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Prevalence of Type 1 Diabetes Correlates with Daily Insulin Dose, Adverse Outcomes and with Autoimmune Process Against Glutamic Acid Decarboxylase in Adults

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1. Introduction

The territorial differences in the prevalence of type 1 diabetes mellitus (T1D) around the world were previously reported (Amos et al., 1997; Green & Patterson, 2001; Lévy-Marchal, 2001), but the data were based on the study of juvenile T1D epidemiology, i.e., in patients diagnosed with T1D before the age of 15 years. These data became the basis for the epidemiological evaluation of the whole T1D patient population. With the relatively limited number of children with T1D within the current territory, less effort is required for data gathering. Besides, as the age increases, it becomes more difficult to relate a diabetic condition to a certain diabetes type (Keen, 1998), thus, making it impossible to directly use the diabetes-type data obtained from Primary Care. In modern epidemiological studies, the key data concern the age at the time of the diagnosis—patients who were diagnosed before the age of 30 years and are insulin-treated, are considered to suffer from T1D.

1.1 T1D epidemiology in adults

European researchers have proved that the epidemiological characteristics of T1D in children significantly differ from that in young adults (Kyvik et al., 2004). Therefore, studying the peculiarities of T1D in adults is a major concern. Furthermore, data on the number of diabetic patients usually found in the reports of the healthcare system are unstructured according to the history of the disease, and cannot be a source of epidemiological information on patients suffering from T1D. Owing to the development of the Diabetes Register in Ukraine, it has become possible to conduct analytical comparisons and further studies on almost all the T1D adult populations.

1.2 Diabetes Register

The Diabetes Register contains individual, structured information on the disease history, and has already been used in some epidemiological studies (Khalangot et al., 2009a;

Khalangot et al., 2009[b]; Vaiserman et al., 2009; Khalangot et al., 2009[d]; Vaiserman & Khalangot, 2008). Until recently there was no evidence on age and gender structure of patients diagnosed with diabetes mellitus in Ukraine. Neither is there any information on risk factors that may influence main aetiological diabetes mellitus type's incidence, as well as development of diabetic complications in Ukraine. Diabetes register is recognized as an important tool of diabetes research: it is a fully functioning diabetes register created in Ukraine. It includes over 620 000 diabetes patients (2010) and gives a unique possibility to analyze the structure of aetiological types, gender and age features, prevalence, trends of incidence, risk factors of non-fatal events and mortality among Ukrainian diabetes patients. Observational cross-sectional (distribution of diabetes types and treatment, trends of life span) and cohort (assessment of mortality risks) epidemiological studies using national patient register based on data provided by primary care doctors became possible. The register included most of Ukraine's insulin treated patients, as well as significant part of patients receiving oral glucose lowering drugs (OGLD). The insulin-treated patient data covers 24 out of 25 Ukrainian regions, meaning that at least nearly all of Ukraine's T1D population is included in the register. According to the Health Ministry data, the total amount of patients with known diabetes is 1 048375 (2006), which means that nearly half of type 2 diabetes (T2D) patients have yet to be included in the register, which consists of 509 933 patients, including 37 406 death cases.

1.3 Register-based diabetes epidemiology studies

Systematic epidemiological study of main diabetes mellitus (DM) types through analysis of electronic population registers has been lasting for over 10 years. Usage of DM population registers has become quite advanced in the UK, in particular in Scotland, where by the end of 2004, 161 946 diabetics have been included into local diabetic registers which is equal to 3.2% of the general population. In Scotland, 14 out of 15 healthcare institutions are involved in controlling treatment of DM patients. An important aspect is that Scottish DM registers include all DM patients, unlike others, that only include patients receiving certain kind of treatment. It seems that at the moment, the most advanced and successful Scottish local register is Tayside (Boyle et al., 2001; Leese et al., 2006; Morris et al., 1997). It should be noted that this relatively small, but constantly functioning register became a source of not just "traditional" epidemiologic information concerning prevalence and annual incidence of T1D and T2D, dynamics of DM complications frequency, and quality of treatment, which is a generalization of routine data from active GPs working in the region, and can be accessed through the register's website (http://www.diabetes-healthnet.ac.uk/), but also of purely scientific fundamental data (Doney et al., 2003, 2005; Evans et al., 2005, 2006; Schofield et al., 2006). A few of these papers have entirely clinically-epidemiological nature, comparing mortality among patients with limb amputations depending on presence of DM (Schofield et al., 2006), or mortality risks depending on certain type of treatment (Evans et al., 2005, 2006), while others use the register to study genetic characteristics among different categories of DM patients (Doney et al., 2003, 2005). One of the researchers of Belgian Diabetic Register (BDR) Prof. Frans K. Gorus (Diabetes Research Center, Vrije Universiteit Brussel) indicated the possibility of such scientific use of diabetic registers (Gorus, 1996). Important epidemiologic, immunologic, and genetic studies of T1D in children and adolescents were carried out using BDR (Gorus, 1996; Vandewalle et al., 1997; Weets et al., 2001, 2002).

1.3.1 Register-based T2D epidemiology studies

Some results obtanied by means of studying electronic registers may at first seem unusual or paradoxic. In particular our studies of T2D patients (Khalangot et al., 2009b) indicate that Hazard Ratios (HRs) of cardiovascular disease (CVD) mortality among extremely obese patients [body mass index (BMI) ≥ 35 kg/m^2] adjusted for age, smoking and alcohol consumption were higher than for overweight patients [BMI 25-29 kg/m^2]: HR=1.54 (95% CI 1.16-2.05) and 1.35 (95% CI 1.15-1.59) among men an women respectively, p<0.01. Furthermore, the graph that shows risks of general and CVD mortality for T2D patients depending on BMI has the shape of an asymmetric parabola: HRs associated with low and normal BMI were significantly higher comparing to those, related to overweight or moderate obesity. The above phenomenon partially corresponds to "obesity paradox" that has been recently discovered among patients suffering from CVD (Gruberg et al., 2002; Curtis et al., 2005) , however in our study this effect concerns T2D patients. An observational study that included 25 361 T2D patients showed that glibenclamide treatment is associated with much higher risk of general and CVD mortality, comparing to treatment with another derivative of sulfonylurea – gliclazide. HRs for total and CVD mortality within the glibenclamide patient cohort were 2.57 (95% CI 1.73–3.82) and 2,93 (95%CI 1.83–4.71) respectively; (p < 0,001). These data correspond to changes of OGLD distribution and trends of life duration among DM patients that we have revealed as well (Khalangot et al., 2009 e). Previously, there had been only one study where similar results concerning total mortality associated with the use of glibenclamide or gliclazide in a cohort of 568 T2D patients were obtained (Monami et al., 2007). Our study broadens this tendency onto CVD mortality.

1.3.2 Register-based T1D epidemiology studies

T1D incidence among Ukrainian adults from 1994 till 2004, that we have evaluated retrospectively according to the register data, had a decreasing tendency (Khalangot, 2009). Our assessment of T1D incidence dynamics among adults does not confirm the information about steady increase of global T1D incidence (Green et al., 2001; Gale, 2002), however these studies only concerned child incidence. As Ukraine is also experiencing a rise of DM incidence among children, our data can be easily explained by earlier DM manifestation among people, who carry the genotype predisposing to T1D. Researchers of Danish DM register have recently reported a decrease of DM incidence among young adults. National diabetic register of Denmark has collected data on 359 000 DM cases between 1995 and 2006, and it includes the total population, diagnosed with DM. This register has recorded a clear tendency towards reduction of mortality among DM patients, which has been observed since 2003 (Carstensen et al., 2008). We have recently conducted a series of studies as well that focused on factors influencing mortality and territorial heterogeneity of T1D in Ukraine (Khalangot, 2008; Khalangot et al., 2009 c; 2010). The purpose of these studies (Khalangot et al., 2009 d) was also to determine whether the insulin requirement can change systematically in T1D patients, and whether this requirement depends on the same factors that determine its prevalence. This chapter is mainly a review of these studies.

2. Methods

A database with 282,988 records of diabetic patients was developed on the basis of epidemiological analysis conducted during the 2005–2006 register verification (01.12.2006). To evaluate the completeness of the register data, we compared it to the official 2005

Ministry of Health statistical data (Anonymous, 2006). The integrity of the register, i.e., the data on the number of patients who have received insulin, was assessed based on the information provided by the primary care doctors (district endocrinologists) to the regional diabetic registers. Consequently, the regional endocrinologists were responsible for updating the data and endorsing it to the central level. Accordingly, by assuming that the data were encoded into the regional registers with various degrees of completeness, significant limitations were noted in the assessment of the prevalence of insulin-dependent diabetes as well as in further epidemiological evaluations. Considering the fact that Ukraine has a national, free-of-charge insulin supply to the patients who require it, the Ministry of Health data reflect the number of these patients to the fullest extent. However, the Ukrainian Ministry of Health receives only non-personalized data that are difficult to verify. A comparison of the data from the 2006 Diabetes Register with the 2005 data on the insulin-treated patients from the Ministry of Health (considered 100%) revealed certain similarities: the fraction of the patients included in the register was 91.1%, based on the number of the patients according to the Ministry of Health data. However, in the Kharkiv region, only 58.6% of the Ministry of Health patients were in the register. It was assumed that the Kharkiv region data in the register could be incomplete, and hence, was not used in the analysis of T1D prevalence among adults.

2.1 T1D cases selection

Therefore, the analysis was carried out using the T1D criteria used by the epidemiologists–researchers for the European diabetes population databases (Kyvik et al., 2004; Soedamah-Muthu, 2006). The patients were selected based on the following conditions: T1D primary care diagnosis; age at the time of being included in the register ≥15 years; place of residence and gender; and data on diagnoses before the age of 30 years.

2.2 T1D prevalence assessment

The prevalence of T1D in the Ukrainian regions was determined as of the end of 2004. The T1D prevalence was calculated using the official data on the adult population of the corresponding regions (Anonymous, 2006), and 95% confidence interval (CI) was determined using arcsine transformation (Altman et al., ed-s., 2003). Multiple comparisons of T1D regional prevalence were subsequently carried out using the modified (Liakh & Gurianov, 2004) L. Marascuilo mathematical procedure (Marascuilo, 1966). The MedStat statistical package was used for the calculations (Liakh & Gurianov, 2004). Logistic regression analysis was used to determine the influence of the explanatory variables on the resulting variable (Bland, 2000). For each input variable, we evaluated the estimated logistic regression coefficient with the standard error, estimated as the odds ratio (OR) with a CI for its actual value and associated p value, and performed a Wald test (testing the null hypothesis on the congruency of the OR of the "disease" associated with the increase of this variable by 1). We used this information to determine whether each variable was related to the outcome of interest, and to quantify the extent of such a relationship (Bland, 2000). The Statistica 5.5 (StatSoft Inc., 1999) package was used in this set of calculations.

2.3 T1D outcomes assessment

We have evaluated the prevalence of proliferative retinopathy (PR), arterial hypertension (AH), and mortality risks in the retrospective cohort of T1D (27,896 patients); these data was

published elsewhere (Khalangot et al., 2009[c] ; 2010). In brief, mortality was assessed using the Cox regression model, determining hazard ratios (HRs) and corresponding 95% confidence intervals (95% CI). We calculated odds ratios (ORs), and used a logistic regression to compare PR and AH.

2.4 Diabetes-associated antibodies and c-peptide measurements

A total of 86 T1D patients (42 males and 44 females), with a mean age of 27.5 years (0.86) and mean diabetes duration of 10.3 (0.72) years (SE), were randomly selected from four regional diabetes-mellitus registers: Chernihivska, Zaporizka; Ivano-Frankivska, and Chernivetska. The glutamic acid decarboxylase 65 antibody (GADA), insulin antibody (IA), and plasma c-peptide levels were determined using radioimmunoassay (RIA) kits (IMMUNOTECH™) after obtaining the patients' informed consent. The model of the logistic regression was used for the multifactor data analysis of GADA, IA, c-peptide persistence, OR, and the 95% CI that were determined. The plasma was considered GADA- or IA-positive, if GADA >1 U/ml or IA >0.4 U/ml, and low c-peptide, if its level was <32.6 pmol/l.

3. Register analysis results and discussion

The analysis of the register of diabetic patients has allowed for the first time to assess the adult prevalence of T1D in Ukraine in comparison with important clinical (daily insulin dose, mortality, and complications) and some paraclinical (GADA) characteristics of the disease (Khalangot et al., 2009 [c]; Khalangot et al., 2009 [d]; 2010).

3.1 T1D territorial dissimilarity and clusterization

The data on adult T1D prevalence in 24 Ukrainian regions (Table 1) indicated territorial dissimilarity: chi-square = 648.30, degree of freedom, k =23 (p< 0.001).

Further multiple comparisons using the modified Marascuilo procedure (Marascuilo, 1966) allowed conducting a pairwise assessment of each region. This assessment enabled clustering of the regions according to T1D prevalence. The flagged regions that did not statistically differ from the minimal level according to prevalence were considered as a cluster. This procedure was repeated for the remaining regions as well. The following regional clusters were distinguished according to the T1D prevalence:

Minimal prevalence cluster = AR Crimea, Ivano-Frankivska, Mykolaivska, Odeska, Chernivetska, and Luganska regions.

Intermediate prevalence cluster = Vinnitska, Volynska, Dnipropetrovska, Donetska, Zhytomyrska, Zakarpatska, Kirovogradska, Lvivska, Rivnenska, Kievska, Sumska, Ternopilska, Poltavska, Khersonska, and Cherkaska regions.

Maximal prevalence cluster = Zaporizka, Khmelnytska, and Chernigivska regions.

Cases of T1D in each regional cluster were unified and the prevalence was calculated for the actual clusters. The T1D prevalence was found to be 6 (5–6), −7 (6–7), and −9 (8–9) per 10,000 adults, for the minimal, intermediate, and maximal prevalence clusters respectively. A comparison of the differences between these groups indicated a high level of confidence (χ^2 = 214.4; p< 0.001), as shown in figure 1.

Region (oblast')	Gender		Number of type1 adult diabetic patients		Total adult population
	males	females	total, n	per 10 000 adults (95 % CI)	
AR Crimea	564	513	1077	5 (5-6)	2 032 600
Vinnitska	600	464	1064	7 (7-8)	1 440 600
Volynska	354	271	625	7 (7-8)	844 300
Dnipropetrovska	1107	1017	2124	7(6-7)	2 992 000
Donetska	1477	1282	2759	7 (6-7)	4 071 100
Zhytomyrska	387	339	726	6 (6-7)	1 122 300
Zakarpatska	354	264	618	6(6-7)	1 000 700
Zaporizka	732	712	1444	9 (8-9)	1 619 200
Ivano-Frankivska	351	274	625	5 (5-6)	1 137 500
Kievska	1476	1514	2990	8 (7-8)	3 804 900
Kirovogradska	334	327	661	7 (7-8)	913 500
Luganska	604	623	1227	6 (5-6)	2 127 900
Lvivska	802	700	1502	7 (6-7)	2 136 000
Mykolaivska	292	279	571	5 (5-6)	1 041 600
Odeska	470	438	908	4 (4-5)	2 037 900
Poltavska	552	464	1016	7 (7-8)	1 345 600
Rivnenska	355	316	671	7 (7-8)	930 000
Sumska	408	321	729	7 (6-7)	1 071 700
Ternopilska	411	297	708	8 (7-8)	925 000
Kharkivska	*597*	*493*	*1090*		*2 479 700*
Khersonska	303	286	589	6 (6-7)	957 000
Khmelnitska	510	468	978	8 (8-9)	1 163 000
Cherkaska	408	366	774	7 (6-7)	1 154 600
Chernivetska	267	177	444	6 (5-6)	746 000
Chernigyvska	473	403	876	9 (8-9)	1 020 300
Total	14188	12608	26796		40 115 000

Table 1. Prevalence of Type 1 Diabetes Mellitus in Adults Diagnosed Before the Age of 30 in Ukrainian Regions (Khalangot et al., 2009d)

3.2 T1D gender assessment

The fraction of males among the 26,796 adults diagnosed before the age of 30 years corresponded to 52.95%, and varied from 49.2% in Luganska to 60.1% in Chernivetska regions. In the majority (23 out of 25) of the regions, this fraction was >50%. Comparison of

the 25 regions with the fraction of T1D males revealed a certain variation according to the territorial attribute (chi-square = 67.70, the degrees of freedom, k =24; p <0.001). However, multiple comparisons failed to reveal any distinctions according to the fraction of T1D males between the specific regions. Furthermore, it must be noted that there was no increase in the female fraction among T1D adults, which is common in the general population.

It is possible that an increase in the male fraction in this population reflects the epidemiological peculiarities of this disease, which have not yet been described by the identified (as well as the unknown) factors that could lead to the increase in the mortality among males.
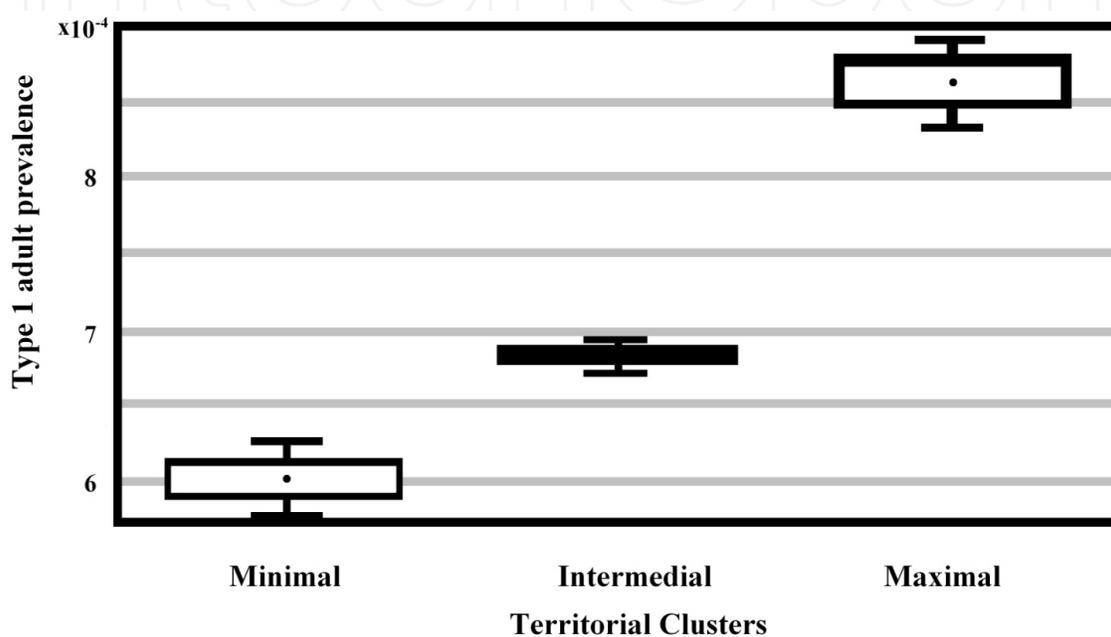
Note: given Means ± SE (the dot within the box and height of boxes respectively), 95% CI (lines that emerge above and below the boxes)

Fig. 1. Prevalence of Type 1 Diabetes Mellitus Diagnosed in Patients Under the Age of 30 in Territorial Clusters of Ukrainian Regions (per 10 000 adults, 95% CI) (Khalangot et al., 2009 [d])

3.3 T1D insulin doses assessment

The data analysis of the 23,633 T1D patients (Table 2) from the register, who were classified according to insulin dose, age, and disease duration, indicated that women have a higher average age and disease duration, but lower daily insulin dose, when compared with men.

Number of T1D patients (n)	Mean age, yrs(SD)	Mean diabetes duration, yrs(SD)	Mean insulin dose, U/day (SD)
Man (12364)	32.48 (11.60)	14.11 (10.47)	52.03 (18.56)
Women (11269)	33.38 (12.43)	15.69 (10.99)	49.50 (17.98)
Total (23633)	32.91 (12,01)	14.86 (10.75)	50.83 (18.33)

Note: P (man/women) < 0.001

Table 2. Average Age, Disease Duration, and Daily Insulin Dose of Type 1 Diabetes Mellitus Patients in Ukraine According to the Diabetes Register data (Khalangot et al., 2009 [d])

3.3.1 T1D insulin doses and diabetes duration

As the average duration of the disease was found to be 14.86 years, the average daily insulin doses were calculated for each year of the duration, from 0 (<1) to 15 years.

The regression analysis (figure 2) indicated that in this range, the insulin dose rises with the increase in the disease duration:

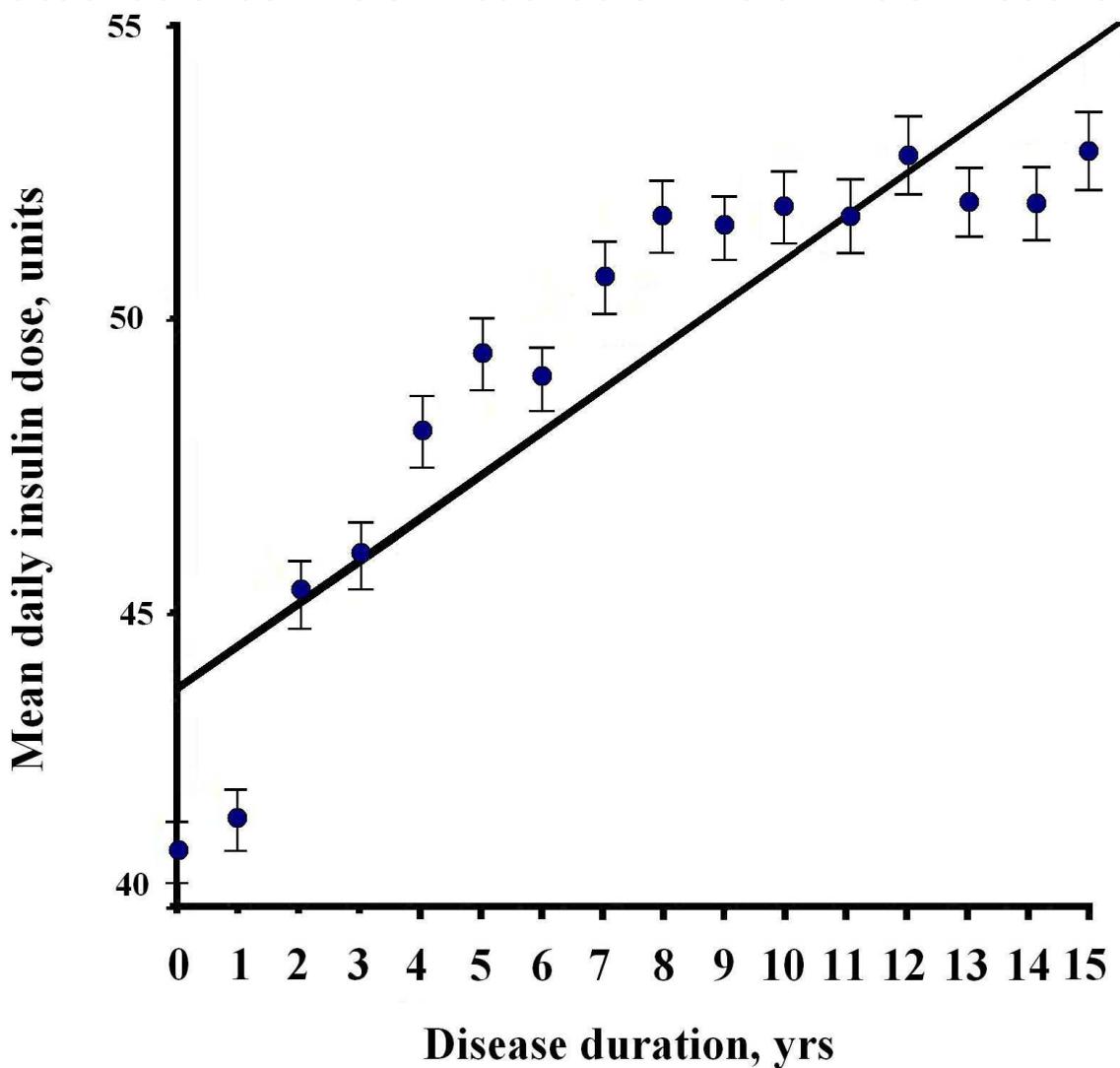Insulin (units/day) = 0.7326 × duration (years) + 43.74 (coefficient of linear correlation, R = 0.899, $p < 0.001$).

Fig. 2. Average (Mean ± SE) daily insulin doses of type 1 diabetes mellitus patients depending on the disease duration in the range of 0-15 years (Khalangot et al., 2009 [d])

A further increase in the disease duration in the range of 16–31 years was not accompanied by regular changes in the insulin dose. The regular rise of insulin dose, observed with the increase in the duration of T1D in adults diagnosed before the age of 30 years, is still an unknown phenomenon. However, this phenomenon was observed to correspond to the

observation that T1D patients have long-standing insulin secretion at times (the study of c-
peptide level), which was proven by Bonora (Bonora et al., 1984) and confirmed by the
Diabetes Control and Complications Trial (DCCT). These research efforts uncovered the
diverse influence of different insulin-therapy patterns on the process described (*The DCCT
Research Group,* 1987; 1998). The confirmation of this data with the prospective observation
was undertaken in Germany (Linn et al., 2003). Our results could be viewed as an indirect
confirmation of the extended continuation of the β-cell secretion, obtained through the
cross-sectional treatment data analysis of almost the entire population of T1D patients in
Ukraine. The standardization of the daily insulin doses, depending on the disease duration,
enables the necessary quantitative comparisons of the treatments for T1D adult patients.

3.3.2 T1D insulin doses in territorial clusters

It would be logical to consider that the rate of decrease in insulin secretion among the T1D
patients that differs according to the prevalence of such autoimmune disease, as T1D will
also vary. Table 3 presents the comparisons of the daily insulin doses (median) in all the
three clusters of the regions selected according to the prevalence of T1D in adults.

Type 1 diabetes prevalence cluster	Insulin doses standardized according to diabetes duration, median, U/day	95%CI	P
1. minimal	45.89	45.28 - 47.19	< 0.01 (1 vs 3)
2. intermediate	52	47.61 - 52.78	< 0.05 (1 vs 2)
3. maximal	56.59	53.33 -57.88	< 0.05 (2 vs 3)

Note: Number of diabetes duration yearly groups (n) in all clusters is 16.

Table 3. Comparison of daily insulin doses standardized for every year of disease duration
in the range of 0-15 years in clusters of regions singled out according to prevalence of
diabetes mellitus type 1 (Khalangot et al., 2009 [d]).

Insulin doses standardized according to the disease duration within the range of 0–15 years
in the minimal prevalence cluster of T1D prevalence were significantly lower, when
compared with the intermediate and maximal prevalence clusters. The values in the
intermediate prevalence cluster were lower than those in the maximal prevalence cluster
(figure 3, table 3).

By evaluating the data presented in table 3, it should be noted that the probability
coefficients (*P*), in this case, reflect a relatively small number of the "yearly" groups (*n*=16)
in each cluster. If we were to assess the individual data on the insulin dose in each cluster
without yearly grouping, then the number of cases (*n*) corresponding to the number of
patients would greatly increase: 4,658; 14,712 and 2,879 in the minimal, intermediate, and
maximal prevalence clusters, respectively. The unstandardized according to the diabetes
duration average doses and their standard deviations (SD) in each of the three clusters, were
observed to be 46.62 (19.38); 51.54 (17.57); and 55.94 (19.46) units/day, respectively, which
was found to increase ($p < 0.0001$) in the clusters with higher T1D prevalence. However, the
correlation of the insulin dose and the T1D prevalence found in this current region needs to
be explained. One of the explanations for the difference in the daily insulin doses could be
that in different Ukrainian regions, the doctors administer different levels of diabetes
control: the lower dose is explained not only by the lower requirement of insulin by
patients, but rather by the lower quality of treatment. An alternative explanation could be

the higher intensity of the autoimmune process in patients residing in a territory with higher T1D prevalence.
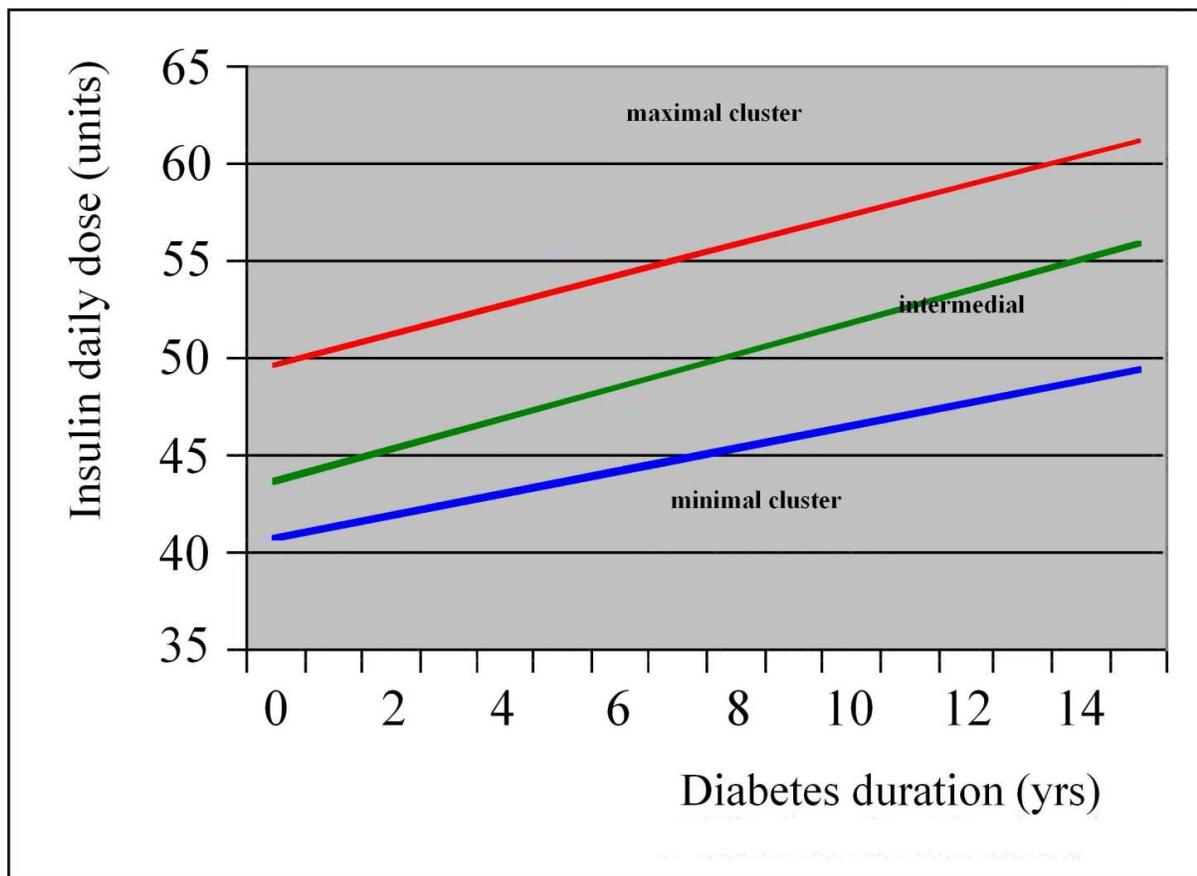

Fig. 3. Average daily insulin doses of diabetes mellitus type 1 patients depending on the disease duration (in the range of 0-15 years) as well as on the territorial cluster, selected according to disease prevalence (Khalangot et al., 2009 [d])

3.3.3 Quality of glucose lowering treatment and mean insulin doses in T1D prevalence clusters

Glycated hemoglobin (HbA1c) is considered as the most evident criteria in determining the quality of glucose-lowering treatment. We have analyzed and compared the levels of HbA1c of 1,288 T1D patients, included in the register. Table 4 shows the average HbA1c levels and the daily insulin doses according to the T1D prevalence clusters.

Type1 diabetes prevalence cluster	N	Mean HbA1c level, % (SD)	Mean insulin dose, U/day (SD)
1. Minimal	111	8.57 (3.29)	40.91(16.24)
2. Intermediate	778	8.24 (2,3)	51.5 (14.8)
3. Maximal	240	9.52 (2.24)	54.79 (18.05)
P (1 vs 3)		< 0.01	< 0.001

Table 4. Average levels of HbA1c (%) and insulin doses (units/day) considering territorial clusters with various diabetes type 1 prevalence (Khalangot et al., 2009 [d])

The level of HbA1c in the maximal prevalence cluster was significantly greater than that in the minimal prevalence cluster, which does not support the assumption of lower treatment quality in the regions with lower T1D prevalence. Therefore, the alternative explanation using the discovered phenomenon remains rather the most likely one. Its confirmation may include c-peptide determination as well as the determination of antibodies associated with diabetes in patients residing in the Ukrainian territories with different T1D prevalence. However, the reason for the heterogenic prevalence of T1D is still unknown.

3.4 GADA, IA and c-peptide levels in plasma of T1D patients from different prevalence clusters

The GADA and IA levels in children recently diagnosed with T1D are observed to be higher in countries with a greater incidence of this disease, such as Sweden, when compared with those where the T1D incidence is lower, such as Lithuania (Holmberg et al., 2006). In our study, the GADA levels and persistence in patients from the maximal T1D prevalence cluster (n=38), were higher than that in patients from the minimal prevalence cluster (n=48): 14.1±4.6 and 3.2±1.2 U/ml, respectively, mean ± SE = 0.028; OR = 9.66 (3.31–28.17), p< 0.001. Adjusting for age, gender, and duration of diabetes affected the results only slightly: OR = 7.91 (2.44–25.57), p< 0.001. However, the IA and c-peptide levels and their persistence were not observed to be associated with T1D prevalence. It should be noted that persistence of IA is common only for children with T1D (reviewed by Dib & Gomes, 2009), when our study analyzed adults. These data was obtained in 2007 and published earlier elsewhere (Khalangot et al., 2009 [d]). In another series of our studies (unpublished data) conducted in 2010 on T1D patients (11 from Minimal cluster and 18 from Maximal one) selected in the same way, the GADA levels also differed significantly: 0.92 (0.61-3.04) and 24.43 (3.28-61.42) U/l, Me , 95% CI, p = 0.003; adjusted for diabetes duration OR = 8.6 (1.1-65.7), p=0.036.

That is, the chance to have high GADA levels is almost 9 times higher for patients from the Maximal cluster as compared to the Minimal cluster, and this ratio was stable during repeated trials in these populations of T1D. Thus, the phenomenon of stable GADA persistence was discovered among adult T1D patients, residing in Ukraine within the maximal prevalence cluster.

3.5 T1D outcomes assessment in territorial prevalence clusters

The obtained results allow us to assume that there may be differences in the incidence of adverse outcomes of the disease among populations with varying prevalence of T1D. The gathered large cohort (29 708 T1D patients) may be viewed as almost complete data on this category of patients in Ukraine (Khalangot et al., 2009 [c], 2010). It should be noted, that the average duration of T1D is low (17.32 years). According to the data from a cross sectional study of Swedish National Diabetic Register (NDR), in 1997 the duration of T1D was 23.1 years and in 2004 it increased to 26.1 years. The criteria for T1D in the NDR study were treatment by insulin only and diagnosis before the age of 30 (Eeg-Olofsson et al., 2007), which corresponds to criteria used by us. According to the data from one of the regional diabetic registers in the US, the average T1D duration in a cohort of patients who were diagnosed before 19 years of age exceeded 25 years (Nishimura et al., 2001).

3.5.1 Main characteristics of T1D patients from the cohort studied

The number of men in this cohort is greater than the number of women. Men have shorter disease duration (P <0,001) and higher levels of blood pressure (BP) (p <0,001), whereas

women have slightly higher levels of fasting glycemia (P <0,05). Blindness, cataracts and proliferative retinopathy more common for women (P <0,001). During 122,656.9 person-years (median observation period 4.7 years) 1958 deaths were recorded. The main cause of death was kidney failure. Cancer was very insignificant among other causes of death (table 5) . Possible reason for this phenomenon may be a short life expectancy of patients with diabetes.

| Characteristics	Men	Women	All
Number of patients, n	15738	13970	29 708
Mean age, years (SD)	34.35(12.55)	34.61(13.30)	34.47(12.91)
Body mass index, kg/m² (SD)	23.01(3.84) n=14331	23.34(4.37) n=12729	23.16(4.10)
BP systolic, mm Hg (SD)	126.29(18.75)	125.48(20.81)	125.91(19.75)
BP diastolic, mm Hg. (SD)	78.57(10.53) n=14298	77.66(11.38) n=12654	78.15(10.94)
Fasting blood glucose, mmol/l (SD)	9.23(2.82) n=13747	9.30(2.87) n=12174	9.26(2.85)
HbA1c, % (SD)	8.68(2.53) n=1784	8.83(2.61) n=1789	8.75(2.57)
Smoking, n (%)*	3223 (20.48)	414(2.96)	3637(12.24)
Mean T1D duration, years	16.73	17.98	17.32
Nephropathy treatment, n (%)*	4627(31.42)	4921(37.59)	9548(34.32)
Cataract, n (%) *	1573(10.68)	2041(15.59)	3614(12.99)
Proliferative retinopathy, n (%) *	1187(8.06)	1297(9.91)	2484(8.93)
Blindness, n (%) *	459(3.1)	506(3.9)	965(3.47)
Follow up period, median, years	4.7	4.73	4.71
Total mortality cases, n (%)	1149 (100)	809(100)	1958(100)
CVD mortality, n (%)	266(23.15)	182(22.5)	448(22.88)
Cancer mortality, n (%)	16(1.39)	7(0.87)	23(1.17)
Renal failure, n (%)	295(25.67)	262(32.39)	557(28.45)
DKA and Coma	25(2.18)	36(4.45)	61(3.12)
Other reasons (%)	344(29.94)	174(21.51)	518(26.46)
Unknown	203(17.68)	148(18.29)	351(17.93)

Notes. BP – blood pressure, DKA – diabetic ketoacydosis;
* - data concerned to 14723 man and 13092 women

Table 5. Same characteristics of T1D patients' cohort (Khalangot et al., 2010)

Life expectancy of T1D patients in Ukraine in 2007, assessed according to age at the time of death did not exceed 40.2 yrs (Khalangot, 2008). In UK, according to similar cohort study this value is 55 yrs (Soedamah-Muthu et al., 2006), however the British cohort also included children, which could influence the assessment of average T1D duration and age at the time

of death. Renal failure is the leading cause of death (28.4%) in T1D patient cohort, whereas according to a British study of DM patient register containing primary care data, the leading cause of death among T1D patients was CVD (Laing et al., 1999). Similar results were obtained by a European study EURODIAB (Soedamah-Muthu et al., 2008). Comparison of main causes of death according to EURODIAB data and Ukrainian Diabetes Register (UDR) data is shown in figure 4. Apparently death from renal failure among T1D patients in Ukraine prevails several times over other causes, while in other parts of Europe the main cause of death is CVD. It was previously noted by epidemiologists that the main cause of death for T1D patients is renal failure (Dorman et al., 1984), however these data were relevant in 1960s-1970s. Today's experts believe that the shift in mortality structure towards CVD happened due to intensification of hypotensive therapy and insulin treatment (Maahs et al., 2006), therefore the mortality structure of T1D patients that we have revealed when analyzing UDR can be assumed to conform to earlier time period of clinical practice.
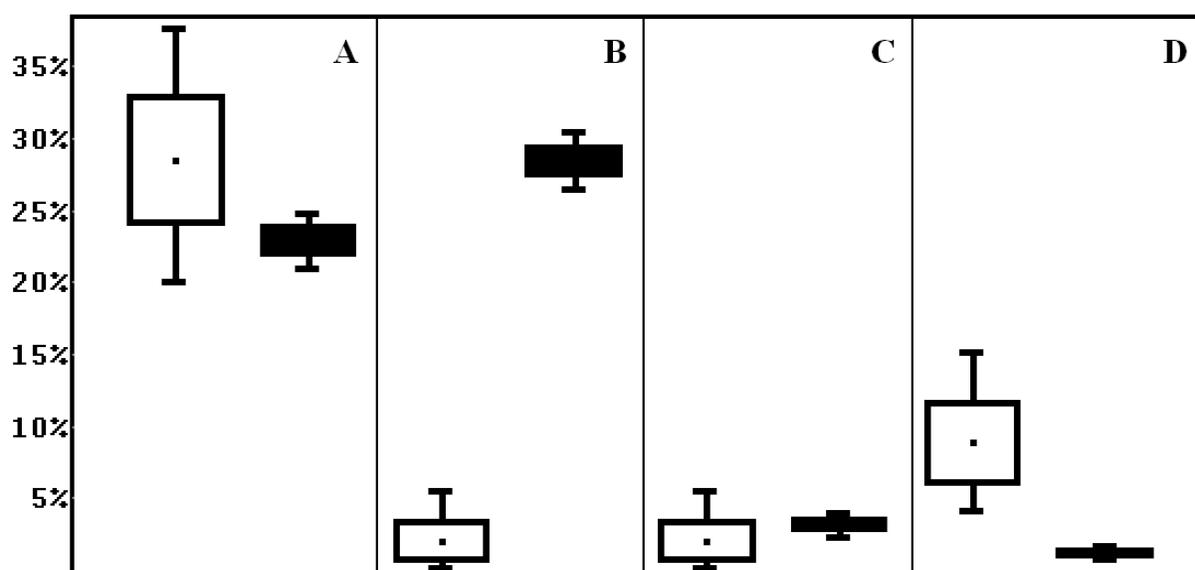
Note: given Means (%) ± SE (the dot within the box and height of boxes respectively), 95% CI (lines that emerge above and below the boxes). Data from Ukrainian Diabetes Register given according to Khalangot et al., 2010; EURODIAB given according to Soedamah-Muthu et al., 2008.

Fig. 4. Interval estimation of structure (%) of the main death causes among T1D patients, diagnosed before 30 years of age according to EURODIAB data (white boxes) and Ukrainian Diabetes Register (black boxes). Death causes: CVD (A); renal failure (B); DKA or coma (C); cancer (D).

3.5.2 Mortality assesment in territorial T1D prevalence clusters

To build the regression model we used 1925 deaths recorded among 27 896 patients. We have found that the patients living on the territory belonging to the maximal T1D prevalence cluster associated with increased risk of total mortality compared with the minimal prevalence cluster. In the minimal territorial cluster mortality was 15.68, and in the maximal -- 22.64 cases per 1000 person-years of follow up, $p < 0.001$. The risk (hazard ratio - HR) of death from all-cause mortality in patients from maximal in relation to the the minimal cluster was 1.5 (95% CI 1.31-1.79). Adjusting for gender had almost no effect on this risk: HRs standardized according to age, gender, and T1D duration for all cause mortality in

the maximal T1D prevalence cluster compared to the minimal made up 1.56 (95 % CI 1.33-1.81), p<0.001, whereas the same value for diabetes-related mortality was 1.5 (95 % CI 1.14-1.96), p<0.001. The risk of total mortality for patients from the intermediate cluster did not differ from the minimal one (fig. 5, 6).

During the whole period of observation, 57 cases of death from acute T1D complications among 27510 patients have been recorded. It has been established, that prevalence of T1D is directly associated with the increase of mortality from acute T1D complications (table 6, figure 7). Hazard ratios, determined using Cox model of regression, and standartized according to gender, duration, and age in maximal territorial cluster of T1D prevalence comparing to the minimal cluster, exceeded 5 : HR= 5.25 (95% CI 1.76-15.63), p<0.001.

T1D prevalence cluster	Patients, n	Follow up period, person years	Mean Follow up, years	SD	Death cases, n	Death cases per 1000 person-years
Minimal	5 769	20 079,52	3.48	1.74	4	0.2
Intermedial	17 898	77 323,3	4.3	1.69	36	0.47
Maximal	3 919	17 974,66	4.59	1.79	17	0.95

Table 6. Mortality related to acute T1D complications (Khalangot et al., 2010)
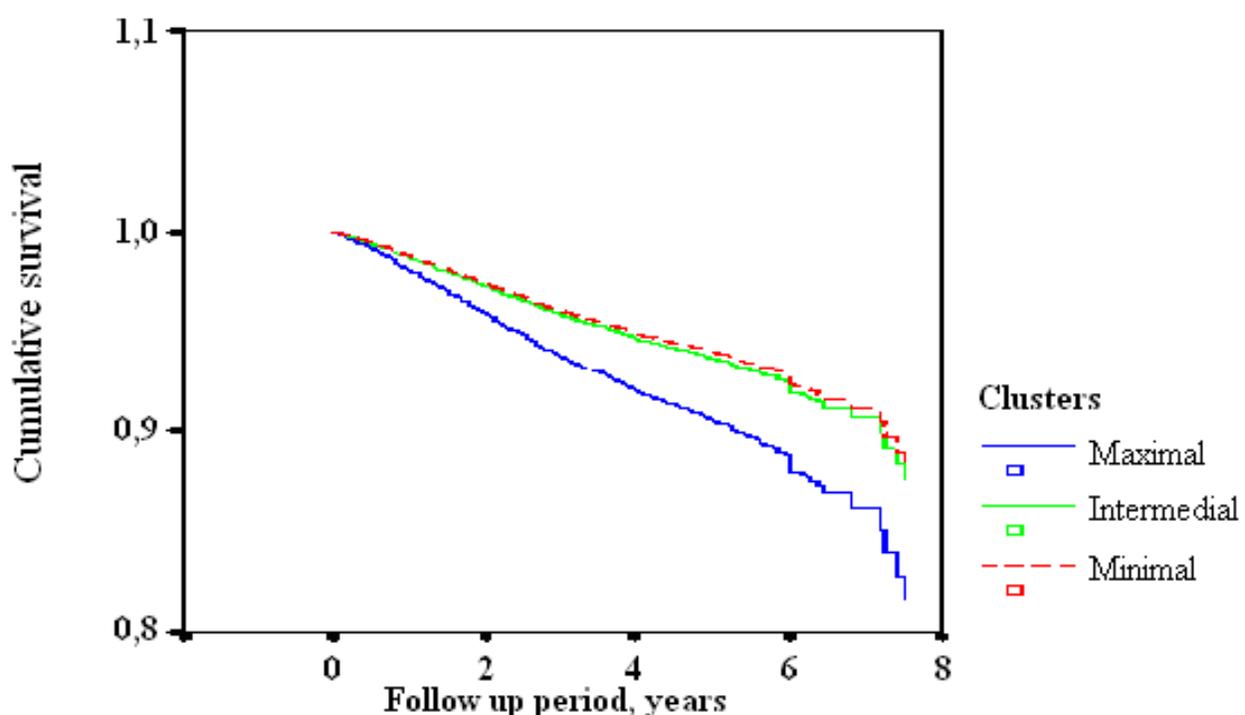
Fig. 5. All cause mortality represented by survival function in minimal, intermediate, and maximal clusters of T1D prevalence (Khalangot et al., 2009c)

3.5.3 Assesment of high blood pressure and proliferative retinopathy prevalence in territorial T1D prevalence clusters

Assessment of arterial hypertension (AH) incidence among patients in regional clusters was performed using the same cohort of 27 896 patients. A total of 4159 hypertension cases, or
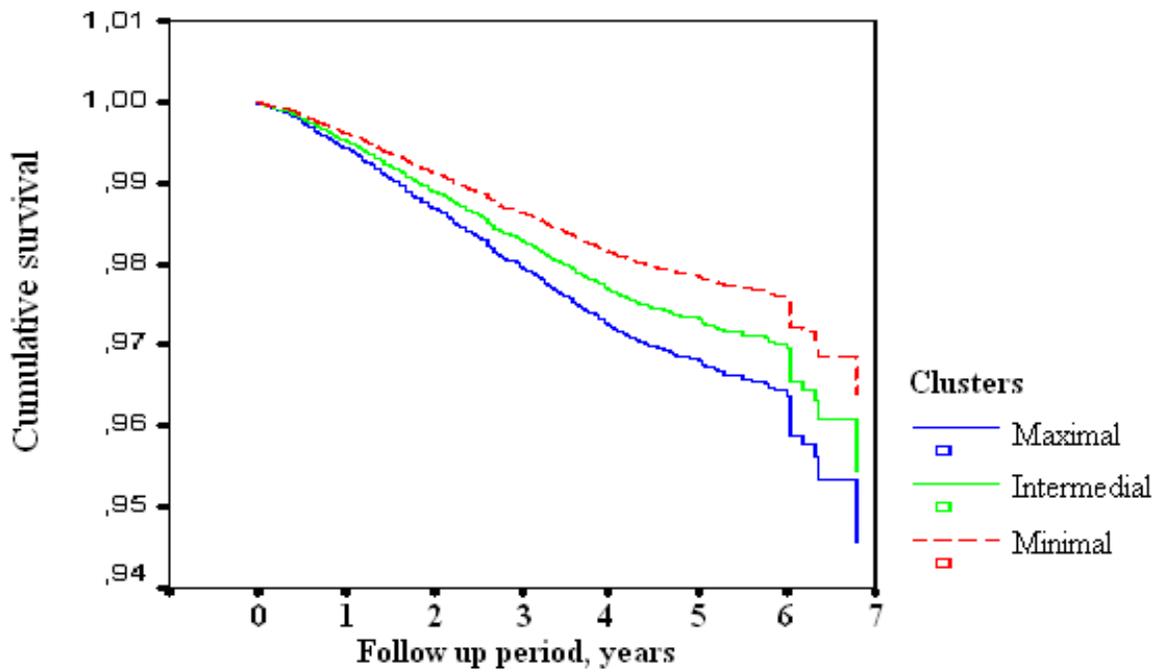
Fig. 6. DM-related mortality represented by survival function in minimal, intermediate, and maximal clusters of T1D prevalence (Khalangot et al., 2009c)
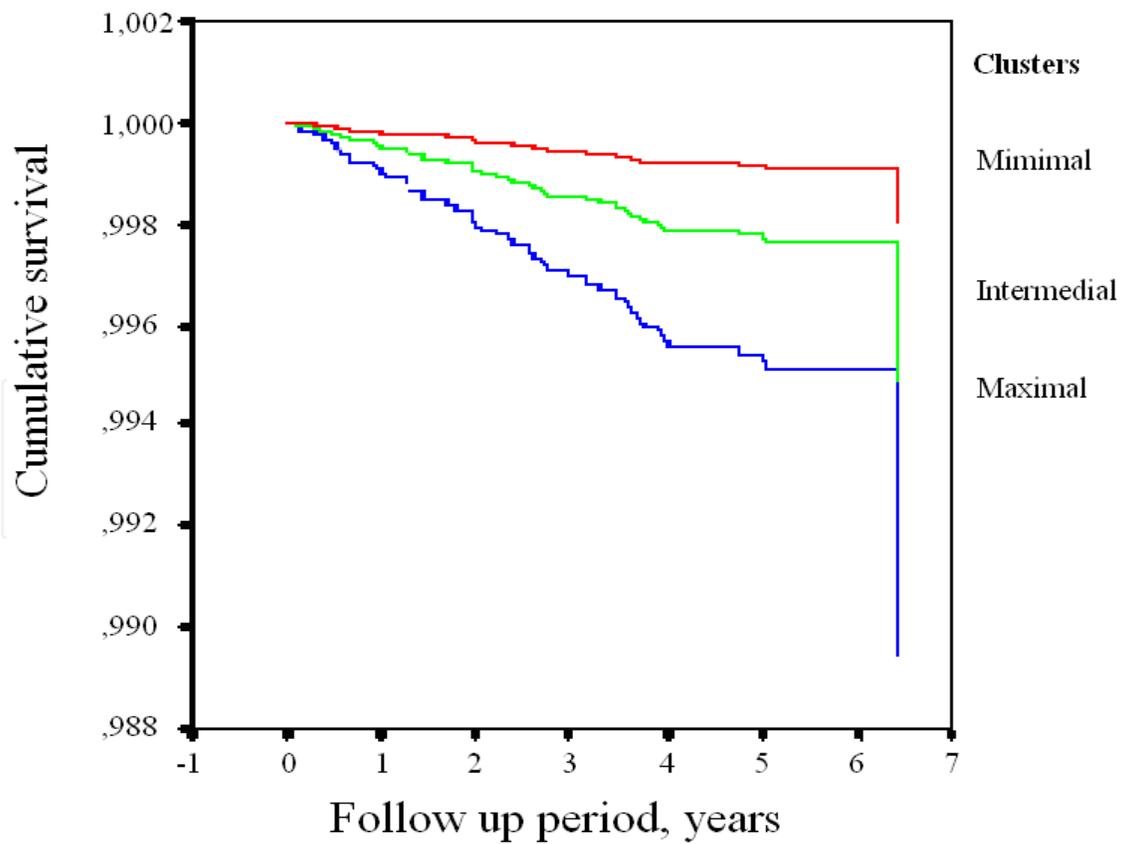

Fig. 7. Mortality related to acute T1D complications (cumulative survival) in different territorial clusters (Khalangot et al., 2010)

14.91%, were recorded. The minimal cluster included 691 AH cases (11.79%), maximal cluster had 570 cases (14.46%), and intermediate cluster included 2898 AH cases (16.02%). The prevalence of AH or proliferative retinopathy (PR) in the maximal or intermediale clusters is greater in relation to the minimal one (Table 7, Fig. 8). Hazard ratios were 1.36 and 1.46 for maximal and intermediale clusters in relation to the minimal cluster, the HR of which was considered as 1. Each year the T1D duration increases the risk of having hypertension. Adjusting according to gender, age and diabetes duration did not significantly change the risk of AH (table 6). Corresponding ORs for AH and PR were 1.36 (95% CI 1.2-1.54), $p<0,001$ and 2.04 (95 % CI 1.72-2.41), $p<0.001$. It was revealed that T1D prevalence is directly linked to the increase of all-cause and diabetes-related mortality risks, as well as to PR and AH prevalence.

T1D prevalence cluster	Patients, n	Cases of Arterial Hypertension, n	%	95 % CI
Minimal	5860	691	11.8	11.0-12.6
Intermedial	18095	2898	16.0	15.5-16.6
Maximal	3941	570	14.5	13.4-15.6

Table 7. Prevalence of arterial hypertension in T1D patients in different territorial clusters (Khalangot et al., 2009c)
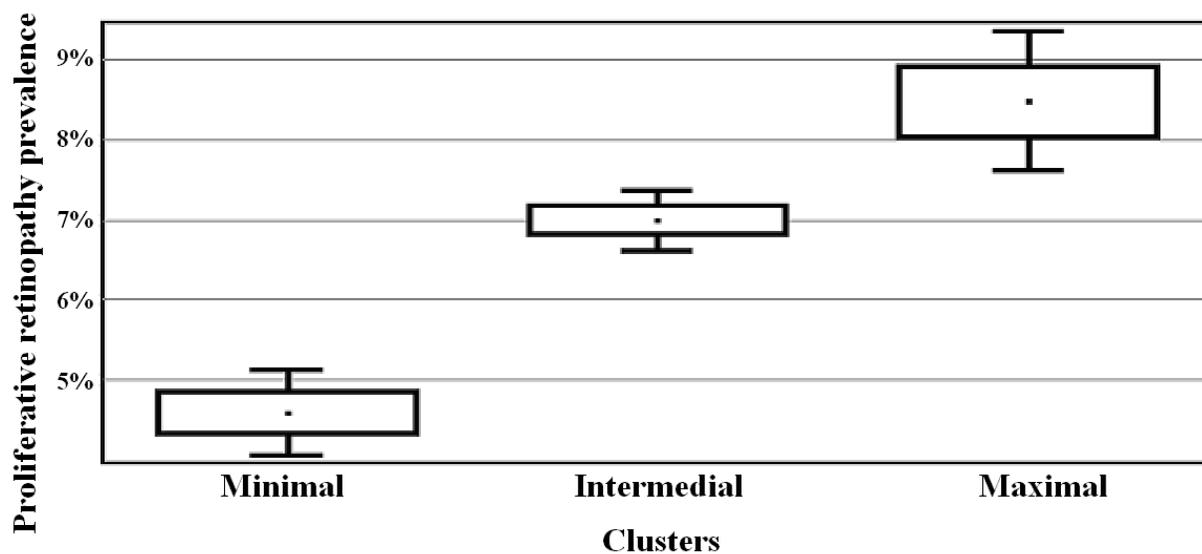

Fig. 8. Fraction (%) of patients with proliferative retinopathy (PR) in different clusters of T1D prevalene. The levels of PR prevalence (the dot within the box), its standart errors (the box height) and 95% CI (lines that emerge) are shown (Khalangot et al., 2009c).

We have found only one study that compared mortality between populations that differ in prevalence of T1D. This was a joint study of epidemiologists from Finland and Japan (Asao et al., 2003). Previously it was known that the incidence and prevalence of T1D in Finland is several times higher than in Japan, however mortality is higher among Japanese patients. The researchers explain this phenomenon by the fact that Finland was "disturbed" by its world's highest incidence of T1D, and because of that the Finnish health care system has

long been implementing public programs of relevant quality for treating diabetes (Asao et al., 2003). Comparison of our mortality data among patients with T1D in Ukraine (from 15.7 to 22.6 per 1000 person-years, respectively, in the minimal and maximal prevalence clusters) with mortality among patients with juvenile T1D in Japan and Finland (6.07 and 3.52 per 1000 person-years, respectively), demonstrates a considerably higher mortality in Ukraine and the presense of an opposing relationship between the frequency of T1D in compared countries and mortality in cohorts of patients with juvenile diabetes. Please note that cited Asao et al. study (2003) compared the mortality in cohorts of patients with infantile T1D from different countries, while our study compares T1D that develops in patients before the age of 30 in the same country.

4. T1D sybtype may be responsible for the T1D territorial heterogenity in Ukraine

Currently, researchers (eg. Dib & Gomes, 2009) distinguish such subtypes of T1D, as T1A (characterized by selective destruction of beta-cells by an autoimmune process that quickly leads to absolute insulin deficiency; most common among caucasians), LADA (Latent Autoimmune Diabetes in Adults with an onset usually after 35 years of age and characterized by slowly developing insulin deficit), and T1B, also called idiopathic (clinical course is similar to T1A, but without the autoimmune component). Fulminant diabetes is one of the subtypes of T1B. Its is common in asian countries, such as Japan, China, and Korea. It is characterized by a very quick progression of acute metabolic decompensation, damage of alpha and beta cells of pancreas, and absence of autoimmune disorders. The discovered positive relationship between T1D prevalence, exogenic insulin requirement level, development of diabetes complications, and mortality does not allow us to associate T1D territorial heterogenity with LADA. Furthermore, the increase of GADA persistence in T1D patients who reside in regions with higher prevalence of this disease does not allow to consider T1B as responsible for this phenomenon. Thus, T1A rather than T1B subtype of T1D determines the territorial differences in the risk of developing T1D as well as course severity of this autoimmune disease.

5. Future studies

Causal link between the territorial distribution of autoimmune T1D in adults and the severity of its course and outcomes remains unknown. The recently discovered antibodies to the type 8 zinc transporter (ZnT8As) have substantially improved the clinical stratification of autoimmune diabetes in adults, demonstrating the link to a more severe insulin deficiency (Lampasone et al., 2010). Swedish researchers point out the possibility of low zinc content in drinking water as a possible T1D risk factor in children (Samuelsson et al., 2010; Haglund et al., 1996). Interestingly, in accordance with our preliminary results (unpublished data), there is no shortage of zinc in blood plasma in adults without diabetes, residing on territories with high prevalence of T1D, and we have even observed an increase of plasma zinc levels among adults with T1D comparing to similar patients from the minimal cluster. Plasma zink levels may be low (T2D) or high (T1D), zink supplementation may improve glycemic control in the two major types of diabetes, however the underlying molecular mechanisms have been elucidated very insignificantly (reviewed by Jansen et al. , 2009). It is possible that the study of ZnT8As in

comparison to the levels of zinc in the environment and human body will provide new information about the cause of territorial heterogeneity of T1D.

6. Conclusions

We have shown, that the prevalence of T1D in the Ukrainian regions differs substantially. The daily insulin dose was found to increase regularly with the duration of the disease. This study also revealed a positive relation between T1D prevalence and the daily insulin doses, and observed a difference in the blood GADA levels among the T1D adults residing in territories with different T1D prevalence.

A unique feature of this study is that instead of examining the incidence, the prevalence of T1D was examined. This can be attributed to the relatively recent development of the Ukrainian diabetes-mellitus register (Khalangot & Tronko, 2007). Nevertheless, we believe that such an approach enabled us to study virtually the entire Ukrainian T1D population, and reveal a positive correlation between T1D prevalence, intensity of insulin treatment, hyperglycemia (HbA1c), and GADA levels, and its prevalence in adults. However, an earlier study of GADA in children recently diagnosed with T1D did not find any relation between GADA positivity and the clinical parameters of the disease (Holmberg, 2006).

7. Acknowledgements

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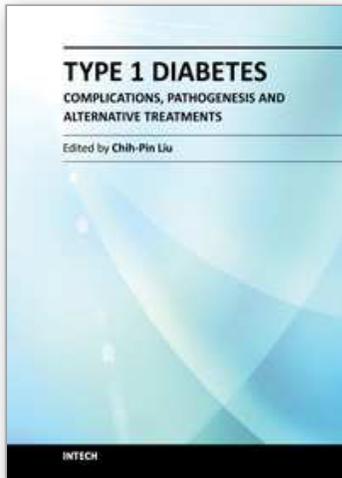
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This book is intended as an overview of recent progress in type 1 diabetes research worldwide, with a focus on different research areas relevant to this disease. These include: diabetes mellitus and complications, psychological aspects of diabetes, perspectives of diabetes pathogenesis, identification and monitoring of diabetes mellitus, and alternative treatments for diabetes. In preparing this book, leading investigators from several countries in these five different categories were invited to contribute a chapter to this book. We have striven for a coherent presentation of concepts based on experiments and observation from the authors own research and from existing published reports. Therefore, the materials presented in this book are expected to be up to date in each research area. While there is no doubt that this book may have omitted some important findings in diabetes field, we hope the information included in this book will be useful for both basic science and clinical investigators. We also hope that diabetes patients and their family will benefit from reading the chapters in this book.

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