma insulin levels. Generally, an increased level in plasma insulin in obese people is considered to be related to a decrease in peripheral insulin sensitivity, which is obviously a secondary and reversible phenomenon. By a misinterpretation of plasma insulin levels in obese people, some postulated the putative insulin resistance as being the primary defect leading finally to a decompensation of the β-cell function as a secondary disturbance [47-49], thus placing the cart before the horses. A critical review of this topic can be found elsewhere [14,25].

The pathogenic relationship between obesity and T2D started to be uncovered after the discovery of the various functions of the adipose tissue [6] which include not only the role in energy homeostasis by its "buffer" function for fatty acids [50]. Other roles include that of maintaining the temperature homeostasis, especially through the brown adipose tissue dispersed in the various parts of the body (especially in the upper part) [51-53]. By storing an important part of the exogenous heavy metals in a shielded manner, the adipose tissue takes part in the protection of liver or other tissues against their harming effects. Apart these physiological functions, the adipose tissue (especially the visceral one) is a very reactive tissue, which explains the high number of macrophages found in it in overweight and especially in obese people. These macrophages interact with adipocytes and from this interaction a number of cytokines are released by both the adipocytes (like leptin and others collectively called adipocytokines) and macrophages (like

TNF-α, IL6 and others) [54-58]. This process (named low grade inflammation) has numerous side effects especially on endothelial cells but also on β-cells.

The pathogenic relationship between obesity and T2D results from three mechanisms: The *first* is that of the decrease of adiponectin in overweight/obese people, especially in those who associated blood glucose dysregulation [30,59,60]; *the second* is that of increasing overload of an already dysfunctional β-cell, leading to increased production of proinsulin, ending finally in decompensation of blood glucose regulation as a results of the decreasing β-cell mass/function [13,34,61]; *the third* mechanism is related with the above mentioned proinflammatory reaction acting on β-cells through the rich network of capillaries found inside the Langherhans's islets.

In the last years, following the genetic revolution, a great interest was directed to finding the common genes associated with both obesity and T2D [30]. From the 138 loci associated with BMI in various Genome Wide Association Studies/meta-analyses [62], part are mapping to non-coding sequences which increases the difficulty to find the molecular pathway in which they are involved. It has been estimated that the heritability of T2D is around 25% [63] whereas, that of obesity between 50-80% [64]. We hope that in the near future a common risk score for both T2D and obesity will be identified, being useful in selecting the subjects with high risk to develop in their future one or both syndromes.

Conclusions

Our current data confirm the previous ones showing that overweight/obesity is strongly associated with T2D. We also found a relationship between the onset age of T2D and the degree of overweight/obesity, suggesting that the duration of obesity is an important pathogenic factor. Since obesity is a preventable syndrome, the decrease in body weight could be the best preventive method for T2D.

Acknowledgements and duality of interest: There is no conflict of interest related to the content of this paper. This paper is supported by the Sectorial Operational Program Human Resources Development (POSDRU) 2007-2013, financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/107/1.5/S/82839.

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