

ASSESSMENT OF CURRENT INSULIN USAGE IN TYPE 2 DIABETICS ACCORDING TO DIABETES TYPE DISTRIBUTION AMONG INSULIN-TREATED PATIENTS IN UKRAINE

Mykola Khalangot¹, Victor Kravchenko¹, Mykola Tronko¹, Alexander Vaiserman²

Key words: type 2 diabetes, insulin, age at diagnosis, sex, primary care databases

SUMMARY

Use of insulin in the treatment of type 2 diabetics may vary among different countries from 5% to 50%. The validity of this evaluation may depend on the diabetes type classification of adult insulin-treated patients (ITP). An attempt at such evaluation was made by using data of the Ukrainian Diabetes Mellitus Register (102,580 ITP aged ≥ 30). ITP were stratified into subgroups according to age at diagnosis (ATD). The numbers of patients with insulin-free period < 2 yrs (IFP < 2) and female/male distribution were compared. The proportion of ITP with IFP < 2 decreased and the female/male relative risk increased with an increase in ATD. Taking only the number of patients with ATD ≥ 40 in consideration yielded a 7.8% rate of insulin use by type 2 patients. The majority of ITP aged > 29 in Ukraine probably are type 2 diabetics.

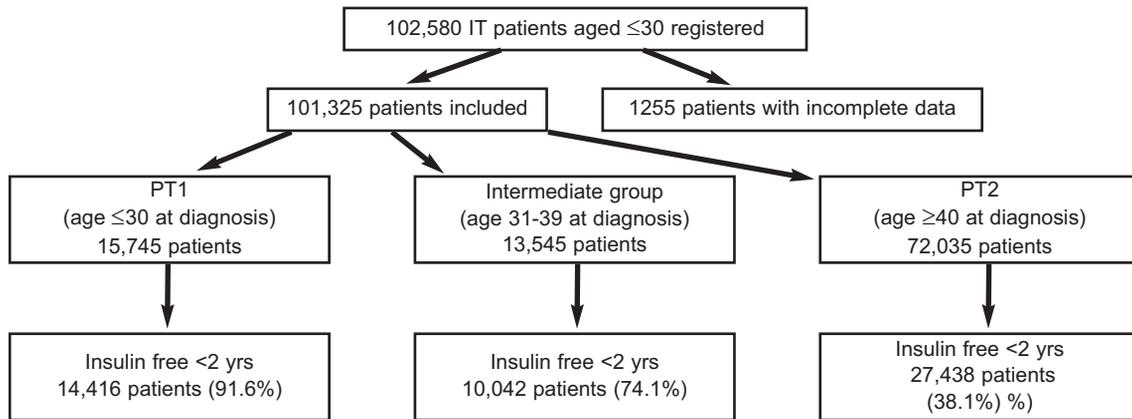
*Corresponding author: Mykola Khalangot, MD, PhD, Department of Diabetes Epidemiology, Institute of Endocrinology and Metabolism, st. Vishgorodskaya 69, 04114, Kiev, Ukraine
E-mail: nikhalangot@ukr.net*

INTRODUCTION

Primary Care Diabetes (PCD Europe) Approved Guidelines for Type 2 Diabetes include a chapter on insulin treatment (1). It appears to be a reflection of a general tendency to increase insulin use when treating type 2 patients, particularly after receiving the UKPDS data, which demonstrated that for 1% decrease in HbA_{1c} there was a 35% reduction of the risk of complications (2). While going around the discussion concerning positive and possible negative effects of the above tendency, we must indicate that in different countries, insulin is used in the treatment of type 2 diabetics at a very variable rate, ranging from 5% in France (3) to 57.1% in Sweden (4). Data on insulin use in 19% of 8036 type 2 diabetics, collected from 142 primary health care centers in Spain, were presented at the PCD Europe meeting in 2000 (5).

There is a worldwide evaluation of differences in the rate of insulin usage in industrialized and developing countries. Some 65% of people with diabetes live in developing countries and account for only 30% of the world's total insulin usage *per year*. It is in sharp contrast to the industrialized world that has 35% of the world's diabetic population but accounts for about 70% of the world's total insulin usage *per year* (6). This difference cannot be entirely due to the low incidence and prevalence of type 1 in developing

Figure 1. Stratification of adult insulin treated diabetics according to disease history (UDR 2004).



countries. Two major issues of importance related to type 1 diabetes in developing countries are missed diagnosis and unavailability of insulin (7). Taking into account that type 2 diabetics make the majority of all DM patients, they can compile into a quite significant part among insulin treated adult patients, thereby for the most part determining insulin use in a country or region. A wider use of insulin in the treatment of type 2 diabetics will certainly lead to a classification problem of adult-diagnosed insulin treated patients, which has been previously specified (8). Researchers in diabetes mellitus admit difficulties of practical classification of this patient category according to DM type, and are today using data on age at diagnosis (9-12) in the disease type stratification. The possibility of such assessment has increased due to utilization of population-based DM registers, use of patient stratification depending on their disease history. Therefore, such data from different countries are interesting. In Ukraine, reliable population-based data on the real distribution of DM types are still lacking. Health care systems in East European countries are usually aware of insulin treated DM patients and total number of diagnosed DM patients (13). Due to non-medical reasons, insulin treated patients can often be diagnosed by primary care physicians as insulin-dependent, i.e. type 1 DM.

PATIENTS AND METHODS

The study was conducted using the nationwide population-based Ukrainian diabetes register, System of Supervision of Diabetic Patients in Ukraine (SINADIAB), created in 2001-2005 at the Institute of Endocrinology, Kiev, Ukraine (14). SINADIAB data have been repeatedly used in epidemiological studies (14-16). In the present observational, cross-sectional study, 26 regional registers were used. Reports from primary care physicians from the entire country were used as the primary data source during the register development. Cross-sectional analysis of Ukrainian DM Register (UDR) was conducted in order to assess the proportion of insulin treated type 2 diabetics. Until November 1, 2004, the complete register of insulin treated patients included 120,085 persons, 102,580 of them aged ≤ 30 (Fig. 1). Cases were classified according to age, sex, age at diagnosis, and duration of insulin-free period; 1255 cases with missing data were excluded leaving a total of 101,325 cases included in the analysis. In the above group, stratification was carried out according to age at DM diagnosis, as follows: probably type 1 (PT1), insulin treated patients included in UDR as type 1, diagnosed with DM at age ≥ 30 ; and probably type 2 (PT2), insulin treated patients diagnosed with DM at age ≥ 40 , irrespective of DM type that was determined by PCD. As in type 1 DM usually progresses towards insulin dependence within 2 years of the clinical diagnosis, as noted in the pre-insulin era (18), the number of patients with insulin-free period (IFP) < 2 years was compared

between PT1 and PT2 groups. As only the year but not the exact date of disease onset and insulin treatment were registered in the UDR, the main methodological weakness of our study was the impossibility of exact IFP determination. The same was done in the “intermediate” group (IG), in which DM was diagnosed between 31 and 39 years of age. Similar DM onset age limits for classifying patients as DM1 or DM2 were used in the analysis of Swedish DM register, but IFP evaluation was not carried out by the Swedish researchers (4). Sex distribution was standardized according to the 2001 Ukrainian national census. Besides, the distribution according to age of diabetes manifestation, included into UDR as DM1 and DM2 by November 1, 2004 and 2005, respectively, were compared. In the framework of UDR development, consultations with primary care physicians were conducted, during which attention was drawn to the inadmissibility of insulin treatment, a fact used as the only valid proof of DM1 diagnosis. The national Guidelines, which included a protocol for DM type diagnosis, were published in 2005 (19). In 2005, data on patients receiving insulin were updated in 79,503 persons included in the register. This update could include a change in DM type classification. Data sets were analyzed using 2-way chi-square analysis. For 95% confidence interval (95% CI) computing

arcsine transformation was used. The study protocol was approved by the Ethics Committee of the Institute of Endocrinology and Metabolism, Kiev.

RESULTS

The majority of insulin treated patients aged ≥ 29 belonged to PT2 group (72,035 persons in 2004), and only 27,438 (38.1%) of them had IFP < 2 years. The respective figures in PT1 patients were 15,745 and 14,416 (91.6%). Thus, their “insulin dependence” seems to be more significant ($p < 0.001$) than in PT2 patients. Only 28,890 (40.1%) PT2 patients were determined by PCD as type 2, while the rest were diagnosed as type 1.

In the IG (13,545 insulin treated patients), 10,042 (74.1%) had IFP < 2 years, which differed from either PT1 or PT2 group ($p < 0.001$). In 2005, the same proportions of patients with IFP < 2 years in the groups determined according to age at disease onset were recorded. Data from the 2005 register are presented in Table 1. The percentage of patients who had IFP < 2 years decreased, and the proportion of females as well as the female/male relative risk (RR) increased with the increase in age at DM diagnosis (Table 1). If analyzing DM typology according to data given to the register by PCD, then patient age at the time of diabetes diagnosis was connected with IFP only in type 1 but not in type 2 cases from UDR (Table 2). The

Table 1. Sex distribution of adult insulin treated diabetic patients according to age at diabetes diagnosis

Group (age at diagnosis, yrs)	n	Percentage of patients with insulin-free period < 2 yr (%; 95% CI)	Proportion of females (%; 95% CI)	Female/male RR (95% CI)
PT1DM (≤ 30)	16821	88.2 (87.7-88.7)	47.5 (46.7-48.2)	0.69 (0.67-0.71)
IG (31-39)	16754	63.3 (62.5-64.0)	49.4 (48.6-50.1)	0.74 (0.72-0.76)
PT2DM (≥ 40)	71789	40.6 (40.2-40.9)	64.0 (63.7-64.4)	1.27 (1.25-1.29)
<i>p</i>		< 0.001 (between groups)	< 0.001 (between groups)	< 0.001 (for each group)

Table 2. Proportion of insulin treated patients with insulin-free period < 2 years according to age at diabetes diagnosis and diabetes type (UDR 2004 and 2005)

Diabetes type (included in UDR)	Age at diabetes diagnosis (yrs)	Patients in 2004 (n)	Patients with insulin-free period < 2 yrs (%; 95% CI)	Patients in 2005 (n)	Patients with insulin-free period < 2 yrs (%; 95% CI)
DM type1	≤ 30	15747	91.5* (91.1-92.0)	14321	92.9* (92.5-93.3)
	≥ 40	44242	91.5* (91.1-92.0)	31999	59.0* (58.4-59.5)
DM type 2	≤ 30	650	26.6 (23.9-29.3)	998	26.6 (23.9-29.3)
	≥ 40	23961	22.9 (22.4-23.3)	35250	22.9 (22.4-23.3)

UDR=Ukrainian Diabetes Register; *p (≤ 30 vs ≥ 40 yrs) < 0.001

proportion of patients with age at disease onset ≥ 40 and classified by PCD as type 1 in 2005 decreased as compared with 2004, but increased in case of type 2 DM.

The number of type 2 DM patients in Ukraine may be approximately determined as $TN - IT + PT2 = 921219$ (2004). If considering only the number of PT2 patients, as IT DM2, these data yield a rate of insulin use by type 2 patients of 7.8% (estimated proportion of IT type 2 DM patients = (number PT2 patients/number of type 2 DM patients) $\times 100\%$).

DISCUSSION

Utilization of some insulin treated DM patient disease history data analysis, with the help of a nationwide electronic DM patient register, allowed the possible number of insulin treated type 2 DM patients and their proportion in relation to all known DM patients to assess. In Ukraine, this part turned out to be significantly lower than in others but not all (3-5) European countries. Along with this, even in Ukraine, most insulin treated patients have a disease history that is more common for DM type 2. King (6) has pointed to fourfold disproportion in insulin use between industrialized and developing countries. Data from the Swedish diabetes register on insulin use in the treatment of 57.1% of type 2 diabetics (4) allows us to suppose that the above disproportion was determined by different levels of insulin use in type 2 DM treatment. Essential to us is the fact that our analysis of UDR for the first time pointed quantitatively to the problems connected with difficulties in DM type classification of adult-onset insulin treated diabetics, as well as to terminological misunderstanding connected with the existence of terms such as “insulin-dependent diabetes mellitus”. Comparison of data on current insulin treated diabetes typology, which was included into the UDR between 2004 and 2005, shows a tendency of conquering terminological errors. The limitations of our study were determined by our quantitative evaluation of insulin treated DM type 2 patients being based exclusively on patient stratification according to disease history. For the purpose of this study, we considered diabetic patients as having insulin treated type 2 diabetes (PT2) if they

were aged over 40 at diagnosis and were treated with insulin. In this way, those who could have been diagnosed before age 39 were not included as insulin treated PT2 patients, but those insulin treated patients that may have had type 1 diabetes diagnosed after age 39 were not included in the PT1 group. Data from the UKPDS indicate that about 10% of people who are initially diagnosed as type 2 DM may have slow-onset type 1 diabetes (20). Nevertheless, the age limit (>39 years) for separation of PT2 diabetics that we used, at the time of diagnosis is much higher than the one used in the work by Carter *et al.* from 2006 (9) or Morris *et al.* from 1997 (10) (>25 and >35 years, respectively). According to our knowledge, the duration of insulin-free period has not yet been considered on stratification of DM types. Only in one study that was based on the usage of General Practice Research Database (11), patients under 35 years of age were considered as DM 1 if the continuous oral hypoglycemic treatment had not exceeded 1.5 years. The accuracy of our evaluation of the number of insulin treated type 2 DM patients has recently proved to be true through data analysis of one of the Ukraine’s regional diabetic registers, which held the information on 92.5% of the known diabetic patients: 8% out of 25,896 patients determined by PCD as type 2 diabetics were insulin treated.

From the practical and epidemiological point of view, the quantitative data on insulin treated diabetes typology, presented in Tables 1 and 2, seem to be interesting. Quite a high number of insulin treated patients with age at diagnosis below 30, classified by PCD as type 2 diabetics, as well as the great number of type 1 patients, including those with a disease history typical of this diabetes type, also appear significant. Type 2 diabetes in younger people is being increasingly reported in the literature, and some of them might require insulin for control. According to Diabetes Incidence Study conducted in Sweden (DISS), which was based on primary health care data, 73% of 6771 incident cases of diabetes aged 15-34 at diagnosis, were classified as type 1 diabetes, 17% as type 2 diabetes, 1.4% as secondary diabetes, and 8.3% were considered unclassifiable by the reporting physician. This means that, even during classification

of DM patients diagnosed before age 35, quite a significant proportion of them were not considered as type 1. Nevertheless, 54% of patients classified as having type 2 diabetes and 83% of patients with unclassifiable diabetes were treated with insulin (12). There are very few epidemiological reports of adult-onset type 1 diabetes yet, partially due to the difficulty of distinguishing individuals with type 2 diabetes on insulin therapy. The currently available estimate of the number of type 1 diabetics in Ukraine (9,500 patients aged over 15) (21) differs drastically from the data presented in this study. The reason for this contradiction is most likely connected to the fact that the author's initial data were based on a 3-year children's diabetes incidence in only one specific Ukrainian region.

Our data mean that only clinical estimate is sometimes insufficient on diabetes type classification. Clinical data (e.g., body mass index, history of diabetic ketoacidosis, age at onset of disease, duration of insulin-free period, etc.) should be complemented by special laboratory studies. For example, a recent study aimed at practical classification of recent-onset diabetes among young adults in Sweden (22) showed the assessment of islet antibodies to be necessary for etiological classification of diabetic patients. In patients without islet antibodies, HLA-DQB1 genotyping together with C-peptide measurement may be of value in differentiating between "idiopathic" type 1 and type 2 diabetes. Unfortunately, specific tests are still rarely used in diabetes primary care in the majority of countries, and particularly in Ukraine. We already have some positive experience with the use of GAD antibody measurement in practical classification of the type of adult diabetes (23), however, it is based on a small number of cases.

The typological problem (classification according to type of diabetes) in diabetic patients diagnosed at middle age is occasional underestimate by reducing

the problem to the choice between insulin treatment and oral therapy. Specification by the type can have practical importance, for example, for acceptance of the decision on insulin treatment only or use of a combination of insulin treatment and oral therapy. This combination sometimes appears more favorable to insulin treatment only for type 2 diabetic patients. According to data from the Swedish diabetes register, such a combination is applied in 24% of type 2 diabetic patients (4).

A positive relationship between earlier disease onset, reduction of IFP and male sex was obtained in our large cross-sectional study of the prevalence of type 1 and type 2 diabetes among insulin treated diabetics in Ukraine. Therefore, it seems that sex can also be used on clinical assessment of the probability of type 1 and type 2 diabetes. In a recently published Swedish study (22) it was shown that the male prevalence among type 1 diabetics and female/male ratio decreased with the increase in age at DM diagnosis.

In conclusion, in this study we showed the main part of adult insulin treated diabetics aged >29 in Ukraine to probably be type 2 patients. A considerable fraction of insulin treated patients may not belong to type 1. Nevertheless, insulin use in the treatment of type 2 DM in Ukraine is lower than in Sweden. Implementation of national standards of DM type determination in primary care seems to be useful.

Our analysis does not apply to an exact estimate of valid distribution of DM types among insulin treated patients. We take into account that a significant part of the patients who have received insulin therapy for more than 2 years of the diagnosis actually have latent autoimmune diabetes in adults (LADA). In these cases, beta cell antibody studies may prove crucial to reach an accurate diagnosis.

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Erratum

In the article: **Assessment of current insulin usage in type 2 diabetics using estimation of diabetes type distribution among insulin-treated patients in Ukraine** published in *Diabetol Croat* 2007;36(1):15-21, the following error occurred:

In the first paragraph under “Patients and Methods” (p.16) the sixth sentence: “By November 1, 2004, the complete register of insulin treated patients included 120,085 persons, 102,580 of them aged ≤ 30 ...” should have been: “By Nov 1, 2004, a complete register of IT patients was consisting of 120 085 persons, including 102 580 ≥ 30 years of age (see Fig. 1).”

The appropriate change was made in Fig. 1:

102,580 IT patients aged ≤ 30 registered,
was printed instead of:
102 580 IT patients ≥ 30 yrs of age registered.

The complete, corrected Figure 1 is reproduced below.

Figure 1. **Stratification of Adult Insulin-Treated Diabetics According to Their Disease History (UDR 2004).**

