

Obesity in Type 2 Diabetes: Prevalence, Treatment Trends and Dilemmas

Tamara Poljičanin¹, Ivana Pavlić-Renar² and Željko Metelko¹

¹ University of Zagreb, »Vuk Vrhovac« University Clinic for Diabetes, Endocrinology and Metabolic Diseases, Zagreb, Croatia

² University of Zagreb, Zagreb University Hospital Center, Zagreb, Croatia

ABSTRACT

This retrospective observational study investigated the prevalence of obesity in persons with type 2 diabetes, trends in obesity resulting from the duration and treatment of diabetes, and treatment-related changes in HbA1c and body mass index (BMI). Data on 1773 type 2 diabetics (802 men and 971 women) were obtained from the CroDiabNET registry. Follow-up included the analysis of patients' age, disease duration, diabetes treatment, BMI and HbA1c values. A significantly higher rate of overweight and obesity was found in persons with type 2 diabetes as compared to the general population. A significant decrease in BMI was observed in the groups treated by diet, and in those treated by oral hypoglycaemic agents ($p < 0.05$), regardless of their pharmacotherapeutic group, in contrast to a significant increase in BMI observed in the groups treated with insulin (alone or in combination with oral hypoglycaemic agents) ($p < 0.05$). Persons with type 2 diabetes lost weight only during the first years of the disease, while with diabetes duration and insulin treatment they regained weight. A significant increase in HbA1c was observed in the groups treated with sulfonylureas ($p < 0.05$), whereas all other groups revealed either a significant decrease ($p < 0.05$) or no change in HbA1c. Our findings suggest the necessity of an integrated approach to managing type 2 diabetic patients that would simultaneously address both diabetes and obesity. Good glycaemic control is imperative and diabetes treatment should not be postponed. Because of a possible concomitant weight gain, aggressive weight control measures should be applied concurrently in order to achieve maximum treatment benefit.

Key words: diabetes mellitus, epidemiology, obesity, overweight, prevalence, weight gain

Introduction

Obesity has long been considered a product of the modern life style in developed countries. Its increasing frequency in developing countries, however, points to a global paradox: a double burden of a still unsolved problem of malnutrition and of the epidemic of obesity and its comorbidities such as diabetes, hypertension, cancer and cardiovascular diseases¹. Over the past decades advanced work technology, sedentary leisure-time behaviour², and greater availability, lower cost and enhanced flavour of food have led to energy imbalance. A seemingly small imbalance between the intake and the expenditure causes a major weight gain and is sufficient to explain the epidemic^{3,4}. Obesity is the first step towards chronic diseases⁵⁻⁷, not only increasing the risk of their onset, but also affecting their course and determining their treatment and prognosis^{8,9}. Diabetes is a chronic disease closely associated with obesity, its growing prevalence in the world

being parallel to and conditioned by the global epidemic of obesity. On the other hand, obesity is the most important risk factor for the development of type 2 diabetes, weight gain being estimated to be responsible for up to 90% of diabetes worldwide¹⁰.

Obesity is considered to promote insulin resistance, although exact mechanisms are not clear¹¹. Obese persons have been known to have decreased glucose stimulated insulin secretion and increased hepatic gluconeogenesis¹², and to be at a much greater risk of developing diabetes^{13,14}, the age at the onset of diabetes being earlier¹⁵ and the risk rising almost exponentially with an increase in body mass index. This higher risk of diabetes in obese persons is responsible for a significantly greater prevalence of type 2 diabetes in this population as compared to the general one. Obesity influences not only the

onset, but also the course of this type of diabetes¹⁶. Type 2 diabetic patients who have lost weight have significantly better diabetes control¹⁷ and even their intention to lose weight is associated with a reduced risk of all-cause mortality, independent of whether they actually lose weight or not¹⁸. The multiple association between obesity and diabetes is amplified by the fact that persons with diabetes lose weight much harder¹⁹, the vicious circle thus being closed.

The goal of this study was to establish the prevalence of obesity in persons with type 2 diabetes and compare it with that in the general population. A further aim was to assess trends in the duration and treatment of diabetes with respect to obesity in order to enable physicians to maximize the benefit of treatment.

Patients and Methods

To examine the association between type 2 diabetes and body weight, body mass index (BMI) was determined at initial (BMI 1) and final (BMI 2) examinations in 1,773 consecutive patients with type 2 diabetes (971 women and 802 men). Annual changes in body mass index and glycated haemoglobin A1c (Δ BMI; Δ HbA1c) were followed for 1.5 years (median 1.58 yrs.; range 1.08–2.58 yrs.). The subjects (median age 66 years, range 23–91 yrs.) had diabetes for an average of 11 years (range 2–47 yrs.).

Data from outpatients regularly attending the Clinic in 2003 were retrieved from the CroDiab NET, a software developed to improve the quality of diabetes care and record keeping, and to simultaneously create a database for the national diabetes registry²⁰. Medical history, laboratory and physical examination data of all patients visiting the outpatient department of the Vuk Vrhovac University Clinic are incorporated into unique electronic medical records within the database. As the Clinic is a Croatian referral centre for diabetes, data from patients from all over the country were included. All participants were Caucasians, as are >99% of the Croatian population. For the purpose of this study last entries from 2003 and those from the first half of 2005 were included.

HbA1c was determined by an automated immunoturbidimetric method on an Olympus AU600 analyser (Olympus Optical Co., Tokyo, Japan) using Bayer reagents (Tarrytown, IL, USA)²¹. BMI was calculated as weight (kg) divided by the square of height (m). Δ BMI and Δ HbA1c were calculated as final minus baseline values divided by the duration of the follow-up.

The study was approved by the Clinic's Ethics Committee. An estimate of the required sample size was made according to the published reports and recommendations^{22–24}.

Statistical methods

All statistical analyses were performed using SAS (version 9.1.3).

Variance homogeneity was tested by Lindman's test prior to the analysis of correlation and between-group

differences. Normality of distribution was tested by using Shapiro-Wilks' W test. Differences between groups for independent variables were analyzed using Mann-Whitney U test (for two groups) and Kruskal-Wallis test (for three or more groups). Wilcoxon matched pairs test was used to determine differences between initial and final values, while differences in the prevalence of individual conditions were tested using chi² test. The level of significance of correlation between variables and the correlation trend were analyzed by Spearman Rank Order Correlation Test. Statistically significant differences were defined as p value less than 0.05 ($p < 0.05$) in all analyses.

Results

At the beginning of the study median BMI and HbA1c were 28.08 kg/m² (interquartile range 25.81–30.85 kg/m²) and 7.83% (interquartile range 6.85–9.18 %), respectively. By the end of the study BMI decreased by 0.04 kg/m² (interquartile range –0.43–0.48 kg/m²), while HbA1c decreased by 0.21% (interquartile range –0.31–0.79 %) on average.

Prevalence of overweight and obesity

To establish the prevalence of overweight and obesity in the investigated population, the subjects were divided into groups according to their BMI values (Group 1 consisted of subjects with BMI < 25 kg/m², Group 2 of overweight subjects with 25 kg/m² ≤ BMI < 30 kg/m², and Group 3 consisted of obese subjects with BMI ≥ 30 kg/m²). Out of the total number of studied persons, 54% (433/802) of men and 45% (437/971) of women were overweight, and 25% (201/802) of men and 39% (379/971) of women were obese. A statistically significant difference was found in the degree of obesity between persons with type 2 diabetes of both sexes and the general population of Croatia ($p < 0.001$)²³.

Disease duration

Mean Δ BMI values according to the duration of diabetes and sex are shown in Figure 1.

Weight loss was observed in the first years from the onset of diabetes, decreasing with time, and switching to a weight gain later in the course of the disease until occurring again approximately 20 years after the diagnosis. Δ BMI increased with the duration of diabetes, showing statistically significant positive correlation with disease duration ($p < 0.001$).

Treatment method

To establish possible differences among the groups as defined by the treatment method, all subjects with type 2 diabetes were divided into 6 groups as shown in Table 1.

Statistically significant among-group differences were observed in patients' age and diabetes duration ($p < 0.001$), with the longest duration identified in the insulin groups (i-i and iOHA-iOHA) and the oldest age in the insulin (i-i and iOHA-iOHA) and sulfonylurea (s-s) groups.

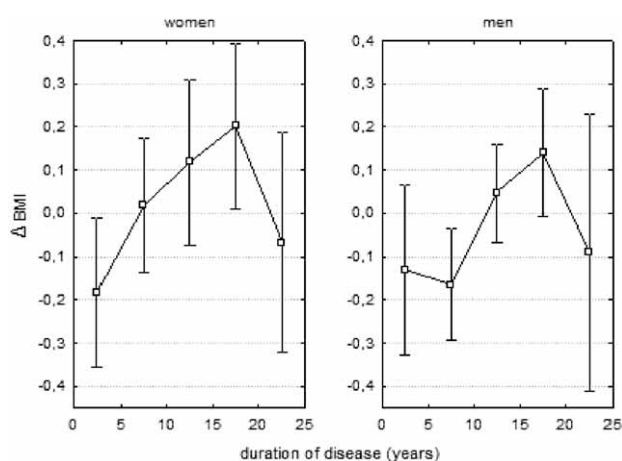


Fig. 1. – Mean Δ BMI values according to disease duration. \square Mean \pm 1T Mean \pm 0.95 Confidence Interval.

Initial BMI and HbA1c values also significantly differed among the groups ($p < 0.001$), with the highest BMI values observed in the biguanide (metformin) group (b-b) and the highest HbA1c in the insulin (i-i and iOHA-iOHA) and sulfonylurea (s-s) groups.

A statistically significant decrease in BMI values was found in the groups treated with diet and exercise (d-d), and with oral hypoglycaemic agents (d-OHA, s-s, b-b) ($p < 0.001$) regardless of their pharmacotherapeutic group and mechanism of action. In contrast, groups treated with insulin alone (i-i) or combined with oral hypoglycaemic agents (iOHA-iOHA) revealed a statistically significant increase in BMI ($p < 0.001$, $p = 0.015$). As a result of an increase in some groups and a comparable decrease in others, diabetic population as a whole did not differ significantly in its initial and final BMI values ($p = 0.472$). HbA1c values showed a statistically significant decrease

in the groups treated with diet (d-d), biguanides (metformin) (b-b), insulin (i-i) and insulin + oral hypoglycaemic agents (iOHA-iOHA) on both visits ($p < 0.001$), but a statistically significant increase ($p = 0.002$) in the group treated with sulfonylurea (s-s). In the group which was treated with diet on the initial visit and with oral hypoglycaemic agents on the final visit (d-OHA) there was no significant change in HbA1c ($p = 0.995$). As the decrease occurred in the majority of groups, diabetic population as a whole was found to differ significantly in its initial and final HbA1c values ($p < 0.001$). Δ BMI and Δ HbA1c of individual groups are shown in Figure 2.

Discussion and Conclusion

The prevalence of overweight and obesity in persons with type 2 diabetes in Croatia was found to be higher than that in the general population²³, the results being comparable to those of the UKPDS²⁵. Correlation between disease duration and Δ BMI was found to be both positive and statistically significant. The follow-up revealed a decrease in the studied patients' BMI values during the first years of diabetes. The decrease rate diminished with time, switching to an increase in BMI, which was found to rise with longer diabetes duration. In the patients with long-standing diabetes, however, the decrease in BMI occurred again. These results confirm previously published conclusions that the diagnosis of diabetes is preceded by an increase in body weight, and followed by a continuous slow decrease in body weight and BMI – a reversed V curve with a peak at diagnosis and/or time immediately following the diagnosis (0–2 years)²⁶. In the patients with long-standing diabetes weight loss could be partially explained by the participants' older age which is accompanied by commonly seen weight loss caused with other chronic diseases and by loss of lean

TABLE 1
BASELINE CHARACTERISTICS OF PATIENTS BY THE TREATMENT GROUPS

Group symbol	Therapy characteristics		Sample size	Age	Disease duration	BMI	HbA1c
	Initial	End					
d-d	Diet	Diet	94	65.5 (31–91)	5 (2–31)	27.97 (20.34–40.91)	6.60 (4.50–11.24)
d-OHA	Diet	Oral hypoglycaemic agents	89	62 (36–86)	5 (2–37)	28.63 (21.83–53.06)	7.55 (5.10–12.91)
s-s	Sulfonylurea	Sulfonylurea	352	67 (33–89)	7 (2–32)	27.74 (18.29–44.64)	8.08 (4.80–12.94)
b-b	Biguanides*	Biguanides*	325	61 (32–80)	7.5 (2–34)	29.76 (22.04–49.84)	7.43 (4.82–12.64)
i-i	Insulin	Insulin	592	68.5 (31–88)	16 (2–47)	27.22 (15.78–41.40)	8.24 (4.99–13.94)
iOHA-iOHA	Insulin + oral hypoglycaemic agents	Insulin + oral hypoglycaemic agents	321	68 (43–91)	14.5 (2–38)	27.99 (20.28–42.90)	8.03 (5.40–12.60)

Data are presented as medians and ranges

*metformin

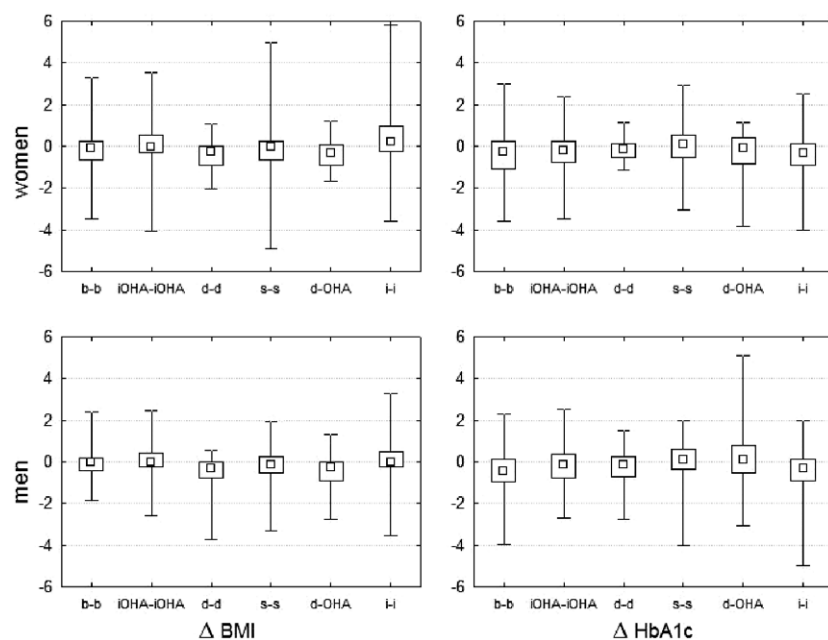


Fig. 2. Boxplot diagram of the differences in BMI and HbA1c according to the type of treatment. \square Median 25%–75% \perp Min-Max * Abbreviations: type of treatment=initial-end; i-i=insulin-insulin; s-s=sulfonylurea-sulfonylurea; b-b=biguanides-biguanides; d-OHA=diet-oral hypoglycaemic agents; iOHA-iOHA=insulin + oral hypoglycaemic agents-insulin + oral hypoglycaemic agents; d-d=diet-diet.

mass²⁷. An increase in the BMI of individuals treated with insulin, and a decrease in those treated with diet and exercise, and/or oral hypoglycaemic agents in the period of time immediately following the diagnosis of diabetes (0–2 yrs.) and 10 years later has also been reported²⁶.

The results of the UKPDS²⁸ have pointed to an increase in body weight in both patients on insulin and in those on sulfonylureas, whereas in our study weight gain was observed only in insulin-treated patients. What is more, the patients treated with sulfonylurea showed weight loss as did those from both studies treated with diet only or other oral hypoglycaemic agents. On the assumption that this weight loss could be attributed to a too long insistence on sulfonylurea treatment despite the unsatisfactory diabetes regulation we analyzed HbA1c changes in the investigated groups and found an increase in the patients treated with sulfonylurea as opposed to a decrease or lack of changes observed in other studied groups. As this was an observational study based on data collected from daily practice, decisions about treatment changes were made relying on recommendations, and not strict protocols as is the case in clinical trials such as UKPDS. Previous observational studies have reported diabetes duration and baseline HbA1c values to be predictors of poor glycaemic control; therefore, we analysed these parameters in our study groups²⁹. Both groups treated with oral hypoglycaemic agents throughout the study period (b-b and s-s) had comparable disease duration, whereas patients treated with sulfonylurea (s-s) had higher baseline HbA1c values than the patients treated with biguanides (b-b), although they were above the target ones in the majority of patients from both groups. Nevertheless, deterioration in glycaemic control

was observed in the sulfonylurea group (s-s) and not in the biguanide group (b-b). The analysis of other potential reasons for clinical inertia such as the number of medications, time since last HbA1c measurement and ethnicity showed that they were comparable in both groups treated with oral hypoglycaemic agents throughout the study period (b-b and s-s)^{30–32}. Although there can also be other reasons for clinical inertia, the fact that in Croatia at the time of the study sulfonylurea treatment preceded the introduction of insulin led us to assume that the underlying fear of weight gain could also be responsible for the results obtained in this study and for their divergence from those obtained in the UKPDS²⁸. Weight gain in insulin-treated patients is caused in part by the metabolic recovery which leads to a decreased glucose excretion via urine. Increase in the basal metabolism conditioned by weight gain is annulled by its simultaneous decrease against better glycaemic control and reduced demand for glucose production³³. According to the results of the Diabetes Intervention Study (DIS)³⁴, patients with stable body weight experience statistically significantly less cardiovascular events than those who gain weight over a 10-yr period. On the other hand, the results of the UKPDS study²⁸ have shown that intensified glycaemic control reduces the risk of the development of microvascular complications, but significantly increases weight gain. Practitioners are thus faced with the dilemma of whether to intensify the treatment likely to cause weight gain with all its consequences or insist on current treatment and try to motivate patients to improve their adherence to diet.

Although starting insulin therapy can nowadays be delayed with the use of new classes of hypoglycaemic

agents, the dilemma is just postponed and has to be tackled at some time or other³⁵. When good metabolic control and target values of cardiovascular risk factors are achieved in only a minority of patients with diabetes^{36,37}, postponing a more aggressive treatment of diabetes is not a solution; rather, it should be accompanied by measures equally addressing obesity. Good glycaemic control must be achieved, whilst simultaneously striving to maintain body weight^{38,39}.

Type 2 diabetic patients were found to be more obese than the general population, gaining weight with disease duration and insulin treatment. In order to reconcile aspiration to as good glycaemic control as possible with that to a stable body weight due to their respective effects on the development of complications, both factors should be considered when deciding on the method of treatment⁴⁰. To avoid intensifying therapy aimed at improving glycaemic control is certainly not the solution.

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Our findings suggest the necessity of an integrated approach to managing type 2 diabetic patients that would simultaneously address both diabetes and obesity instead of treating them separately. A good insight into diabetic patients' body weight pattern increases the awareness of critical points and thence enables physicians to maximize the benefit of treatment.

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T. Poljičanin

University of Zagreb, »Vuk Vrhovac« University Clinic, Dugi dol 4a, 10000 Zagreb, Croatia
e-mail: Tamara.Poljicanin@idb.hr

PRETILOST U ŠEĆERNOJ BOLESTI TIPA 2: PREVALENCIJA, TRENDOVI U LIJEČENJU I DILEME

S A Ž E T A K

Ovo retrospektivno opažajno istraživanje ispitalo je prevalenciju pretilosti kod osoba sa šećernom bolešću tipa 2, trendove pretilosti proizašle iz trajanja i liječenja šećerne bolesti te promjene HbA1c i indeksa tjelesne mase (ITM) uzrokovane liječenjem. Podaci o 1773 bolesnika sa šećernom bolešću tipa 2 (802 muškarca i 971 žene) dobiveni su iz registra CroDiabNET, a pratilo se životnu dob bolesnika, trajanje bolesti, liječenje šećerne bolesti, ITM i HbA1c. Prekomjerna težina i pretilost bile su značajno veće kod osoba sa šećernom bolešću tipa 2 nego u općoj populaciji. Skupine liječene dijetom i oralnim hipoglikemicima bez obzira na farmakoterapijsku skupinu značajno su snizile ITM ($p < 0,05$), za razliku od skupina liječenih inzulinom (samim ili u kombinaciji s oralnim hipoglikemicima) kod kojih je došlo do porasta ITM-a ($p < 0,05$). Bolesnici sa šećernom bolešću tipa 2 izgubili su na težini samo tijekom prvih nekoliko godina od nastupa bolesti, dok je s trajanjem bolesti i inzulinskom terapijom ponovno došlo do porasta težine. HbA1c se značajno povećao u skupinama liječenima sulfonilurejom ($p < 0,05$), dok se u svim drugim skupinama ili značajno snizio ($p < 0,05$) ili ostao jednak. Naši rezultati ukazuju na potrebu integriranog pristupa liječenju bolesnika sa šećernom bolešću tipa 2 koji bi se istovremeno bavio i šećernom bolešću i pretilošću. Dobra regulacija glikemije je nužna, stoga se liječenje šećerne bolesti ne smije odgađati. Radi mogućeg pratećeg porasta tjelesne težine potrebno je primijeniti pojačane mjere njene kontrole kako bi se postigla najveća moguća korist liječenja.